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Health Technology Assessment

Volume 26 • Issue 7 • January 2022

ISSN 1366-5278

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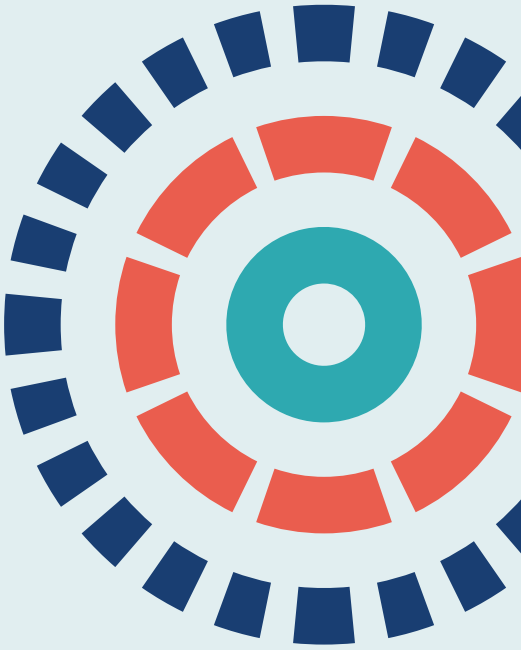

DOI 10.3310/UGEZ4120

Biomarkers for assessing acute kidney injury for people who are being considered for admission to critical care: a systematic review and cost-effectiveness analysis

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Declared competing interests of authors: Lorna Aucott is a member of the National Institute for Health Research Public Health Research funding committee (February 2017 to present).

Published January 2022
DOI: 10.3310/UGEZ4120

This report should be referenced as follows:

Brazzelli M, Aucott L, Aceves-Martins M, Robertson C, Jacobsen E, Imamura M, *et al.* Biomarkers for assessing acute kidney injury for people who are being considered for admission to critical care: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2022;**26**(7).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was commissioned and funded by the Evidence Synthesis Programme on behalf of NICE as project number NIHR128897. The protocol was agreed in May 2019. The assessment report began editorial review in November 2019 and was accepted for publication in November 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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Abstract

Biomarkers for assessing acute kidney injury for people who are being considered for admission to critical care: a systematic review and cost-effectiveness analysis

Miriam Brazzelli,[1*] Lorna Aucott,[1] Magaly Aceves-Martins,[1] Clare Robertson,[1] Elisabet Jacobsen,[2] Mari Imamura,[1] Amudha Poobalan,[3] Paul Manson,[1] Graham Scotland,[1,2] Callum Kaye,[4] Simon Sawhney[3] and Dwayne Boyers[2]

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Background: Acute kidney injury is a serious complication that occurs in the context of an acute critical illness or during a postoperative period. Earlier detection of acute kidney injury may facilitate strategies to preserve renal function, prevent further disease progression and reduce mortality. Acute kidney injury diagnosis relies on a rise in serum creatinine levels and/or fall in urine output; however, creatinine is an imperfect marker of kidney function. There is interest in the performance of novel biomarkers used in conjunction with existing clinical assessment, such as NephroCheck® (Astute Medical, Inc., San Diego, CA, USA), ARCHITECT® urine neutrophil gelatinase-associated lipocalin (NGAL) (Abbott Laboratories, Abbott Park, IL, USA), and urine and plasma BioPorto NGAL (BioPorto Diagnostics A/S, Hellerup, Denmark) immunoassays. If reliable, these biomarkers may enable earlier identification of acute kidney injury and enhance management of those with a modifiable disease course.

Objective: The objective was to evaluate the role of biomarkers for assessing acute kidney injury in critically ill patients who are considered for admission to critical care.

Data sources: Major electronic databases, conference abstracts and ongoing studies were searched up to June 2019, with no date restrictions. MEDLINE, EMBASE, Health Technology Assessment Database, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Web of Science, World Health Organization Global Index Medicus, EU Clinical Trials Register, International Clinical Trials Registry Platform and ClinicalTrials.gov were searched.

Review methods: A systematic review and meta-analysis were conducted to evaluate the performance of novel biomarkers for the detection of acute kidney injury and prediction of other relevant clinical outcomes. Random-effects models were adopted to combine evidence. A decision tree was developed to evaluate costs and quality-adjusted life-years accrued as a result of changes in short-term outcomes (up to 90 days), and a Markov model was used to extrapolate results over a lifetime time horizon.

Results: A total of 56 studies (17,967 participants), mainly prospective cohort studies, were selected for inclusion. No studies addressing the clinical impact of the use of biomarkers on patient outcomes, compared with standard care, were identified. The main sources of bias across studies were a lack of

information on blinding and the optimal threshold for NGAL. For prediction studies, the reporting of statistical details was limited. Although the meta-analyses results showed the potential ability of these biomarkers to detect and predict acute kidney injury, there were limited data to establish any causal link with longer-term health outcomes and there were considerable clinical differences across studies. Cost-effectiveness results were highly uncertain, largely speculative and should be interpreted with caution in the light of the limited evidence base. To illustrate the current uncertainty, 15 scenario analyses were undertaken. Incremental quality-adjusted life-years were very low across all scenarios, ranging from positive to negative increments. Incremental costs were also small, in general, with some scenarios generating cost savings with tests dominant over standard care (cost savings with quality-adjusted life-year gains). However, other scenarios generated results whereby the candidate tests were more costly with fewer quality-adjusted life-years, and were thus dominated by standard care. Therefore, it was not possible to determine a plausible base-case incremental cost-effectiveness ratio for the tests, compared with standard care.

Limitations: Clinical effectiveness and cost-effectiveness results were hampered by the considerable heterogeneity across identified studies. Economic model predictions should also be interpreted cautiously because of the unknown impact of NGAL-guided treatment, and uncertain causal links between changes in acute kidney injury status and changes in health outcomes.

Conclusions: Current evidence is insufficient to make a full appraisal of the role and economic value of these biomarkers and to determine whether or not they provide cost-effective improvements in the clinical outcomes of acute kidney injury patients.

Future work: Future studies should evaluate the targeted use of biomarkers among specific patient populations and the clinical impact of their routine use on patient outcomes and management.

Study registration: This study is registered as PROSPERO CRD42019147039.

Funding: This project was funded by the National Institute for Health Research (NIHR) Evidence Synthesis programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 7. See the NIHR Journals Library website for further project information.

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List of abbreviations

ACEI	angiotensin-converting enzyme inhibitor
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	angiotensin receptor blocker
AUC	area under the curve
CI	confidence interval
CKD	chronic kidney disease
DAP	Diagnostics Assessment Programme
EAG	External Assessment Group
ED	emergency department
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol-5 Dimensions
ESRD	end-stage renal disease
HR	hazard ratio
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ICU	intensive care unit
IGFBP7	insulin-like growth factor-binding protein 7
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KDIGO	Kidney Disease: Improving Global Outcomes
LOS	length of stay
NEWS	National Early Warning Score
NGAL	neutrophil gelatinase-associated lipocalin
NICE	National Institute for Health and Care Excellence
OR	odds ratio
PRaCTICaL	Pragmatic Randomised, Controlled Trial of Intensive Care follow up programmes in improving Longer-term outcomes from critical illness
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROBAST	Prediction model Risk Of Bias ASsessment Tool
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies, version 2
RCT	randomised controlled trial
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage disease
ROC	receiver operating characteristic
RR	relative risk
RRT	renal replacement therapy
SD	standard deviation
SHARP	Study of Heart and Renal Protection
SMR	Scottish Morbidity Record
SROC	summary receiver operating characteristic
TIMP-2	tissue inhibitor of metalloproteinase-2
TRIBE	Translational Research Investigating Biomarker Endpoints
WHO	World Health Organization

Plain English summary

Among people who are very ill or have undergone surgery, the kidneys may suddenly stop working properly. This is known as acute kidney injury. Acute kidney injury can progress to serious kidney problems and can be fatal. Currently, to decide whether or not acute kidney injury is present, doctors use the level of creatinine (a waste product filtered by the kidneys) in the blood or urine. However, creatinine levels are not a precise indicator and they can take hours or days to rise; this may lead to delays in acute kidney injury recognition. Novel biomarkers may help doctors to recognise the presence of acute kidney injury earlier and treat patients promptly. This work evaluates current evidence on the use of biomarkers for acute kidney injury with respect to clinical usefulness and costs.

We reviewed the current evidence on the use of biomarkers for assessing the risk of acute kidney injury among people who are very ill, and assessed whether or not the evidence was of good value for the NHS. We assessed the ARCHITECT® urine neutrophil gelatinase-associated lipocalin (NGAL) (Abbott Laboratories, Abbott Park, IL, USA), urine and plasma BioPorto NGAL (BioPorto Diagnostics A/S, Hellerup, Denmark) and urine NephroCheck® (Astute Medical, Inc., San Diego, CA, USA) biomarkers.

We checked studies published up to June 2019 and found 56 relevant studies (17,967 patients). Most studies were conducted outside the UK and investigated people already admitted to critical care. We combined the results of the studies and found that NephroCheck and NGAL biomarkers might be useful in identifying acute kidney injury or pre-empting acute kidney injury in some circumstances. However, studies differed in patient characteristics, clinical setting and the way in which biomarkers were used. This could explain why the number of people correctly identified and missed by the biomarkers varied across studies. Hence, we do not completely trust the pooled results.

We also found that acute kidney injury is associated with substantial costs for the NHS, but there was insufficient good-quality evidence to decide which biomarker (if any) offered the best value for money.

Scientific summary

Background

Acute kidney injury is a common and serious complication that typically occurs in the context of an acute critical illness or during a postoperative period. It is associated with prolonged hospital stay, increased morbidity and increased mortality. Earlier detection of kidney injury may facilitate the adoption of strategies to preserve renal function and prevent further progression of kidney disease.

Currently, acute kidney injury diagnosis relies on a rise in serum creatinine levels and/or fall in urine output. Despite its widespread use in the monitoring of kidney health and disease, creatinine is an imperfect marker of kidney function because its level in the blood is not solely dependent on kidney function, and changes in creatinine lag behind reductions in kidney function. The limitations have led to the search for novel biomarkers that may detect kidney stress or damage earlier and more reliably.

Biomarker tests for acute kidney injury include neutrophil gelatinase-associated lipocalin (NGAL), which can be measured in urine or blood. NGAL is released from neutrophils and is induced by inflammation, indicating tubular injury. Another recent biomarker for acute kidney injury is NephroCheck® (Astute Medical, Inc., San Diego, CA, USA), which tests for the presence of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) in the urine. Both TIMP-2 and IGFBP7 are cell-cycle arrest proteins and are used as markers of cellular stress in the early phase of tubular cell injury. Both NephroCheck and NGAL immunoassays are intended to be used in conjunction with existing clinical care. This assessment focuses specifically on the ARCHITECT® and Alinity i™ urine NGAL assays (Abbott Laboratories, Abbott Park, IL, USA), the BioPorto urine and plasma NGAL tests (BioPorto Diagnostics A/S, Hellerup, Denmark) and the NephroCheck test.

If these biomarkers allow early identification of patients at risk of acute kidney injury, they could enhance current acute kidney injury management by enabling timely measures to prevent progression of kidney injury and by informing decisions about the 'step-down' of low-risk patients to a lower level of hospital care, thereby reducing the use of hospital resources.

Objectives

The aim of this project was to summarise the current evidence on the clinical effectiveness and cost-effectiveness of the NephroCheck test, the ARCHITECT and Alinity i urine NGAL assays, and the BioPorto urine and plasma NGAL tests to assess the risk of acute kidney injury in critically ill hospitalised patients (adults and children) who are considered for admission to critical care.

Methods

Assessment of clinical effectiveness

Comprehensive electronic searches were undertaken to identify relevant reports of published studies up to June 2019.

The population of interest was critically ill people at risk of developing acute kidney injury who are considered for admission to critical care. Studies were eligible for inclusion only if they enrolled at least 100 participants at risk of acute kidney injury. The biomarkers under investigation were the

NephroCheck test, the ARCHITECT and Alinity i urine NGAL assays, and the urine and plasma BioPorto tests, used in conjunction with existing care. At present, there is no universally accepted reference standard for diagnosing acute kidney injury. The relevant comparator for this assessment was existing clinical criteria for monitoring serum creatinine levels and urine output, in conjunction with clinical judgement and in line with current clinical classification systems [risk, injury, failure, loss of kidney function, and end-stage disease (RIFLE); paediatric-modified RIFLE; the Acute Kidney Injury Network classification; and the Kidney Disease: Improving Global Outcomes (KDIGO) classification system] (see National Institute for Health and Care Excellence. *Acute Kidney Injury: Prevention, Detection and Management. Clinical guideline [CG169]*. London: National Institute for Health and Care Excellence; 2013).

The outcomes of interest were detection of acute kidney injury, prediction of acute kidney injury, prediction of mortality, prediction of the need for long-term renal replacement therapy and prediction of developing chronic kidney disease after acute kidney injury.

The quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies, version 2, tool and the Prediction model Risk Of Bias ASsessment Tool.

Assessment of cost-effectiveness

A decision tree, using a linked-evidence approach based on observational data, was used to model the impact of test accuracy on acute kidney injury status and associated 90-day costs and outcomes, including need for intensive care unit care, length of hospital stay, 90-day mortality or development of chronic kidney disease. These observational associations necessitate causal assumptions, but, although a causal link between acute kidney injury and poor outcomes is plausible, the extent of this relationship is uncertain and controversial. These hypothesised links were tested extensively in sensitivity analyses.

The surviving proportion from each decision tree pathway at 90 days entered a Markov cohort model (starting age 63 years) with six mutually exclusive health states (outpatient follow-up, chronic kidney disease stages 1–4, end-stage renal disease without dialysis, end-stage renal disease with dialysis, transplantation and death). The cohort can enter the Markov model in the outpatient or chronic kidney disease states, with the starting proportions dependent on the experience of acute kidney injury up to 90 days.

The NHS-perspective costs (2018 Great British pounds values) in the first 90 days included costs of diagnostic biomarkers; costs of 3 days of a KDIGO care bundle for test-positive patients; and hospital costs, including days in intensive care unit, days on ward and need for acute renal replacement therapy. Markov health-state costs included post-discharge follow-up and costs of chronic kidney disease, end-stage renal disease, long-term dialysis, transplantation, immunosuppression and post-transplant follow-up.

Health-state utility values were sourced from the literature, based on the EuroQol-5 Dimensions questionnaire when possible, and were combined with mortality estimates for each health state to calculate quality-adjusted life-years. Utilities were applied separately for the duration of stay in an intensive care unit or hospital ward, or discharged up to day 90 with an additional utility decrement for acute renal replacement therapy and to each Markov health state. It was assumed that, following transplant recovery, utility reverted back to the outpatient post-discharge state. All utilities were adjusted for UK age- and sex-specific general population norms.

The model captured the cumulative cost and quality-adjusted life-year implications of transitions through the health states in annual cycles over a lifetime time horizon from an NHS perspective. All future costs and quality-adjusted life-years were discounted at 3.5% per annum. All analyses were reported probabilistically.

Results

Assessment of clinical effectiveness

A total of 56 studies, mainly prospective cohort studies, were included in the systematic review of clinical effectiveness. No studies addressing the impact of routine use of biomarkers on clinical outcomes were identified. Forty-six studies enrolled adults only, eight enrolled children only and two enrolled both adults and children. The total number of participants was 17,967, of whom 16,247 were adults (average age range 49 to 77 years) and 1720 were children (average age range 1 day to 5 years). The 46 studies on adults assessed patients after cardiac surgery ($n = 12$), non-surgical cardiac care ($n = 4$), major abdominal surgery ($n = 1$) or hepatobiliary surgery ($n = 1$); patients admitted to intensive care units ($n = 16$); patients with liver disease ($n = 5$, mainly cirrhosis), sepsis ($n = 2$) or chronic kidney disease ($n = 2$); and patients presenting to the emergency department ($n = 3$). Of the eight studies assessing children only, six assessed children (including neonates) undergoing cardiac surgery and two assessed children admitted to a paediatric or neonatal intensive care unit. The two studies that included both adults and children assessed patients undergoing cardiac surgery.

For statistical and cost-effectiveness analyses, participants were grouped into three categories according to clinical setting: patients undergoing cardiac surgery, patients undergoing major non-cardiac surgery and patients admitted to critical care (mixed patient population).

Of the 56 studies, 41 studied NGAL: 37 used urine NGAL assays and four used plasma NGAL assays. NephroCheck was assessed in eight studies. Seven studies provided data on more than one assay (six studies on urine NGAL and plasma NGAL assays; and one study on NephroCheck, urine NGAL and plasma NGAL assays). Of the NGAL studies, 24 used the urine NGAL ARCHITECT platform and 20 used the urine BioPorto NGAL assay. All 11 plasma NGAL studies used the BioPorto NGAL assay. No studies used the Alinity i NGAL platform.

The included studies were considered applicable to the remit of this assessment. The main sources of bias across diagnostic studies were the lack of information on blinding and the lack of a common threshold for NGAL. The statistical prediction models differed between prediction studies and often were not sufficiently detailed.

Few studies assessed patients after cardiac surgery or major non-cardiac surgery. The results of the meta-analyses of sensitivity and specificity estimates suggest that the biomarkers under investigation may have a role in the detection of acute kidney injury in patients already admitted to critical care. The NephroCheck test at a common threshold of 0.3 ng/ml^2/1000 had the higher pooled sensitivity (0.83), but the worst pooled specificity (0.51), whereas the ARCHITECT urine NGAL and the BioPorto urine NGAL tests had slightly lower pooled sensitivity estimates (0.70 and 0.72, respectively), but better pooled specificity estimates (0.72 and 0.87, respectively). The BioPorto urine NGAL pooled sensitivity was similar to that of the BioPorto plasma NGAL (0.72 and 0.76, respectively), whereas the pooled specificity was better for the BioPorto urine NGAL than for the BioPorto plasma NGAL (0.87 and 0.67, respectively). NGAL thresholds varied across studies. The biomarkers had a similar performance across all clinical settings.

Although these findings show some diagnostic usefulness of biomarkers, this should be tempered by the considerable heterogeneity observed across studies.

Moreover, for studies with a small number of acute kidney injury events, the relationship between sensitivity and specificity estimates appeared to be quite different from that of studies for which prevalence of acute kidney injury events was higher.

There was an indication that the addition of biomarkers to existing clinical models might improve the prediction of relevant clinical outcomes; however, few studies were available for each biomarker in each clinical setting, and studies varied substantially in terms of study characteristics and statistical methods used to assess prediction, thereby hindering any reliable conclusion.

In general, studies varied considerably in terms of clinical setting, NGAL threshold levels, time of sample collection, definition of acute kidney injury, time of acute kidney injury diagnosis, number of acute kidney injury events and assay platforms. Therefore, we have limited confidence in the validity and reliability of the findings.

Results of the cost-effectiveness model (including sensitivity analyses)

Published data show that NephroCheck-guided implementation of a KDIGO care bundle may avert acute kidney injury. However, no such data exist for the NGAL tests. Therefore, two base-case analyses were considered. Base case 1 can be considered an optimistic scenario for the NGAL biomarkers: assuming that all NGAL tests are equally as effective as NephroCheck in terms of the potential to avert acute kidney injury. Base case 2 can be considered a more conservative analysis. It assumes, in the absence of evidence, that only NephroCheck can avert acute kidney injury, but that all tests have the potential to reduce acute kidney injury severity if it occurs.

Fifteen scenario analyses were conducted for each potential base case, ranging from a set of optimistic assumptions whereby biomarker-guided care bundles led to substantial improvements in health outcomes (need for intensive care unit, hospital length of stay, chronic kidney disease, mortality) to a set of more conservative assumptions whereby change in acute kidney injury status had no effect on health outcomes.

Incremental cost-effectiveness ratios were highly uncertain, and subject to wide variation depending on the set of scenarios chosen. The probability of cost-effectiveness at an incremental cost-effectiveness ratio of < £20,000 per quality-adjusted life-year gained for scenarios in which all NGAL biomarkers were assumed to be equally as effective as NephroCheck in preventing acute kidney injury ranged from 0% to 15% (NephroCheck), from 0% to 55% (BioPorto urine NGAL), from 0% to 2% (ARCHITECT urine NGAL) and from 0% to 48% (BioPorto plasma NGAL). BioPorto urine NGAL was usually the test associated with the greatest probability of cost-effectiveness, albeit with great uncertainty, when compared with standard care. This was because the BioPorto urine NGAL biomarker was estimated to have slightly better diagnostic test accuracy data from the meta-analysis and incurred slightly lower test costs than the comparators. However, there was substantial uncertainty in diagnostic accuracy information, driven by substantial study heterogeneity. The cost-effectiveness results should therefore be interpreted with caution.

When it was assumed that NGAL biomarkers could not avert acute kidney injury but could only reduce its severity, the cost-effectiveness case for NephroCheck improved substantially, while remaining highly uncertain, with a probability of cost-effectiveness ranging from 0% to 99% across the explored scenarios.

Discussion

Strengths and limitations of the analyses, and uncertainties

The methods used to conduct this assessment were detailed, thorough and in line with current methodological standards.

The main limitations of the clinical effectiveness assessment were as follows:

- considerable clinical and statistical heterogeneity in the diagnostic and prediction analyses
- use of an imperfect reference standard for detection of acute kidney injury (clinical assessment based on serum creatinine levels and urine output)
- variation in the use of the NGAL assays and lack of a common threshold for identification of acute kidney injury
- uncertainty regarding the best timing of biomarker measurements
- variation in acute kidney injury prevalence across studies, with a very small number of acute kidney injury events in some studies
- lack of data on the impact of the routine use of the biomarkers on health outcomes.

The majority of the included studies were conducted outside the UK and assessed hospitalised patients admitted to critical care, with large variation in the delivery of critical and intensive care across the world. There is great uncertainty in how well findings of studies that are predominantly conducted outside the UK, based in intensive care, and heterogeneous, could be applied to a UK clinical scenario of people at risk of acute kidney injury who do not currently receive critical care.

With regard to the economic modelling, we identified three key areas of uncertainty, which mirror those identified for the clinical effectiveness assessment and limit the robustness of the cost-effectiveness results:

1. lack of direct evidence on the impact of the use of the biomarkers on health outcomes
2. heterogeneity in the diagnostic accuracy data (including uncertainty in the prevalence of acute kidney injury in a broad, poorly defined population)
3. uncertainty around the impact of an NGAL-guided implementation of a KDIGO care bundle on the frequency and severity of acute kidney injury.

Given these uncertainties, the results of the cost-effectiveness modelling were largely speculative and should be interpreted with caution. Although we conducted extensive probabilistic analyses for all scenario analyses, these may still not capture the full magnitude of uncertainty faced in the implementation of these biomarkers in clinical practice.

Generalisability of the findings

Owing to the limitations listed previously, it is unclear how the findings of this assessment can be generalised to current UK practice.

Conclusions

Future studies should evaluate the targeted use of the biomarkers among specific clinical populations and in circumstances where there is potential for benefit with a plausible and feasible intervention. They should focus on the assessment of the impact of routine biomarker use on mortality, major clinical adverse events, modification of clinical care, and resource use.

There is also a need to harmonise the methods and platforms for collection, and handling and storage of urine and plasma biomarker samples, as well as reporting of biomarkers' concentrations (units of measurement).

Study registration

This study is registered as PROSPERO CRD42019147039.

Funding

This project was funded by the National Institute for Health Research (NIHR) Evidence Synthesis programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 7. See the NIHR Journals Library website for further project information.

Chapter 1 Objectives

The overall objective of this assessment was to summarise the current evidence on the clinical effectiveness and cost-effectiveness of using the NephroCheck® test (Astute Medical, Inc., San Diego, CA, USA), the ARCHITECT® and Alinity i™ urine neutrophil gelatinase-associated lipocalin (NGAL) assays (Abbott Laboratories, Abbott Park, IL, USA), and the BioPorto urine and plasma NGAL tests (BioPorto Diagnostics A/S, Hellerup, Denmark) to help assess the risk of acute kidney injury (AKI) in critically ill hospitalised patients who are considered for admission to critical care. AKI is still a challenging clinical problem for hospitalised patients, especially for those in need of critical care. Earlier detection of kidney injury may facilitate the adoption of strategies to preserve renal function and prevent further progression of kidney disease.

There are several components to this assessment that fall within the scope of the following research questions:

- Do novel biomarkers (i.e. the NephroCheck test, ARCHITECT and Alinity i urine NGAL assays, and BioPorto urine and plasma NGAL tests) accurately detect emerging AKI in critically ill people who are considered for critical care?
- Do the novel biomarkers (i.e. the NephroCheck test, ARCHITECT and Alinity i urine NGAL assays, BioPorto urine and plasma NGAL tests) predict the development of future events [e.g. AKI, mortality, need for long-term renal replacement therapy (RRT)] in critically ill people at risk of developing AKI who are considered for admission to critical care?
- Does the use of novel biomarkers (i.e. the NephroCheck test, ARCHITECT and Alinity i urine NGAL assays, and BioPorto urine and plasma NGAL tests) lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care (i.e. reduction in events rates, such as mortality and long-term RRT, among patients whose management is guided by the novel biomarkers)?
- Does routine use of novel biomarkers (i.e. the NephroCheck test, ARCHITECT and Alinity i urine NGAL assays, and BioPorto urine and plasma NGAL tests) affect costs to the NHS, length or quality of life [i.e. quality-adjusted life-years (QALYs)], or cost-effectiveness, measured as incremental cost per QALY gained for critically ill people who are considered for admission to critical care?

In brief, the main objectives of this assessment were as follows:

- to determine the diagnostic accuracy, prognostic accuracy and clinical impact of the use of novel biomarkers (i.e. the NephroCheck test, ARCHITECT and Alinity i urine NGAL assays, and BioPorto urine and plasma NGAL tests) for the assessment of AKI in critically ill patients (adults and children) who are being assessed for admission to critical care
- to develop an economic model to assess the cost-effectiveness of the use of novel biomarkers (i.e. NephroCheck test, ARCHITECT and Alinity i urine NGAL assays, and BioPorto urine and plasma NGAL tests) for the assessment of AKI in critically ill patients (adults and children) who are considered for admission to critical care.

Chapter 2 Background and definition of the decision problem

Health problem

Acute kidney injury is a common and serious complication that typically occurs in the context of an acute critical illness or during a postoperative period. It is associated with prolonged hospital stay, severe morbidity and increased mortality.[1,2] Delayed identification of AKI contributes to worse outcomes.[3]

To pre-empt or avoid lasting consequences of AKI, early detection may be beneficial. Traditionally, AKI diagnosis relies on a rise in serum creatinine levels and/or fall in urine output. Despite its widespread use in the monitoring of kidney health and disease, creatinine is an imperfect marker of kidney function because its level in the blood is not solely dependent on kidney function, and changes in creatinine lag behind reduction in kidney function in AKI.[4] When kidney function suddenly falls, even if a reduction in renal excretion occurs instantly, it can take hours or sometimes days for the level of creatinine to rise in the blood sufficiently for AKI to be diagnosed according to current international definitions.[5] Moreover, in response to stress, or even kidney damage, the kidneys have reserve capacity and can compensate so that kidney function is maintained. For this reason, in some clinical settings, significant kidney damage can occur without AKI being apparent from changes in blood creatinine. In other settings, such as during a temporary reduction in blood flow to the kidneys, rises in creatinine and a reduction in urine can occur, even when no significant damage has occurred. These limitations related to the use of creatinine assessment have led to the search for novel biomarkers that may detect kidney damage or stress earlier and more reliably.

Biomarker tests for AKI include the NGAL test, which can be measured using a sample of urine or blood.[6] NGAL is released from neutrophils and is induced by inflammation, indicating tubular injury.[4] One limitation of NGAL is that it is produced throughout the body, making it difficult to distinguish systemic inflammation from localised renal inflammation.[4] Novel NGAL tests include the ARCHITECT and Alinity i urine NGAL assays, the BioPorto NGAL plasma test and the BioPorto NGAL urine test.

Another biomarker for AKI is the NephroCheck test, which is a combination of two urinary biomarkers: the tissue inhibitor of metalloproteinase-2 (TIMP-2) and the insulin-like growth factor-binding protein 7 (IGFBP7). Both TIMP-2 and IGFBP7 are cell-cycle arrest proteins that are released into urine as markers of cellular stress in the early phase of tubular cell injury due to a variety of insults (e.g. toxins, drugs, oxidative stress and inflammation), which leads to AKI.[7] The US Food and Drug Administration has approved these combined biomarkers to assess the risk of AKI in critically ill patients.[4]

These novel biomarkers have been developed to detect early damage or stress in the kidneys. If reliable use of these biomarkers can be demonstrated, they may enable earlier identification of AKI, and, therefore, early management of those with a modifiable disease course, with potential for downstream benefits in patients' clinical outcomes. If demonstrated, the ability of these novel biomarkers for early detection of AKI could have the potential to improve current AKI management by enabling timely measures that could prevent progression to more severe kidney injury, as well as informing decisions about the 'step-down' of low-risk patients to a lower level of hospital care, thereby reducing the use of hospital resources.

The purpose of this assessment was to review the current evidence on the diagnostic accuracy, prognostic accuracy, impact on clinical outcomes and cost-effectiveness of novel biomarkers (i.e. the NephroCheck test, ARCHITECT and Alinity i urine NGAL assays, BioPorto NGAL plasma test and BioPorto NGAL urine test) for the assessment of AKI in critically ill patients who are considered for critical care admission.

Aetiology, pathology and prognosis

Acute kidney injury ranges from minor loss of kidney function to complete kidney failure. In current practice, reduced kidney function is identified by elevated serum creatinine levels and/or reduced urine output.

There are many causes of acute kidney injury,[8] including the following:

- pre renal – reduced oxygen delivery to the kidneys, caused by:
  - low blood volume (after bleeding, excessive vomiting or diarrhoea, and severe dehydration)
  - reduced blood flow from the heart (potentially caused by sepsis or heart/liver failure)
  - damage to blood vessels, which can be caused by inflammation or blockages in the kidneys
  - medications that affect blood flow to the kidneys
- intrinsic/renal – damage to the kidney potentially caused by drugs, infections or contrast agents
- post renal – a blockage preventing drainage from the kidneys (potentially caused by an enlarged prostate, a tumour in the pelvis or kidney stones).

Incidence and/or prevalence

Major surgery is a significant risk factor for the development of AKI.[4] In general, incidence of postoperative AKI depends on the type of surgery. Rates of AKI after cardiac surgery have been reported to range from 8% to 40%, depending on the patient populations.[4] Recent meta-analyses have reported a pooled incidence of AKI in patients admitted to intensive care after abdominal surgery of 13.4% [95% confidence interval (CI) 10.9% to 16.4%],[9] and pooled incidences of AKI after major trauma of 24% (95% CI 20% to 29%)[8] and 21% (95% CI 16.5% to 24.9%).[10]

The incidence of AKI for all major, non-cardiac surgery patients and trauma patients can be as high as 50% (e.g. liver transplant patients). In a retrospective cohort of > 27,000 patients, the incidence of AKI, defined according to the Risk, Injury, Failure, Loss of kidney function and End-stage disease (RIFLE) criteria, was 37%.[11,12]

Impact of the health problem

People with AKI have higher mortality and longer hospital stays.[1,2] In addition, AKI is associated with a higher risk of developing chronic kidney disease (CKD) and a need for long-term dialysis. The risk of CKD increases with the increased severity of AKI. More severe AKI has also been associated with increased mortality, length of hospital stay and use of intensive care services, in addition to a reduced chance of renal recovery.[1,2] People with more severe AKI (and a greater loss of renal function) are more likely to need temporary RRT.

Measurement of disease

Several tools are available for determining the stage of AKI. A summary of staging system[13] for AKI in adults based on the RIFLE,[14] Acute Kidney Injury Network (AKIN)[15] and Kidney Disease: Improving Global Outcomes (KDIGO)[5] systems is presented in *Table 1*. A patient's AKI should be staged by the criteria, and a classification of stage 1 or higher indicates AKI.

TABLE 1 Summary of the staging system for AKI in adults (based on the KDIGO, RIFLE and AKIN systems)

		Definition	
Criteria	**Stage**	**Serum creatinine criteria**	**Urine output**
[a]KDIGO[5]	1	• Increase 1.5- to 1.9-fold from baseline or • ≥ 0.3 mg/dl (26.5 µmol/l)	< 0.5 ml/kg/hour for 6 hours
	2	• Increase 2.0- to 2.9-fold from baseline	< 0.5 ml/kg/hour for 12 hours
	3	• Increase 3.0-fold from baseline or • ≥ 4.0 mg/dl (≥ 354 µmol/l) or • initiation of RRT or • in patients aged < 18 years, decrease in eGFR to < 35 ml/minute per 1.73 m^2	< 0.3 ml/kg/hour for 24 hours or anuria for 12 hours
[b]RIFLE[14]	R	• Increase 1.5-fold from baseline or • GFR decrease > 25%	< 0.5 ml/kg/h for 6 hours
	I	• Increase 2.0-fold from baseline or • GFR decrease > 50%	< 0.5 ml/kg/hour for 12 hours
	F	• Increase 3.0-fold from baseline or • ≥ 4.0 mg/dl (354 µmol/l) with an acute rise of ≥ 0.5 mg/dl (≥ 44 µmol/l) or • GFR decrease ≥ 75%	< 0.3 ml/kg/hour for 24 hours or anuria for 12 hours
	L	• Complete loss of renal function for > 4 weeks	
	E	• ESRD	
[c]AKIN[15]	1	• Increase 1.5- to 2.0-fold from baseline • ≥ 0.3 mg/dl (26.4 µmol/l)	< 0.5 ml/kg/hour for 6 hours
	2	• Increase > 2.0- to 3.0-fold from baseline	< 0.5 ml/kg/hour for 12 hours
	3	• Increase > 3.0-fold from baseline or • ≥ 4.0 mg/dl (354 µmol/l) with an acute rise of ≥ 0.5 mg/dl (≥ 44 µmol/l) • initiation of RRT	< 0.3 ml/kg/hour for 24 hours or anuria for 12 hours

E, End-stage disease; ESRD, end-stage renal disease; F, Failure; GFR, glomerular filtration rate; I, Injury; L, Loss; R, Risk.
a For KDIGO, AKI is defined as serum creatinine increase by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours or increase to ≥ 1.5 times baseline value, which is known or presumed to have occurred within the prior 7 days.
b For RIFLE, AKI should be both abrupt (within 1–7 days) and sustained (> 24 hours).
c For AKIN, the increase in creatinine must occur in < 48 hours.

Description of the technologies under assessment

The NephroCheck test, the ARCHITECT and Alinity i urine NGAL assays, and the BioPorto urine and plasma NGAL tests may help to assess AKI in critically ill people who are considered for admission to critical care in hospital. These tests may be able to detect kidney injury earlier than the methods currently used for monitoring kidney function.

The NephroCheck test

The NephroCheck test measures urine levels of two biomarkers, TIMP-2 and IGFBP7, to assess the risk of moderate to severe AKI (defined as per KDIGO guidelines) in the subsequent 12 hours. The test result must be used in conjunction with clinical evaluation and the results of other tests, such as serum creatinine levels and urine output.

The concentrations of TIMP-2 and IGFBP7 are used to calculate an AKIRisk® Score (Astute Medical, Inc.) [the concentrations of each (ng/ml) multiplied together and divided by 1000]. A score of ≤ 0.3 indicates a low risk of developing moderate to severe AKI within 12 hours of assessment, whereas a score of > 0.3 indicates a high risk of developing moderate to severe AKI within 12 hours of assessment.[6]

When used with the Astute140® Meter (Astute Medical, Inc.), the NephroCheck test system consists of the following components:

- Astute140 Meter kit (a benchtop analyser)
- Astute140 Electronic Quality Control device
- NephroCheck test kit (includes a single-use NephroCheck test cartridge and reagents)
- NephroCheck Liquid Control kit
- NephroCheck Calibration Verification kit.

A fresh or thawed urine sample (mixed with reagent) is added to a single-use test cartridge, which is then inserted into an Astute140 Meter for incubation and result calculation. Preparation takes 3–5 minutes and the results of a NephroCheck test are available in ≈ 20 minutes. In the NHS, the Astute140 Meter would be used in a laboratory and not at the point of care.

The test can also be run on the VITROS® 3600 Immunodiagnostic System (Ortho-Clinical Diagnostics Inc., Raritan, NJ, USA) and on the VITROS® 5600 Integrated System (Ortho-Clinical Diagnostics Inc.) clinical chemistry analysers. All systems generate a single numerical result (the AKIRisk Score).

For surgical patients, it is recommended that the NephroCheck test is administered 2–4 hours after surgery. As NephroCheck exhibits a characteristic rise and fall after various exposures, a second administration of the test within the first 24 hours may be considered in patients with an ongoing risk of developing AKI.

In the UK, the NephroCheck test is marketed for people aged > 21 years.

Neutrophil gelatinase-associated lipocalin assays

ARCHITECT and Alinity i urine neutrophil gelatinase-associated lipocalin assays

The ARCHITECT urine NGAL assay is a chemiluminescent microparticle immunoassay for the quantitative determination of NGAL in human urine. NGAL can be used as a marker of kidney injury.

The ARCHITECT urine NGAL assay might be used as follows:

- for early detection of AKI
- to provide a measure of the severity of AKI
- to predict the requirement for RRT
- to help differentiate AKI from CKD and dehydration.

For diagnostic purposes, the test results should be used in conjunction with clinical assessment and the results of any other testing that has been undertaken (including serum creatinine levels and urine output). In addition, if the NGAL results are inconsistent with clinical assessment and other test results, additional testing can be undertaken to confirm the NGAL results.

The test could be used daily until a diagnosis is made or treatment for AKI is initiated.

The expected range for the assay (for people without kidney injury) is ≤ 131.7 ng/ml, based on the 95th percentile from specimens of non-hospitalised donors, but results from individual laboratories may vary and the manufacturer recommends that each laboratory should determine its own reference range based on the particular locale and population characteristics. The test has no age restrictions in use.

The assay is run on the ARCHITECT system (i1000SR, i2000, i2000SR, ci4100, ci8200 or ci16200) (Abbott Laboratories) in a laboratory. The throughput of the system is up to 200 tests per hour, and the time to first result is 36 minutes.

In addition to the ARCHITECT Urine NGAL Reagent Kit, the following materials are also needed:

- ARCHITECT Urine NGAL Calibrators
- ARCHITECT Urine NGAL Controls or other control material
- ARCHITECT i pre-trigger solution
- ARCHITECT i trigger solution
- ARCHITECT i wash buffer
- ARCHITECT i reaction vessels
- ARCHITECT i sample cups
- ARCHITECT i septum
- ARCHITECT i replacement caps.

The Abbott NGAL assay is also available for use on the Alinity i immunoassay system. The reagents for the Alinity i and ARCHITECT NGAL assays are the same.

The BioPorto neutrophil gelatinase-associated lipocalin test (using urine or plasma)

The BioPorto NGAL test is a particle-enhanced turbidimetric immunoassay for the quantitative determination of NGAL in human urine, ethylenediaminetetraacetic acid (EDTA) plasma and heparin plasma on automated clinical chemistry analysers. NGAL measurements may be useful in pre-empting the diagnosis of AKI, which may lead to acute renal failure. Urinary NGAL can serve as an early marker of AKI after cardiopulmonary bypass surgery, and both urinary and plasma levels of NGAL provide an early indication of acute renal injury in unselected patients in intensive care.

The NGAL test is intended to be used alongside monitoring of serum creatinine levels and urine output (rather than as a standalone test), and the significance of any raised NGAL level should be interpreted in the light of a patient's clinical features.

The NGAL test can be administered as a single measurement, but also as a serial measurement, to detect any further development of AKI during hospitalisation or any improvement in the clinical condition. For patients admitted to intensive care, the test can be used to predict stage 2/3 AKI or as a negative predictive marker to rule out the presence of AKI.

To indicate the presence of AKI, the NGAL concentration in an isolated sample of urine and/or EDTA plasma should exceed 250 ng/ml. This threshold has been chosen to minimise the risk of an unacceptably high proportion of false-positive results.

The assay can be run on clinical chemistry analyser systems from F. Hoffman-La Roche Ltd (cobas®, Modular P) (Basel, Switzerland), Siemens Healthineers (ADVIA®) (Erlangen, Germany), Abbott Laboratories (AEROSET®, ARCHITECT) and Beckman Coulter Inc. (Olympus AU) (Brea, CA, USA) in a laboratory. The assay takes 10 minutes to run.

In addition to the NGAL Test Reagent Kit, the following materials are also needed:

- NGAL Test Calibrator Kit
- NGAL Test Control Kit
- 0.9% weight by volume (w/v) aqueous sodium chloride solution as zero calibrator
- analyser-specific reagent containers.

At present, the test has no age restrictions on use.

Identification of important subgroups

The primary scope of this assessment was the optimisation of current secondary care of critically ill patients to decide whether or not the use of novel biomarkers would improve detection of AKI and, consequently, the current care pathway. The relevant population considered in this assessment was critically ill people at risk of developing AKI (i.e. those who are having their serum creatinine levels and urine output monitored) who are being assessed for possible admission to critical care. There is variation in intensive care utilisation across the world; in most studies conducted outside the UK, critically ill participants are usually admitted to critical or intensive care. The following patient subgroups have been identified as particularly relevant for the purpose of this assessment:

- type of surgery (e.g. major vascular/cardiac surgery, major non-vascular surgery, trauma, solid organ transplant)
- type of setting [e.g. post-surgery care, cardiac care, intensive or critical care, emergency department (ED)]
- type of sample medium (i.e. urine, blood plasma)
- people with a different underlying risk of AKI (e.g. depending on underlying condition: CKD, sepsis, hip fracture, major trauma, chronic liver disease)
- presence or absence of urinary infection and other inflammatory conditions (tests may perform differently in these populations).

Relevant comparator

Novel biomarkers need to be compared for incremental advantage over standard approaches to measuring kidney function. As discussed previously, AKI diagnosis traditionally relies on a rise in serum creatinine levels and/or fall in urine output. Creatinine has limitations as a biomarker because its concentration depends on the total body muscle mass, which varies between individuals. Some creatinine is also eliminated from the body by mechanisms other than filtering by the kidneys, which can be influenced by a variety of medications, including some commonly used antibiotics. In an illness that causes a sudden fall in kidney function (AKI), there may be a lag ranging from hours to days before creatinine levels in the blood rise to a level sufficient for AKI to be diagnosed according to current international definitions.[5] In addition, in response to stress or even kidney damage, the kidneys have reserve capacity and can compensate so that kidney function is maintained. For this reason, in some clinical settings, significant kidney damage can occur without AKI being apparent from changes in blood creatinine. In other settings, such as during a temporary reduction in blood flow to kidneys, rises in creatinine and a reduction in urine can occur even when no significant damage has occurred.

Care pathway

The NICE clinical guideline on AKI[16] recommends measuring serum creatinine and comparing it with the baseline for adults, children and young people with acute illness if risk factors for the condition are likely or present. Risk factors include sepsis, hypovolaemia and deteriorating early warning scores (using a paediatric version for children and young people). NHS England and NHS Improvement have endorsed the National Early Warning Score (NEWS) for use in acute and ambulance settings.[17] An updated version of the score (NEWS2)[17] was published in December 2017. The score should not be used with children (aged < 16 years) or pregnant women.

The NICE guideline[16] further recommends monitoring serum creatinine regularly in all adults, children and young people with or at risk of AKI. The guideline development group did not wish to define ‘regularly’ because this would vary according to clinical need, but recognised that daily measurement was typical while in hospital.

An AKI algorithm to help with detection and diagnosis of the condition has been endorsed by NHS England.[18] In some hospitals, the algorithm has been integrated into laboratory information management systems to help identify potential cases of AKI from laboratory data in real time.

The KDIGO Clinical Practice Guideline for Acute Kidney Injury[19] highlights the importance of screening patients who have had an exposure that may cause AKI (e.g. sepsis or trauma) and recommends that high-risk patients continue to be monitored until the risk subsides. The guideline[19] states that the frequency of serum creatinine measurements is a matter of clinical judgement, but suggests as a general rule that high-risk inpatients should have serum creatinine measured at least daily and more frequently after an exposure. Critically ill patients should also have urine output monitored.

For adults who are at risk of AKI, the NICE AKI guideline[16] also recommends that systems are put in place to recognise and respond to oliguria (urine output < 0.5 ml/kg/hour).

For children and young people who are at risk of AKI, the guideline[16] recommends:

- measuring urine output
- recording weight twice daily to determine fluid balance
- measuring urea, creatinine and electrolytes
- considering measuring lactate, blood glucose and blood gases.

Further detail on these recommendations and further recommendations on the ongoing assessment of the condition of patients in hospital can be found in section 1.2 of the NICE clinical guideline on AKI.[16]

The NICE guideline[16] recommends diagnosing AKI in line with the RIFLE[14] (or the paediatric-modified RIFLE),[20] AKIN[15] or KDIGO[5] definitions, by using any of the following criteria:

- a rise in serum creatinine of ≥ 26 µmol/l within 48 hours
- a $\geq 50\%$ rise in serum creatinine levels known or presumed to have occurred within the previous 7 days
- a fall in urine output to < 0.5 ml/kg/hour for > 6 hours in adults and for > 8 hours in children and young people
- a $\geq 25\%$ fall in estimated glomerular filtration rate (eGFR) in children and young people within the previous 7 days.

There are no direct therapies for treating AKI. Care focuses on optimising haemodynamics and fluid status, avoiding nephrotoxic treatments and carrying out investigations to identity and resolve the underlying cause as quickly as possible. In general, the goal of care is to prevent any further kidney injury and to stop the worsening of the underlying illness to prevent mortality or renal progression to such a degree that RRT is needed.

The NICE clinical guideline on AKI[16] highlights the importance of identifying the cause(s) of AKI and has recommendations on the use of urinalysis and ultrasound for this purpose.

The KDIGO Clinical Practice Guideline for Acute Kidney Injury[19] also recommends prompt evaluation of people with AKI to determine the cause. Identifying possible reversible causes of the condition is highlighted as important in reducing the severity of the condition.

The NICE clinical guideline on AKI[16] has recommendations on managing AKI (section 1.5), covering removing urological obstruction, pharmacological management, RRT and referral to nephrology services. The KDIGO Clinical Practice Guideline for Acute Kidney Injury[19] recommends staging severity

of AKI with serum creatinine and urine output, and to manage the condition according to stage and cause. General management principles for people at high risk of AKI (or with the condition) are to:

- discontinue nephrotoxic agents if possible
- monitor volume status and perfusion pressure
- consider functional haemodynamic monitoring
- monitor serum creatinine and urine output
- avoid hyperglycaemia
- consider alternatives to radiocontrast procedures.

Further actions, such as initiating RRT, should be considered at higher stages of AKI only. Dosages of drugs may also need to be adapted because of reduced kidney function. The KDIGO guideline[19] also has more detailed guidance on the prevention and treatment of AKI (section 3). This includes haemodynamic monitoring and support, glycaemic control and nutritional support, the use of diuretics and vasodilator therapy.

In UK clinical practice, the NephroCheck test and NGAL assays are likely to be used for the assessment of AKI among people who are considered for admission to critical care, rather than among patients already in critical care. It is worth pointing out that the NephroCheck test, the ARCHITECT and Alinity i urine NGAL assays and the BioPorto plasma and urine NGAL tests would not replace serum creatinine and urine output monitoring, but would be used alongside current monitoring to facilitate earlier detection of kidney injury and prompt adoption of strategies to prevent further progression of kidney disease.

Chapter 3 Assessment of clinical effectiveness

Systematic review methods

Identification of studies

Comprehensive electronic searches were conducted to identify relevant reports of published studies. Highly sensitive search strategies were developed, including index terms, free-text words, abbreviations and synonyms, to combine biomarkers and AKI. The electronic databases MEDLINE (via Ovid), EMBASE (via Ovid), Web of Science Core Collection, Health Technology Assessment (HTA) Database, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Central Register of Controlled Trials were searched, with no restriction on date or publication type. Full details of the search strategies are presented in *Appendix 1*. The searches were undertaken between 17 May and 10 June 2019.

In addition, we searched the following sources for ongoing or unpublished studies: ClinicalTrials.gov (www.clinicaltrials.gov/), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (https://apps.who.int/trialsearch/) and the WHO Global Index Medicus (www.who.int/library/about/The_Global_Index_Medicus/en/) (all of these websites were accessed on 10 June 2019). Furthermore, websites of relevant professional organisations and health technology agencies, as well as appropriate clinical experts, were consulted to obtain any additional potentially relevant reports. The reference lists of all included studies were perused to identify further potentially relevant studies. We also considered evidence provided by the manufacturers of the biomarkers included in this assessment (i.e. Astute Medical, Inc.; Abbott Laboratories; and BioPorto Diagnostics A/S).

Inclusion and exclusion criteria

Inclusion and exclusion criteria for each of the clinical effectiveness questions considered in this assessment are summarised in *Table 2*. Only those studies that fulfilled these criteria were deemed suitable for inclusion.

Study selection and data extraction

A screening checklist was developed to assist study selection and data extraction (see *Appendix 2*, *Figure 25*). The data extraction form is provided in *Appendix 3*. One reviewer (CR) screened the titles and abstracts identified by the search strategies for inclusion or exclusion. A second reviewer (MI) double checked all non-selected citations. As a lot of relevant information was not available from the titles or abstracts of the reports identified by the literature searches (e.g. information about the immunoassay used and type of analyses), our selection approach was overinclusive. Full-text copies of all potentially relevant reports were retrieved and assessed for inclusion by one reviewer (MAM, MI or CR). A second reviewer (MAM, MI or CR) double checked 20% of the reports. Any disagreement was resolved by discussion or referred to a third reviewer (MB).

One reviewer (MAM, MB, MI, AP or CR) extracted data from each eligible study using a form developed and piloted for the purpose of this assessment. If multiple publications of the same cohort of participants were identified, the publication with the most complete or suitable data set was considered as the primary source of information. Any uncertainty related to the data extraction process was discussed among reviewers and resolved by consensus.

TABLE 2 Eligibility criteria for the systematic review

Domain	Research question		
	1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**

Population and setting	• Critically ill patients (adults and children) at risk of AKI in an unselected hospitalised population (medical or surgical hospital admissions) in the following settings:
	  ○ general hospital
	  ○ ED
	  ○ post surgery or postoperative care
	  ○ intensive or critical care (e.g. ICU, CCU, ITU, PICU)
		• Critically ill patients (adults and children) at risk of AKI in an unselected hospitalised population (medical or surgical hospital admissions) in the following settings:
		  ○ general hospital
		  ○ ED
		  ○ post surgery or postoperative care
		  ○ intensive or critical care (e.g. ICU, CCU, ITU, PICU)
			• Critically ill patients (adults and children) at risk of AKI in an unselected hospitalised population (medical or surgical hospital admissions) in the following settings:
			  ○ general hospital
			  ○ ED
			  ○ post-surgery or postoperative care
			  ○ intensive or critical care (e.g. ICU, CCU, ITU, PICU)

	• Patients who had established AKI before being admitted to intensive or critical care and those who were managed in the community setting were excluded
	• Although the eligible patient population is an unselected critically ill population considered for admission to critical care, the following subgroups were identified to be particularly at risk of developing AKI:
	  ○ People undergoing major cardiac or cardiovascular surgery
	  ○ People undergoing major non-cardiac or non-vascular surgery
	  ○ People undergoing major trauma surgery
	  ○ People undergoing solid organ transplant (except kidney)
	  ○ People undergoing hip replacement
	  ○ People with sepsis
	  ○ People with CKD
	  ○ People with chronic liver disease
	  ○ People with a serious (non-surgical) acute cardiac event or emergency (e.g. myocardial infarction)
		• Patients who had established AKI before being admitted to intensive or critical care and those who were managed in the community setting were excluded
		• Although the eligible patient population is an unselected critically ill population considered for admission to critical care, the following subgroups were identified to be particularly at risk of developing AKI:
		  ○ People undergoing major cardiac or cardiovascular surgery
		  ○ People undergoing major non-cardiac or non-vascular surgery
		  ○ People undergoing major trauma surgery
		  ○ People undergoing solid organ transplant (except kidney)
		  ○ People undergoing hip replacement
		  ○ People with sepsis
		  ○ People with CKD
		  ○ People with chronic liver disease
		  ○ People with a serious (non-surgical) acute cardiac event or emergency (e.g. myocardial infarction)
			• Patients who had established AKI before being admitted to intensive or critical care and those who were managed in the community setting were excluded
			• Although the eligible patient population is an unselected critically ill population considered for admission to critical care, the following subgroups were identified to be particularly at risk of developing AKI:
			  ○ People undergoing major cardiac or cardiovascular surgery
			  ○ People undergoing major non-cardiac or non-vascular surgery
			  ○ People undergoing major trauma surgery
			  ○ People undergoing solid organ transplant (except kidney)
			  ○ People undergoing hip replacement
			  ○ People with sepsis
			  ○ People CKD
			  ○ People with chronic liver disease
			  ○ People with a serious (non-surgical) acute cardiac event or emergency (e.g. myocardial infarction)

TABLE 2 Eligibility criteria for the systematic review (*continued*)

Domain	Research question		
	1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**
	Excluded: • People with other clinical conditions or illnesses • People assessed immediately after a kidney transplant (within 365 days of index test) • Preterm infants and low-birthweight babies	Excluded: • People with other clinical conditions or illnesses • People assessed immediately after a kidney transplant (within 365 days of index test) • Preterm infants and low-birthweight babies	Excluded: • People with other clinical conditions or illnesses • People assessed immediately after a kidney transplant (within 365 days of index test) • Preterm infants and low-birthweight babies
Biomarkers under investigation	• NephroCheck test • ARCHITECT and Alinity i urine NGAL assays • BioPorto NGAL urine test • BioPorto NGAL plasma test All used in conjunction with existing care The primary time point for biomarker measurement was immediately after surgery or on admission to critical or intensive care. When multiple measurements were reported, we selected that taken at the time closest to the primary time point Exclusion: • Solid tissue (not fluid) biomarkers or imaging modalities for detection of AKI • Biomarkers that used different assays than those listed above or that did not specify the details of the assay	• NephroCheck test • ARCHITECT and Alinity i urine NGAL assays • BioPorto NGAL urine test • BioPorto NGAL plasma test All used in conjunction with existing care The primary time point for biomarker measurement was immediately after surgery or on admission to critical or intensive care. When multiple measurements were reported, we selected that taken at the time closest to the primary time point Exclusion: • Solid tissue (not fluid) biomarkers or imaging modalities for detection of AKI • Biomarkers that used different assays than those listed above or that did not specify the details of the assay	AKI care initiated according to the results of the biomarkers under investigation (the NephroCheck test, the ARCHITECT and Alinity i urine NGAL assays, the BioPorto NGAL urine test and the BioPorto NGAL plasma test)
Reference standard/ comparator	At present, there is no universally accepted reference standard for the diagnosis of AKI. The current methods for detecting or predicting AKI are in line with the RIFLE (or paediatric-modified RIFLE), AKIN and KDIGO classification systems, which are based on the assessment of serum creatinine levels and urine output alongside clinical judgement (see NICE clinical guideline[16])	Existing clinical criteria for the monitoring of serum creatinine and urine output used in conjunction with clinical judgement (reference standard)	AKI care initiated according to standard clinical practice (existing clinical criteria without biomarkers)

continued

TABLE 2 Eligibility criteria for the systematic review (*continued*)

Domain	Research question		
	1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**

Outcomes	Detection of AKI (using measures of accuracy, i.e. sensitivity and specificity)	• Mortality
		• Need for long-term RRT
		• CKD > 90 days post AKI
		
		At abstract screening, studies that did not report any of these selected outcomes were excluded
			• Clinical outcomes:
			  ○ Mortality
			  ○ AKI-associated morbidity (e.g. CKD/ESRD, other organ failure)
			• Patient-reported outcome: health-related quality of life
			• Intermediate outcomes may include:
			  ○ Incidence of AKI (and severity/stage of condition)
			  ○ Incidence/duration of acute RRT within 7 days
			  ○ Incidence of CKD-related RRT post AKI
			  ○ LOS in critical/intensive care
			  ○ LOS in hospital
			  ○ Length of AKI episode
			  ○ Incidence of hospital re-admission post discharge
			  ○ Impact of test result on clinical decision-making
			  ○ Impact on steady-state eGFR at 90 days
			  ○ Time to test results
			  ○ Equivalence of biomarkers (e.g. the NGAL assays)

Study design	• Any cross-sectional study that investigates the diagnostic accuracy of a single biomarker (NephroCheck test or NGAL test) against the reference standard in the same study population • Any fully paired direct comparison (observational or randomised direct comparison) in which one of the biomarkers under investigation (NephroCheck test or NGAL test) is compared with another biomarker in the same study population against the reference standard	Prospective studies reporting: • prognostic accuracy for the specified outcomes (e.g. sensitivity, specificity, ROC curve, AUC) • sufficient information to complete a two-by-two contingency table for the specified outcomes (i.e. true positives, false positives, false negatives and true negatives); at a minimum, the number of disease positives (number of participants with AKI) and disease negatives (number without AKI) • a statistical prediction model for the specified outcomes	• RCTs • Prospective cohort studies with a concurrent comparison group

TABLE 2 Eligibility criteria for the systematic review (*continued*)

Domain	Research question		
	1. Do novel biomarkers accurately detect emerging AKI in critically ill people who are considered for admission to critical care?	**2. Do the novel biomarkers predict the development of future events in critically ill people at risk of developing AKI who are considered for admission to critical care?**	**3. Does the use of novel biomarkers lead to improvements in clinical outcomes of critically ill people who are considered for admission to critical care?**
	Exclusion: • Studies with < 100 participants • Pilot studies or studies of preliminary results only • Case reports • Conference abstracts or proceedings • Studies published in a language other than English • Studies with insufficient information to complete a two-by-two contingency table	Exclusion: • Studies with < 100 participants • Pilot studies or studies of preliminary results only • Case reports • Conference abstracts or proceedings • Studies published in a language other than English	Exclusion: • Studies with < 100 participants • Pilot studies or studies of preliminary results only • Case reports • Conference abstracts or proceedings • Studies published in language other than English

AUC, area under the curve; CCU, critical care unit; ESRD, end-stage renal disease; ICU, intensive care unit; ITU, intensive treatment unit; LOS, length of stay; PICU, paediatric intensive care unit; RCT, randomised controlled trial; ROC, receiver operating characteristic.

From each study, the following data were extracted:

- characteristics of studies – first author, year of publication, study centre, country, inclusion and exclusion criteria, method of participant enrolment
- characteristics of study participants – age, sex, target condition, setting, number of participants enrolled, number of participants analysed, number excluded from analysis, main reasons for exclusion
- characteristics of the biomarkers (e.g. manufacturer, detection method, threshold, timing of the measurement)
- characteristics of the reference standard (i.e. creatinine and urine output criteria for AKI)
- outcome data –
    - data on the diagnostic performance of the biomarkers for detection of AKI [absolute number of true-positive, false-positive, false-negative and true-negative cases; sensitivity and specificity values; area under the curve (AUC) calculated from the receiver operating characteristic (ROC) plot]
    - data on the prediction of development of AKI, worsening of AKI, mortality, need for RRT and CKD, as provided by the study authors [e.g. AUC values, odds ratio (OR) or hazard ratio (HR), duration of follow-up]
    - data on the clinical utility of the biomarkers (impact of the use of the biomarkers on clinical outcomes), as reported by study authors [e.g. number of events and number of participants for each relevant binary outcome; mean, standard deviation (SD) and number of participants for each relevant continuous outcome].

Assessment of risk of bias

Validated tools were used to assess the risk of bias of the included studies according to their study design. We used the Quality Assessment of Diagnostic Accuracy Studies, version 2 (QUADAS-2) tool[21] to assess the risk of bias of studies assessing the diagnostic and prognostic accuracy of the biomarkers under investigation. The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of having a 'low', 'high' or 'unclear' risk of bias, and the first three are also assessed in terms of concern regarding 'low', 'high' or 'unclear' applicability.

We used the Prediction model Risk Of Bias ASsessment Tool (PROBAST),[22] which is structured into four domains (participants, predictors, outcome and analysis) to assess the risk of bias and applicability of prediction model studies.

A single reviewer (MAM, MB, MI, AP or CR) assessed the risk of bias of each of the included studies. Any uncertainty was discussed among reviewers and resolved by consensus.

No other types of study design were identified.

Data synthesis and analysis

For each assay, for each study, we calculated sensitivity, specificity and prevalence values from the reported numbers of true-positive, false-positive, false-negative and true-negative cases. If studies did not provide 2 × 2 data, these were derived from the sensitivity and specificity estimates, if given. We entered diagnostic data into Review Manager software (RevMan version 5.3, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) to produce forest plots of sensitivity and specificity estimates, together with their 95% CIs.

When appropriate, we performed a meta-analysis of each pair of sensitivity and specificity estimates from each included study for each relevant assay. As reported threshold levels for a positive test differed across studies, we conducted random-effects meta-analyses using the hierarchical summary receiver operating characteristic (SROC) model[23,24] implemented in Stata® (metandi command)[25] (StataCorp LP, College Station, TX, USA) to estimate summary values for sensitivity and specificity. The model takes into account both of these measures of accuracy and their correlation, assumes that accuracy and thresholds vary between studies, and incorporates both within- and between-study variability. We constructed a SROC plot using the hierarchical model, produced sensitivity and specificity summary estimates, and hence a summary operating point, and calculated the 95% confidence and prediction regions. In accordance with the Stata requirements, we performed meta-analyses when data from four or more studies were available. For studies that reported multiple thresholds, we selected only one threshold to be included in the analysis. We performed separate meta-analyses for each biomarker, clinical setting, mode of sampling (urine or plasma) and type of patient population (adults or children). To inform the economic model, we also performed separate meta-analyses for each biomarker across all clinical settings.

For each biomarker, heterogeneity was assessed by visual inspection of the forest plots of sensitivity and specificity estimates and of the size of the prediction region in the SROC curve plots.

When possible, we performed meta-analyses of AUC values using a random-effects model to measure the performance of each biomarker for the prediction of each relevant outcome (i.e. AKI, mortality, RRT and CKD). We assessed the proportion of between-study variation in the area under ROC curve due to heterogeneity, rather than sample error, using the prediction interval. We considered an AUC of > 0.70 as indicative of a useful risk predictor.

Stata version 15.0 was used for all statistical analyses. Graphs were made using either Stata or RevMan version 5.3.

Patient and public involvement

There was no patient and public involvement in this study. The study was conducted as part of the NICE Diagnostics Assessment Programme (DAP). We did not deem it necessary to involve further patient representatives and laypeople as a range of stakeholders, including members of the public and national groups representing patients and/or their carers, are already involved as participants in the DAP process for each individual assessment.

Results of the assessment of clinical effectiveness

Results of the literature searches

The literature searches identified 6379 records; 86 additional records were identified in either trial registers (i.e. EU Clinical Trials Register, ICTRP, ClinicalTrials.gov) or other literature collections (i.e. HTA Database, WHO Global Index Medicus), for a total of 6465 retrieved records. After de-duplication, 2348 records were screened for relevance. Of these, 1050 were considered to be potentially relevant and were selected for full-text assessment. Four articles could not be obtained. Of the 1046 records retrieved and assessed in depth, 71 met the inclusion criteria. After excluding secondary or multiple publications, we selected 56 studies for inclusion in the systematic review of effectiveness. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in *Figure 1* shows the flow of studies through the selection process. The bibliographic details of the studies retrieved for full-text assessment and subsequently excluded, together with the main reasons for their exclusion, are presented in *Appendix 5*, *Table 26*.

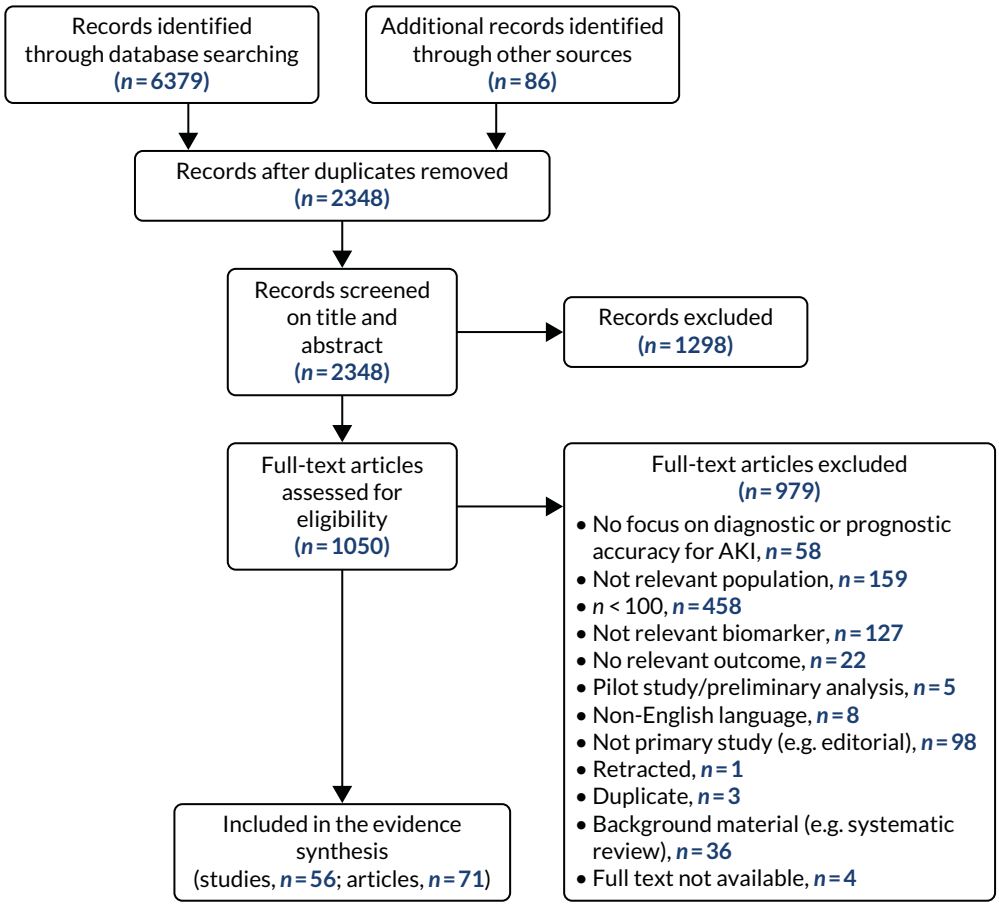

FIGURE 1 The PRISMA flow diagram of selected studies.

Overview of included studies

A list of all included studies can be found in *Appendix 4*. General characteristics of the 56 included studies and their associated references are provided in *Table 3* for the adult population and in *Table 4* for the child population. Further study characteristics are provided in *Appendix 6*, *Table 27*. The majority of studies were cohort studies. In 46 studies, data were collected prospectively;[17–30,34,37,45–48,50–54,56–59,61–63,65–70,72–75,77–81,83,84,86–91,93] in one study, data were collected prospectively but analysed retrospectively;[26] in one study, data were collected retrospectively;[82] and in eight studies information on data collection was unclear.[32,33,35,49,55,60,64,92] Fifty-three studies provided suitable data on the use of the biomarkers for detection or prediction of AKI in critically ill patients admitted to hospital,[26–30,32–35,37,45–56,58–66,68–70,72–75,77–84,87–93] 11 studies provided suitable data for prediction of mortality in critically ill patients at risk of AKI[46,49,53,59,62,70,72,75,82,83,87] and four studies provided suitable data for prediction of need for RRT.[46,72,75,87] No studies provided suitable data for prediction of CKD.

No randomised controlled trials (RCTs) or controlled clinical trials were identified; no studies provided data on the incremental value of the use of the biomarkers compared with standard clinical care.

Of the 56 included studies, 36 involved a single centre[26–28,30,35,45,46,48–50,53–55,58–61,63,66,68–70,73,74,79,80,82,83,86–93] and 13 involved multiple centres.[29,33,34,37,52,56,57,65,72,77,78,81,84] Seven studies did not provide this information.[32,47,51,62,64,67,75] Twenty-eight studies were conducted in Europe (four in the UK, six in Germany, three in Italy, three in Spain, two in Greece, two in Denmark, one in the Netherlands, one in France, one in Belgium, one in France and Belgium, one in Finland, one in Norway, one in Switzerland and one in several European countries); 15 in North America (12 in the USA, two in the USA and Canada and one in Canada); nine in Asia (three in Japan, three in the Republic of Korea, two in Thailand and one in China); two in North America and Europe; and one in Australia. One study did not provide clear information on the geographical location.

NGAL was the most commonly studied biomarker (41/56 studies; 37 studies used urine NGAL assays and four used plasma NGAL assays). NephroCheck was assessed in eight studies. Seven studies provided data on more than one assay (six studies on urine NGAL and plasma NGAL assays and one study on NephroCheck, urine NGAL and plasma NGAL assays). Among the NGAL studies, 24 used the ARCHITECT urine NGAL platform and 20 used the BioPorto urine NGAL assay. All 11 plasma NGAL studies used the BioPorto Diagnostics assay. No studies used the NGAL Alinity i platform.

Of the 56 included studies, 46 enrolled adults only, eight enrolled children only and two enrolled both adults and children. The total number of participants was 17,967, of whom 16,247 were adults (average age ranged from 49 to 77 years) and 1720 were children (average age ranged from 1 day to 5 years). Of the 46 studies that focused on adults only, 12 assessed patients after cardiac surgery, four assessed patients requiring non-surgical cardiac care, one assessed patients undergoing major abdominal surgery, one assessed patients undergoing hepatobiliary surgery, 16 assessed patients admitted to intensive care units (ICUs), five assessed patients with liver disease (mainly cirrhosis), two assessed patients with sepsis, two assessed patients with CKD and three assessed patients admitted to EDs. Of the eight studies that focused on children, six assessed children (including neonates) undergoing cardiac surgery and two assessed children admitted to a paediatric ICU or neonatal ICU. The two studies that included both adults and children assessed patients undergoing cardiac surgery. For the purpose of the clinical effectiveness and cost-effectiveness analyses, the participants were grouped into three categories according to the clinical setting reported in the included studies: patients undergoing cardiac surgery, patients undergoing major non-cardiac surgery and patients admitted to critical care (mixed patient population). The critical care group includes critically ill patients presenting to the ED and participants admitted to the ICU or considered for critical care for various medical conditions or after surgery (but the studies did not specify which type of surgery or provide separate results for medical and surgical ICU participants).

TABLE 3 General characteristics of included studies: adult population

First author, year of publication, country, associated publications	Assay	Target population (setting)	Age (years)	Sample size (*n*)	AKI events (*n*)	AKI definition	Time frame for AKI diagnosis
Cummings 2019,[26] USA	NephroCheck	Cardiac surgery (atorvastatin for AKI cardiac surgery study)	Median 67 (IQR 58–75)	400	14	KDIGO stage 2/3	Within 48 hours of surgery
Oezkur 2017,[27] Germany	NephroCheck	Cardiac surgery (CABG, valve surgery or surgery of the thoracic aorta)	• AKI: median 65 (IQR 59–73) • No AKI: median 71 (IQR 64–76)	150	35	KDIGO	Within 48 hours of surgery
Beitland 2016,[28] Norway	NephroCheck	Critical care – mixed population (out-of-hospital cardiac arrest)	• AKI: mean 60 (SD 13) • No AKI: mean 60 (SD 14)	195	88	KDIGO	Within 3 days of admission
Bihorac 2014,[29] USA	NephroCheck	Critical care – mixed population (ICU/ITU)	Mean 63 (SD 17)	408	71	KDIGO stage 2/3	Within 12 hours of admission
Di Leo 2018,[30] Italy Xie 2019[31]	NephroCheck	Critical care – mixed population (ICU/ITU)	Median 68 (IQR 51–78)	719	234	KDIGO	Within 24 hours of admission
Gayat 2018,[32] France and Belgium	NephroCheck	Critical care – mixed population (ICU, mainly sepsis)	Median 65 (IQR 54–75)	200	Unclear	KDIGO	Within 48 hours of admission
Hoste 2014,[33] USA	NephroCheck	Critical care – mixed population (ICU/ITU)	• AKI (stage 2/3): median 64 (IQR 54–75) • No AKI (stage 0/1): median 65 (IQR 54–78)	153	27	KDIGO stage 2/3	Within 12 hours of admission
Kashani 2013,[34] North America (21 sites) and Europe (15 sites)	NephroCheck	Critical care – mixed population (ICU/ITU)	Median 64 (IQR 53–73)	728	101	KDIGO stage 2/3	Within 12 hours of biomarker measurement (biomarker measurement occurred within 18 hours of ICU admission)

continued

TABLE 3 General characteristics of included studies: adult population (*continued*)

First author, year of publication, country, associated publications	Assay	Target population (setting)	Age (years)	Sample size (*n*)	AKI events (*n*)	AKI definition	Time frame for AKI diagnosis
Kimmel 2016,[35] Germany Kimmel 2016[36]	NephroCheck, BioPorto urine NGAL, BioPorto plasma NGAL	Critical care – mixed population (ED)	Mean 63 (SD 14)	298	46	KDIGO (modified version) stage 2/3	Within 12 hours of sample collection
Parikh 2011,[37] North America Parikh 2013,[38] Koyner 2015,[39] Coca 2014,[40] Brown 2019,[41] Coca 2016,[42] Zhang 2015[43] and Greenberg 2018[44]	ARCHITECT urine NGAL	Cardiac surgery (CABG or valve surgery)	Mean 71 (SD 10)	1200	60	Acute dialysis or doubling of serum creatinine (consistent with RIFLE stage 1 or AKIN stage 2)	AKI developed at a median of 3 days after surgery (IQR 2–4 days)
Albert 2018,[45] Germany	ARCHITECT urine NGAL	Cardiac surgery (open-heart surgery with CPB)	Median 70 (IQR 61–77)	101	15	RIFLE	NR
Garcia-Alvarez 2015,[46] Spain	ARCHITECT urine NGAL	Cardiac surgery	• AKI: median 74 (IQR 68–80) • No AKI: median 69 (IQR 59–76)	288	104	KDIGO	Within 7 days of surgery
Liebetrau 2013,[47] Germany	ARCHITECT urine NGAL	Cardiac surgery (CABG and/or valve replacement with the use of extracorporeal circulation)	• AKI: mean 74 (SD 8) • No AKI: mean 68 (SD 11)	141	47	KDIGO stage 2/3	Within 4 days of surgery
Thanakitcharu 2014,[48] Thailand	ARCHITECT urine NGAL	Cardiac surgery	Mean 51 (SD 15.6)	130	46	Increase in serum creatinine of $\geq$ 0.3 mg/dl within 48 hours	Within 48 hours of surgery
Cullen 2014,[49] UK	ARCHITECT urine NGAL	Non-cardiac surgery (major abdominal surgery)	Mean 68 (SD 11)	109	16	AKIN	NR

First author, year of publication, country, associated publications	Assay	Target population (setting)	Age (years)	Sample size (*n*)	AKI events (*n*)	AKI definition	Time frame for AKI diagnosis
Asada 2016,[50] Japan	ARCHITECT urine NGAL	Critical care – mixed population (ICU/ITU)	• AKI: median 62 (IQR 48–74) • No AKI: median 63 (IQR 51–73)	133	31	KDIGO	Within 7 days of admission
Collins 2012,[51] USA	ARCHITECT urine NGAL	Critical care – mixed population (acute heart failure)	NR	399	20	Increase in serum creatinine of ≥ 0.3 mg/dl or RIFLE	Worsening of renal function assessed at 12–24 hours and 72–96 hours
Dupont 2012,[52] USA	ARCHITECT urine NGAL	Critical care – mixed population (acute decongestive heart failure)	NR	141	35	Increase in serum creatinine of ≥ 0.3 mg/dl	Within 48 hours of admission
Isshiki 2018,[53] Japan	ARCHITECT urine NGAL	Critical care – mixed population (ICU/ITU)	Median 62 (IQR 51–73)	148	33	KDIGO	Within 7 days of admission
Kokkoris 2012,[54] Greece	ARCHITECT urine NGAL	Critical care – mixed population (ICU/ITU)	• AKI: median 63 (IQR 50–81) • No AKI: median 49 (IQR 35–66)	100	36	RIFLE	Within 7 days of admission
Mårtensson 2015,[55] Australia	ARCHITECT urine NGAL	Critical care – mixed population (ICU/ITU)	• Mild AKI: median 69 (IQR 59–74) • Severe AKI: median 68 (IQR 54–76) • No AKI: median 62 (IQR 48–72)	102	28	RIFLE	NR
Nickolas 2012,[56] USA and Germany	ARCHITECT urine NGAL	Critical care – mixed population (ED)	Mean 64 (SD 19)	1635	96	RIFLE	Within 24 hours of admission
Park 2017,[57] USA	ARCHITECT urine NGAL	Critical care – mixed population (CKD)	Mean 59 (SD 11)	2466	NR	Unclear	NR
Pipili 2014,[58] Greece	ARCHITECT urine NGAL	Critical care – mixed population (mechanically ventilated patients admitted to the ICU)	Mean 64 (SD 18)	106	44	RIFLE	NR

continued

TABLE 3 General characteristics of included studies: adult population (*continued*)

First author, year of publication, country, associated publications	Assay	Target population (setting)	Age (years)	Sample size (*n*)	AKI events (*n*)	AKI definition	Time frame for AKI diagnosis
Treeprasertsuk 2015,[59] Thailand	ARCHITECT urine NGAL	Critical care – mixed population (cirrhosis)	Mean 57 (SD 15)	121	35	AKIN	Within 24 hours of admission
Haase 2014,[60] Germany Albert 2018[45]	ARCHITECT urine NGAL and BioPorto plasma NGAL	Cardiac surgery (open-heart surgery with CPB)	Median 72 (IQR 65–77)	100	23	RIFLE	NR
Schley 2015,[61] Germany	BioPorto urine NGAL and BioPorto plasma NGAL	Cardiac surgery	Mean 70 (SD 10)	110	37	AKIN	Within 72 hours of surgery
Jaques 2019,[62] Switzerland	BioPorto urine NGAL and BioPorto plasma NGAL	Critical care – mixed population (cirrhosis)	Mean 58 (SD 10)	105	55	AKIN	Within 7 days of admission
De Loor 2017,[63] Belgium	BioPorto urine NGAL	Cardiac surgery (CPB)	Median 69 (IQR 61–76)	203	95	KDIGO	NR
Tidbury 2019,[64] UK	BioPorto urine NGAL	Cardiac surgery	• AKI: median 73 (IQR 54–87) • No AKI: median 75 (IQR 59–85)	125	54	RIFLE	NR
Yang 2017,[65] China	BioPorto urine NGAL	Cardiac surgery (atorvastatin for AKI cardiac surgery study)	Mean 46 (SD 15)	398	164	Acute dialysis or doubling of serum creatinine consistent with KDIGO stage 2 and 3 criteria	NR
Cho 2014,[66] the Republic of Korea	BioPorto urine NGAL	Non-cardiac surgery (hepatobiliary surgery)	Mean 57 (SD 12)	131	10	AKIN	Within 5 days of admission
Ariza 2016,[67] Europe	BioPorto urine NGAL	Critical care – mixed population (liver disease)	• Acute-on-chronic liver failure: mean 57 (SD 11) • No acute-on-chronic liver failure: mean 57 (SD 12)	716	NR	NR	NR

First author, year of publication, country, associated publications	Assay	Target population (setting)	Age (years)	Sample size (*n*)	AKI events (*n*)	AKI definition	Time frame for AKI diagnosis
Barreto 2014,[68] Spain	BioPorto urine NGAL	Critical care – mixed population (cirrhosis)	Mean 58 (SD 12)	132	65	AKIN	An increase in serum creatinine of $\geq$ 0.3 mg/dl or $\geq$ 50% over the baseline value obtained in the previous 48–72 hours
Cho 2013,[69] the Republic of Korea	BioPorto urine NGAL	Critical care – mixed population (ICU medical or surgical)	• AKI: mean 65.4 (SD 14.8) • No AKI: mean 60.4 (SD 17.4)	145	54	AKIN	Within 24 hours of surgery
Doi 2014,[70] Japan Doi 2011[71]	BioPorto urine NGAL	Critical care – mixed population (ICU/ITU)	• AKI: median 66 (IQR 55–73) • No AKI: median 65 (IQR 53–74)	339	131	RIFLE	NR
Hjortrup 2015,[72] Denmark	BioPorto urine NGAL and BioPorto plasma NGAL	Critical care – mixed population (ICU/ITU sepsis)	Median 66 (IQR 57–75)	151	91	KDIGO	Within 48 hours of admission
Matsa 2014,[73] UK	BioPorto urine NGAL and BioPorto plasma NGAL	Critical care – mixed population (ICU/ITU medical or surgical)	Mean 60 (SD 15)	194	59	RIFLE	Within 72 hours of admission
Nickolas 2008,[74] USA	BioPorto urine NGAL	Critical care – mixed population (ED)	Mean 60 (SD 18)	635	30	RIFLE	NR
Nisula 2015,[75] Finland Nisula 2014[76]	BioPorto urine NGAL	Critical care – mixed population (postoperative)	Median 62 (IQR 50–73)	855	379	KDIGO	NR
Smith 2013,[77] UK	BioPorto urine NGAL	Critical care – mixed population (CKD)	Mean 69 (SD 12)	158	40	KDIGO	NR

continued

TABLE 3 General characteristics of included studies: adult population (*continued*)

First author, year of publication, country, associated publications	Assay	Target population (setting)	Age (years)	Sample size (*n*)	AKI events (*n*)	AKI definition	Time frame for AKI diagnosis
Tecson 2017,[78] USA	BioPorto urine NGAL and BioPorto plasma NGAL	Critical care – mixed population (ICU/ITU)	• AKI (stage 2/3): median 68 (IQR 56–74) • No AKI (stage 0/1): median 63 (IQR 54–73)	245	33	KDIGO stage 2/3	Within 8 days of admission
Verna 2012,[79] USA	BioPorto urine NGAL	Critical care – mixed population (cirrhosis)	Median 56 (IQR 49–62)	118	52	Acute elevation in serum creatinine to > 1.5 and 0.3 mg/dl above baseline	NR
Zelt 2018,[80] USA	BioPorto plasma NGAL	Cardiac surgery (major elective cardiac surgery requiring CPB)	Median 67 (IQR 61–73)	178	35	AKIN	Within 48 hours of surgery
Itenov 2017,[81] Denmark	BioPorto plasma NGAL	Critical care – mixed population (ICU/ITU)	Median 67 (IQR 60–76)	454	87	KDIGO	NR
Lee 2018,[82] the Republic of Korea	BioPorto plasma NGAL	Critical care – mixed population (comatose cardiac arrest survivors treated with therapeutic hypothermia)	Median 59 (IQR 50–71)	279	111	KDIGO stage 3	Within 7 days of return of spontaneous circulation
Marino 2015,[83] Italy	BioPorto plasma NGAL	Critical care – mixed population (sepsis)	Median 77 (IQR 72–83)	101	49	RIFLE	Within 7 days of admission

CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; IQR, interquartile range; ICU, intensive care unit; ITU, intensive treatment unit; NR, not reported.

TABLE 4 General characteristics of included studies: child population

First author, year of publication, country, linked publications	Assay	Population (setting)	Age	Sample size (*n*)	AKI events (*n*)	AKI definition	Time frame for AKI diagnosis
Parikh 2011,[84] North America Zappitelli 2015[85]	ARCHITECT urine NGAL	Cardiac surgery (congenital cardiac lesions)	Mean 4 years (SD 5 years)	311	53	Acute dialysis, or doubling of serum creatinine from baseline	During hospital stay
Bojan 2014,[86] France	ARCHITECT urine NGAL	Cardiac surgery (CPB for surgical correction or palliation of congenital heart lesions)	Mean < 1 year	100	NR	AKIN	NR
Bennett 2008,[87] USA	ARCHITECT urine NGAL	Cardiac surgery (CPB for surgical correction or palliation of congenital heart lesions)	Mean 4 years	196	99	≥ 50% increase in serum creatinine from baseline within 72 hours	NR
Cantinotti 2012,[88] Italy	ARCHITECT urine NGAL	Cardiac surgery (cardiac surgery for correction or palliation of congenital heart defects)	Median 6 months (IQR 1–49 months)	135	52	Paediatric-modified RIFLE	NR
Alcaraz 2014,[89] Spain	ARCHITECT urine NGAL	Cardiac surgery (cardiac surgery, mainly CPB, for congenital cardiac lesions)	Median 25 months (IQR 6.0–72.0 months)	106	36	Paediatric-modified RIFLE	Early AKI defined as renal dysfunction in the first postoperative 72 hours. Late AKI defined as occurring after the fourth postoperative day
[a]Seitz 2013,[90] NR	ARCHITECT urine NGAL	Cardiac surgery (CPB for surgical correction of congenital heart disease)	Median 0 years (IQR 0–8 years)	139	76	Paediatric-modified RIFLE	NR

continued

TABLE 4 General characteristics of included studies: child population (*continued*)

First author, year of publication, country, linked publications	Assay	Population (setting)	Age	Sample size (*n*)	AKI events (*n*)	AKI definition	Time frame for AKI diagnosis
Zwiers 2015,[91] the Netherlands	ARCHITECT urine NGAL	Critical care – mixed population (ICU/ITU)	Median 27 days (IQR 1–85 days)	100	35	RIFLE	Within 48 hours of admission
Dong 2017,[92] USA	BioPorto urine NGAL	Cardiac surgery	• AKI: median 1.4 years (IQR 0.2–2.7 years) • No AKI: median 5 years (IQR 4.1–5.9 years)	150	50	KDIGO	Within 72 hours of surgery
Lagos-Arevalo 2015,[93] Canada	BioPorto urine NGAL	Critical care – mixed population (ICU/ITU)	• AKI: mean 5 years (SD 6 years) • No AKI: mean 4.0 years (SD 5 years)	160	70	KDIGO	NR
Yang 2017,[65] China	BioPorto urine NGAL	Cardiac surgery	• Children: mean 22 months (SD 31 months) • Adults: mean 46 years (SD 15 years)	• Children: 323 • Adults: 398	• Children: 126 • Adults: 164	Acute dialysis or doubling of serum creatinine consistent with KDIGO stage 2 and 3 criteria	NR

CPB, cardiopulmonary bypass; ICU, intensive care unit; IQR, interquartile range; ITU, intensive treatment unit; NR, not reported.
a The Seitz *et al.*[90] study also included 20 adolescents or adults.

Study quality

The risk of bias of studies assessing the accuracy of NephroCheck and NGAL assays in identifying people at risk of developing AKI was assessed using the QUADAS-2 tool. The results are summarised in *Figure 2* and in *Appendix 7*, *Table 28*.

Eleven studies (20%) did not report sufficient information to determine whether or not a selection of patients could have introduced bias; these studies were assessed as having an unclear risk of bias.[32,33,35,49,50,54,55,60,72,82,94] The remaining studies were judged to be at low risk of bias for the patient selection domain.

The main potential source of bias across studies relates to blinding. Most studies (98%) were assessed as having an unclear risk of bias for the conduct and interpretation of the index test because of insufficient information or lack of clarity regarding whether or not the biomarker results were interpreted without knowledge of the reference standard results (see *Figure 2*). The studies that used NephroCheck were judged to be at low risk of bias with regard to the interpretation of the test because all of them used a common threshold. However, because of the differences in threshold level observed across studies and the lack of a common threshold, the risk of bias for NGAL studies was judged to be unclear. Although some studies alluded to the blinding to patients' clinical information of personnel performing the biomarker measurements, it was unclear whether or not the personnel were indeed blinded to serum creatinine measurements (reference standard). With regard to whether or not the reference standard, its conduct or its interpretation may have introduced bias, two studies (4%) were judged to be at unclear risk of bias because baseline serum creatinine levels were determined by reviewing records of previous 12-month measurements.[54,56] The remaining studies (96%) were judged to be at low risk of bias for the reference standard domain.

Two studies (4%) were judged to be at high risk of bias in terms of the patient flow (e.g. attrition) because > 50% of the participants were excluded from the analysis[62] or because the reporting of the patient selection and flow was poorly detailed.[50] Four studies (7%) were at unclear risk.[54,57,64,92] The remaining studies (89%) were considered to be at low risk of bias regarding the patient flow domain.

Across studies, there was no major concern that the patient population and the conduct and interpretation of reference standard were not applicable to the review question. We observed an expected variation between studies in terms of characteristics of the index tests (biomarker assays) and clinical protocols. In particular, applicability of the index test to the review question was judged to be unclear in many studies, mainly because of the variation with regard to the biomarker thresholds and timing of sample collections.

The risk of bias of studies assessing the role of NephroCheck and NGAL assays for prediction of relevant clinical outcomes (i.e. worsening of AKI, mortality and need for RRT) was assessed using the PROBAST tool.[22] The results are summarised in *Table 5*.

Twelve prediction studies were assessed for risk of bias and applicability.[32,46,49,53,55,59,70,72,75,82,83,87] Three of these studies (25%) reported insufficient information to determine whether or not selection of patients could have introduced bias; these studies were judged to be at unclear risk of bias.[32,55,72] The remaining studies were judged to be at low risk of bias for this domain. No studies were judged to have made predictor assessments without the knowledge of outcome data; therefore, the risk of bias for the predictors domain was judged to be unclear for all studies. The risk of bias in the outcome domain was rated as unclear for all studies, mainly because of inadequate information to assess whether or not outcomes were determined without knowledge of predictor information. The risk of bias for the analysis domain was rated as unclear in 58% of studies and as high in 42% of studies.

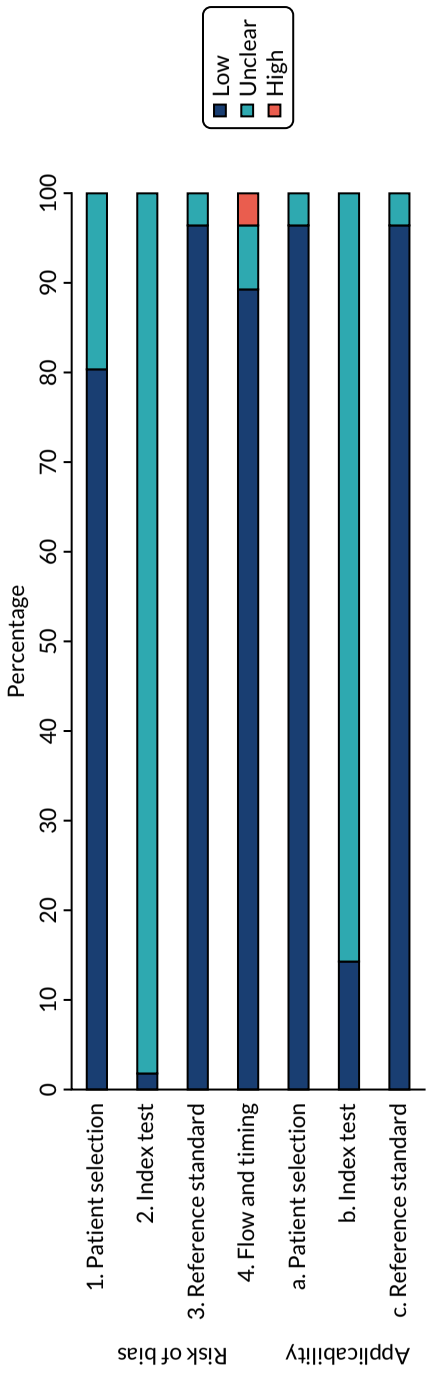

FIGURE 2 Risk-of-bias assessment of studies assessing the diagnostic performance of the biomarkers using the QUADAS-2 tool.

TABLE 5 Summary of diagnostic data for NephroCheck for detection of AKI: adult population

Study	Target population (setting)	Assay	Timing of test	Cut-off point (ng/ml²/1000)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Oezkur 2017[27]	Cardiac surgery	NephroCheck	ICU admission	0.3	0.60	0.88	NR	0.19
Cummings 2019[26]	Cardiac surgery	NephroCheck	ICU admission	0.3	0.31 (0.09 to 0.61)	0.78 (0.74 to 0.82)	0.68 (0.54 to 0.81)	0.035
Kashani 2013[34]	Critical care – mixed population (ICU/ITU)	NephroCheck	ICU admission	0.3	0.89	0.50	0.8	0.14
Bihorac 2014[29]	Critical care – mixed population (ICU/ITU)	NephroCheck	Within 24 hours of admission to ICU	0.3	0.92 (0.85 to 0.98)	0.46 (0.41 to 0.52)	0.82 (0.76 to 0.88)	0.17
Hoste 2014[33]	Critical care – mixed population (ICU/ITU)	NephroCheck	ICU admission	0.3	0.89	0.53	0.79 (0.69 to 0.88)	0.18
Kimmel 2016[36]	Critical care – mixed population	NephroCheck	Admission to the internal medicine service	0.3–2.0	0.76 (0.63 to 0.87)	0.53 (0.48 to 0.57)	0.74 (0.66 to 0.81)	0.15
Di Leo 2018[30]	Critical care – mixed population (ICU/ITU)	NephroCheck	ICU admission	0.3	0.64	0.56	0.63	0.34

ITU, intensive treatment unit; NR, not reported.

The overall risk of bias was considered to be unclear for most studies (70%), mainly because these studies were assessed as being at high risk of bias in the analysis domain. The remaining studies were judged to be at unclear risk of bias.

Most studies were judged to be at low risk of bias for applicability to the review question in each of the domain categories. Overall, applicability was judged to be at low risk of bias for 75% of the studies and at unclear risk of bias for the remaining studies. In general, there was no major concern that the studies were not applicable to the research questions of this assessment. Summaries of the results are shown in *Figures 3* and *4*, and individual study-level results are presented in *Appendix 8*, *Table 29*.

Accuracy of the NephroCheck and neutrophil gelatinase-associated lipocalin assays for identifying acute kidney injury

We were able to extract or derive 2 × 2 data from 33 studies that assessed the performance of the NephroCheck, ARCHITECT urine NGAL and BioPorto urine and plasma NGAL assays for identifying AKI in critically ill hospitalised patients. These studies are summarised in the following sections.

The summary estimates of accuracy and the SROC plots are provided separately for each assay, clinical setting, mode of sampling and type of patient population (adults and children). We also present analyses across all settings. Studies that could not be combined in a meta-analysis (fewer than four) are summarised narratively.

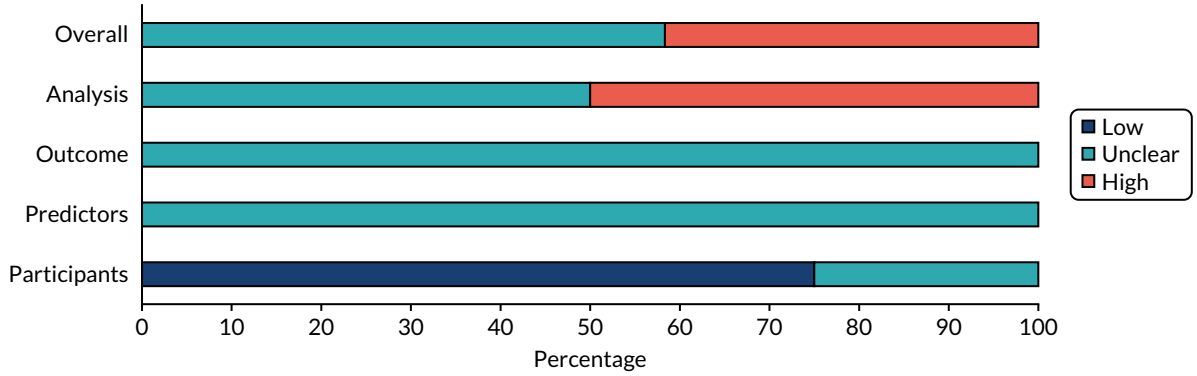

FIGURE 3 Risk-of-bias assessment of studies that assessed the role of biomarkers for prediction of relevant clinical outcomes using the PROBAST tool.

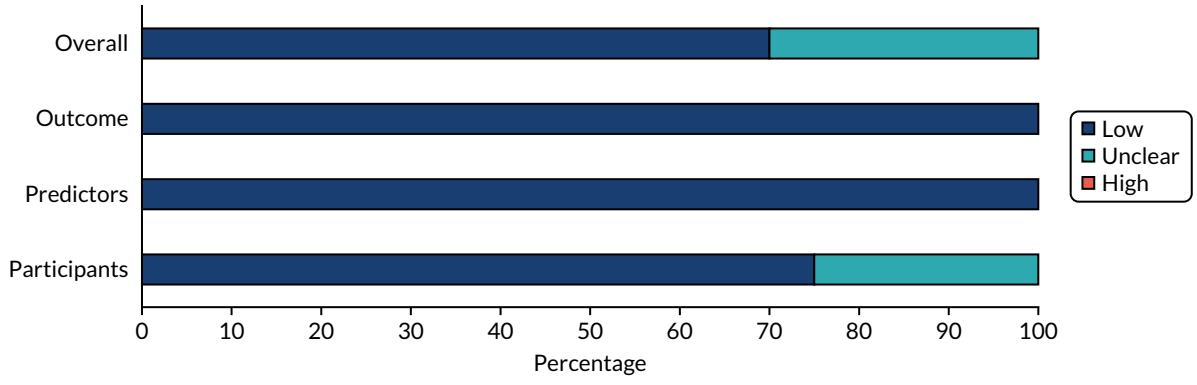

FIGURE 4 Applicability of prediction studies to the research questions using the PROBAST tool.

NephroCheck urine assay: adult population

A summary of the diagnostic data for the seven studies[26,27,29,30,33,34,36] that assessed the use of NephroCheck for detection of AKI in adults is presented in *Table 5*.

Cardiac surgery

Two studies[26,27] assessed the use of NephroCheck for detection of AKI in patients after cardiac surgery (data from a total of 500 participants were available for the analyses). Both studies used the same cut-off point (0.3 ng/ml^2/1000). The study by Cummings *et al.*[26] assessed a total of 400 cardiac patients soon after ICU admission. The sensitivity and specificity values were 0.31 (95% CI 0.09 to 0.61) and 0.78 (95% CI 0.74 to 0.82), respectively. The study was consistent with other cardiac surgery cohorts, but showed a low prevalence of AKI (4%). Only 14 participants developed KDIGO stage 2 and 3 AKI. The study by Oezkur *et al.*[27] analysed 100 patients immediately after cardiac surgery. The reported sensitivity and specificity values were 0.60 (95% CI 0.36 to 0.81) and 0.89 (95% CI 0.80 to 0.95), respectively. The prevalence of AKI was 19%. *Table 5* shows a summary of the diagnostic data for the two studies.

No suitable NephroCheck data in other post-surgical settings (major non-cardiac surgery) were available from the included studies.

Critical care: mixed population

Five studies (2279 participants in total) assessed the use of NephroCheck for detection of AKI in hospitalised patients admitted to ICU or critical care for various clinical reasons. The cut-off point used was consistent across studies (0.3 ng/ml^2/1000). *Table 5* shows a summary of the diagnostic data for the five studies.[29,30,33,34,36] Sensitivity values ranged from 0.64 to 0.92; specificity values ranged from 0.46 to 0.56. The summary estimate of sensitivity was 0.83 (95% CI 0.72 to 0.91) and that of specificity was 0.51 (95% CI 0.48 to 0.54). The SROC plot with 95% confidence region for the summary operating point and 95% prediction region is presented in *Appendix 9*, *Figure 27*. The confidence and prediction regions indicate a greater degree of heterogeneity in sensitivity estimates than in specificity estimates between studies. Specificity estimates were low but reasonably homogeneous (see *Appendix 9*, *Figure 26*).

Figure 5 shows the forest plots of sensitivity and specificity estimates for all NephroCheck studies (2778 patients in total) across clinical settings. Sensitivity values ranged from 0.31 to 0.92 and specificity values ranged from 0.46 to 0.89. Summary estimates for sensitivity and specificity were 0.75 (95% CI 0.58 to 0.87) and 0.61 (95% CI 0.49 to 0.72), respectively. *Figure 6* shows the SROC plot with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are large, indicating considerable heterogeneity between studies. Across studies, estimates of specificity were generally low, apart from two studies that showed higher estimates. Visual inspection of the forest plot and SROC plots shows that the study by Cummings *et al.*[26] is an outlier, with a trend very different from that of the other studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bihorac[29]	65	182	6	155	0.92 (0.83 to 0.97)	0.46 (0.41 to 0.51)
Hoste[33]	24	59	3	67	0.89 (0.71 to 0.98)	0.53 (0.44 to 0.62)
Kimmel[36]	35	118	11	134	0.76 (0.61 to 0.87)	0.53 (0.47 to 0.59)
Oezkur[27]	12	9	8	71	0.60 (0.36 to 0.81)	0.89 (0.80 to 0.95)
Di Leo[30]	153	209	81	249	0.65 (0.59 to 0.71)	0.54 (0.50 to 0.59)
Kashani[34]	90	313	11	314	0.89 (0.81 to 0.94)	0.50 (0.46 to 0.54)
Cummings[26]	4	85	9	301	0.31 (0.09 to 0.61)	0.78 (0.74 to 0.82)

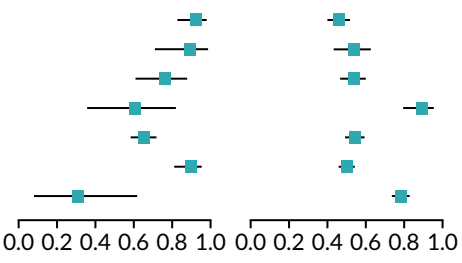

FIGURE 5 Forest plots of sensitivity and specificity for NephroCheck studies: all clinical settings. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

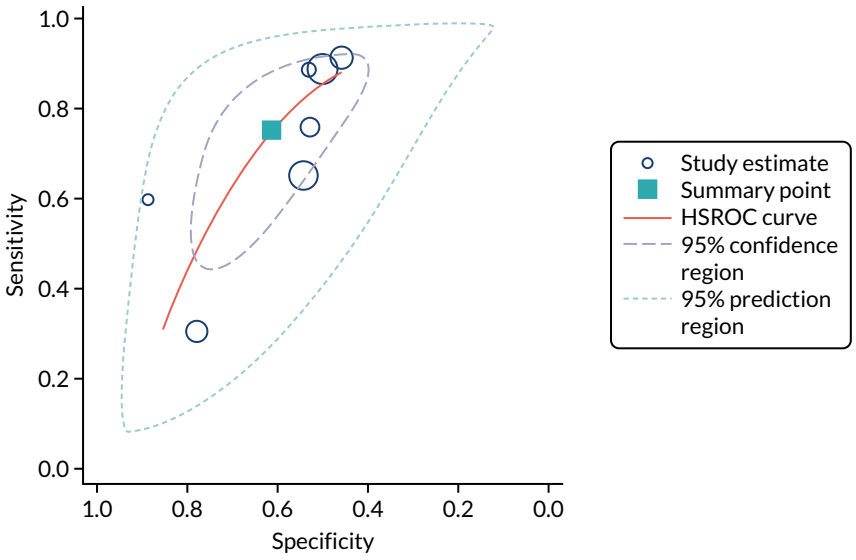

FIGURE 6 The SROC plot for NephroCheck studies: all clinical settings. HSROC, hierarchical summary receiver operating characteristic.

There were no studies assessing the use of NephroCheck in children, as this biomarker is recommended for adult use only (people aged ≥ 21 years).

ARCHITECT urine neutrophil gelatinase-associated lipocalin assay: adult population

Cardiac surgery

Two studies[37,48] provide test accuracy data on the use of the ARCHITECT urine NGAL assay for detection of AKI in patients who underwent cardiac surgery (*Table 6*). The multicentre cohort study by Parikh *et al.*[37] assessed a total of 1219 adults after cardiac surgery. The sensitivity and specificity values for the first urine sample collected soon after ICU admission were 0.46 (95% CI 0.33 to 0.59) and 0.81 (95% CI 0.79 to 0.83), respectively. The prevalence of AKI in the study was 5%, similar to that observed previously in the Cummings *et al.*[26] study, which assessed the role of NephroCheck in 400 participants in the same clinical setting. The single-centre study by Thanakitcharu *et al.*[48] assessed 130 patients immediately after cardiac surgery. The sensitivity and specificity values for the urine sample collected immediately after surgery were 0.74 (95% CI 0.49 to 0.91) and 0.6 (95% CI 0.51 to 0.70), respectively. The prevalence of AKI in the study was 35%.

No suitable ARCHITECT urine NGAL assay data in other post-surgical settings (major non-cardiac surgery) were available from the included studies.

Critical care: mixed population

Four studies (1998 patients in total) assessed the use of the ARCHITECT urine NGAL assay for the detection of AKI in patients admitted to an ICU or critical care for various clinical reasons. Cut-off values varied across studies (see *Table 6*). In three studies, urine NGAL levels were reported as ng/ml (per ml of urine), whereas, in one study, urine NGAL levels were normalised by units of urine creatinine (per mg of creatinine). Prevalence of AKI ranged from 6% to 36% across studies. *Table 6* shows a summary of the diagnostic data, as reported by the six studies. Sensitivity values ranged from 0.63 to 0.78 and specificity values ranged from 0.58 to 0.81. The summary estimate of sensitivity was 0.70 (95% CI 0.63 to 0.76) and that of specificity was 0.72 (95% CI 0.63 to 0.80). The forest plot of sensitivity and specificity estimates and the SROC plot with 95% confidence region for the summary operating point and 95% prediction region are presented in *Appendix 9* (see *Figures 28* and *29*). The large confidence and prediction regions of the SROC plot indicate considerable heterogeneity in estimates of accuracy across studies, especially for specificity. The analysis appears to be dominated by the Nickolas *et al.*[56] study, the largest study, which shows a small number of true-positive cases and, subsequently, low sensitivity.

TABLE 6 Summary of diagnostic data for the ARCHITECT urine NGAL assay for the detection of AKI in adults

Study	Target population (setting)	Assay	Timing of test	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Parikh 2011[37]	Cardiac surgery	ARCHITECT urine NGAL	ICU admission	> 102 ng/ml	0.46	0.81	0.67	0.05
Thanakitcharu 2014[48]	Cardiac surgery	ARCHITECT urine NGAL	Immediately after surgery	> 11.3 ng/ml	0.74	0.60	0.69 (0.52 to 0.72)	0.35
Dupont 2012[52]	Critical care – mixed population (acute decongestive heart failure)	ARCHITECT urine NGAL	48 hours after admission	32 µg/g of creatinine	0.63	0.58	0.61	0.25
Kokkoris 2012[54]	Critical care – mixed population (ICU/ITU)	ARCHITECT urine NGAL	ICU admission	58.5 ng/ml	0.78 (0.61 to 0.90)	0.72 (0.59 to 0.82)	0.74 (0.64 to 0.82)	0.36
Nickolas 2012[56]	Critical care – mixed population (ICU/ITU)	ARCHITECT urine NGAL	Admission to ED	104 ng/ml	0.68	0.81	0.81 (0.76 to 0.86)	0.059
Treeprasertsuk 2015[59]	Critical care – mixed population (liver disease)	ARCHITECT urine NGAL	Within 72 hours of admission	56 ng/ml	0.77	0.73	0.83 (0.76 to 0.91)	0.29

ITU, intensive treatment unit.

Figure 7 shows the forest plots of sensitivity and specificity estimates for all ARCHITECT urine NGAL studies (3347 patients in total) across all clinical settings. Sensitivity values ranged from 0.46 to 0.78 and specificity values ranged from 0.58 to 0.81. Summary estimates for sensitivity and specificity were 0.67 (95% CI 0.58 to 0.76) and 0.72 (95% CI 0.64 to 0.79), respectively. *Figure 8* shows the SROC plot with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are large, indicating heterogeneity between studies.

BioPorto urine neutrophil gelatinase-associated lipocalin assay: adult population

Cardiac surgery

One study[65] assessed the use of the BioPorto urine NGAL assay for the detection of AKI in a total of 398 patients who had undergone cardiac surgery (*Table 7*). Urine NGAL levels were normalised by units of urine creatinine (with a cut-off point of 98 µg/g creatinine). The sensitivity and specificity values for the urine sample collected 6 hours after surgery were 0.78 (95% CI 0.71 to 0.84) and 0.48 (95% CI 0.41 to 0.54), respectively. The prevalence of AKI in the study was 41%.

Non-cardiac surgery

One study[66] assessed the use of the BioPorto urine NGAL assay for detection of AKI in 131 patients undergoing hepatobiliary surgery (see *Table 7*). The urine NGAL cut-off point was 92.85 ng/ml. The sensitivity and specificity values for the urine sample collected 12 hours after surgery were 0.78 (95% CI 0.52 to 1.00) and 0.80 (95% CI 0.73 to 0.87), respectively. The prevalence of AKI in the study was 8%.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dupont[52]	22	45	13	61	0.63 (0.45 to 0.79)	0.58 (0.48 to 0.67)
Parikh[37]	28	220	33	939	0.46 (0.33 to 0.59)	0.81 (0.79 to 0.83)
Kokkoris[54]	28	18	8	46	0.78 (0.61 to 0.90)	0.72 (0.59 to 0.82)
Nickolas[56]	65	293	31	1247	0.68 (0.57 to 0.77)	0.81 (0.79 to 0.83)
Thanakitcharu[48]	29	31	17	53	0.63 (0.48 to 0.77)	0.63 (0.52 to 0.73)
Treeprasertsuk[59]	27	23	8	63	0.77 (0.60 to 0.90)	0.73 (0.63 to 0.82)

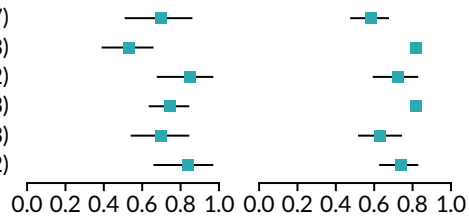

FIGURE 7 Forest plots of sensitivity and specificity for the ARCHITECT urine NGAL assay for the detection of AKI in adults: all clinical settings. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

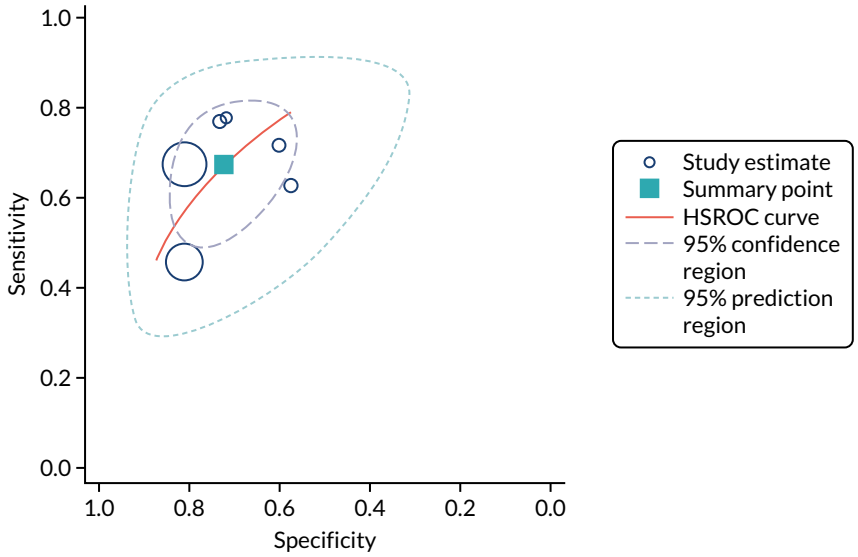

FIGURE 8 The SROC plot for the ARCHITECT urine NGAL assay studies: all clinical settings (adult population). HSROC, hierarchical summary receiver operating characteristic.

TABLE 7 Summary of diagnostic data for the BioPorto urine NGAL assay for the detection of AKI in adults

Study	Target population (setting)	Assay	Timing of test	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Yang, 2017[65]	Cardiac surgery	BioPorto urine NGAL	6 hours after surgery	98 µg/g of creatinine	0.78 (0.71 to 0.84)	0.48 (0.41 to 0.54)	0.72 (0.64 to 0.80)	41%
Cho 2014[66]	Major non-cardiac surgery	BioPorto urine NGAL	12 hours after hepatobiliary surgery	92.85 ng/ml	0.78 (0.52 to 1.00)	0.80 (0.73 to 0.87)	0.78 (0.66 to 0.90)	8%
Nickolas 2008[74]	Critical care – mixed population (ICU/ITU)	BioPorto urine NGAL	Admission to ED	130 µg/g of creatinine	0.90 (0.73 to 0.98)	1.00 (0.99 to 1.00)	0.95 (0.88 to 1.00)	0.047
Cho 2013[69]	Critical care – mixed population (ICU/ITU)	BioPorto urine NGAL	ICU admission	NR	0.74	0.70	0.77 (0.69 to 0.85)	0.37
Matsa 2014[73]	Critical care – mixed population (ICU/ITU)	BioPorto urine NGAL	ICU admission	350 ng/ml	0.58 (0.44 to 0.70)	0.84 (0.75 to 0.91)	0.79	0.38
Barreto 2014[68]	Critical care – mixed population (liver disease)	BioPorto urine NGAL	When the infection was detected	51 µg/g of creatinine	0.66	0.70	0.72 (0.64 to 0.81)	0.49
Hjortrup 2015[72]	Critical care – mixed population (ICU/ITU)	BioPorto urine NGAL	ICU admission	582 ng/ml	0.75	0.77	0.71 (0.59 to 0.82)	0.24
Tecson 2017[78]	Critical care – mixed population (ICU/ITU)	BioPorto urine NGAL	Within 48 hours of ICU admission	98 ng/ml	0.64 (0.45 to 0.80)	0.81 (0.75 to 0.86)	–	0.13

ITU, intensive treatment unit; NR, not reported.

Critical care: mixed population

Six studies[68,69,72–74,78] (1442 patients in total) assessed the use of the BioPorto urine NGAL assay for the detection of AKI in patients admitted to an ICU or critical care for various clinical reasons (see *Table 7*). Some studies reported absolute levels of urine NGAL and other levels normalised to urine creatinine. The threshold varied across studies. The prevalence of AKI ranged from 5% to 49% across studies. Sensitivity values ranged from 0.58 to 0.90 and specificity values ranged from 0.70 to 1.00. The summary estimate of sensitivity was 0.72 (95% CI 0.61 to 0.80) and that of specificity was 0.87 (95% CI 0.66 to 0.96). The forest plots of sensitivity and specificity estimates and the SROC plot with 95% confidence region for the summary operating point and 95% prediction region are presented in *Appendix 9* (see *Figures 30* and *31*). The confidence and prediction regions of the SROC plot are large, indicating heterogeneity between studies, especially for specificity.

Figure 9 shows the forest plots of sensitivity and specificity estimates for the eight studies (1971 patients in total) assessing the BioPorto urine NGAL assay for the detection of AKI in adults across all clinical settings. Sensitivity values ranged from 0.58 to 0.90 and specificity values ranged from 0.48 to 1.00. Summary estimates for sensitivity and specificity were 0.73 (95% CI 0.65 to 0.80) and 0.83 (95% CI 0.64 to 0.93), respectively. The SROC plot with the 95% confidence region for the summary operating point and the 95% prediction region, is shown in *Figure 10*. The confidence and prediction regions are large, indicating considerable heterogeneity between studies.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nickolas[74]	27	3	3	602	0.90 (0.73 to 0.98)	1.00 (0.99 to 1.00)
Cho[69]	40	27	14	64	0.74 (0.60 to 0.85)	0.70 (0.60 to 0.79)
Barreto[68]	43	20	22	47	0.66 (0.53 to 0.77)	0.70 (0.58 to 0.81)
Matsa[73]	34	15	25	80	0.58 (0.44 to 0.70)	0.84 (0.75 to 0.91)
Cho[66]	8	24	2	97	0.80 (0.44 to 0.97)	0.80 (0.72 to 0.87)
Hjortrup[72]	24	23	7	77	0.77 (0.59 to 0.90)	0.77 (0.68 to 0.85)
Yang[65]	128	122	36	112	0.78 (0.71 to 0.84)	0.48 (0.41 to 0.54)
Tecson[78]	21	40	12	172	0.64 (0.45 to 0.80)	0.81 (0.75 to 0.86)

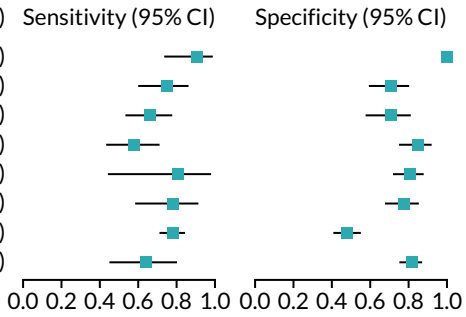

FIGURE 9 Forest plots of sensitivity and specificity for the BioPorto urine NGAL assay studies for the detection of AKI in adults: all clinical settings. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

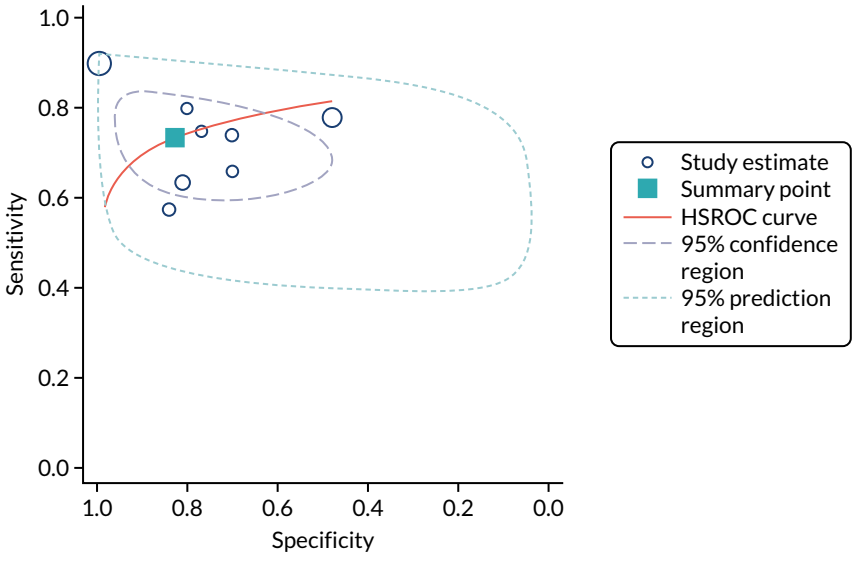

FIGURE 10 The SROC plot for the BioPorto urine NGAL assay studies for the detection of AKI in adults: all clinical settings. HSROC, hierarchical summary receiver operating characteristic.

Urine neutrophil gelatinase-associated lipocalin assays (ARCHITECT and BioPorto): critical care

Ten studies (3441 patients in total) assessed urine NGAL assays (both ARCHITECT and BioPorto) for the detection of AKI in patients admitted to critical care. Sensitivity values ranged from 0.58 to 0.90 and specificity values ranged from 0.58 to 1.00. Summary estimates for sensitivity and specificity were 0.71 (95% CI 0.64 to 0.77) and 0.82 (95% CI 0.67 to 0.90), respectively. The forest plot of sensitivity and specificity estimates and the SROC plot with 95% confidence region for the summary operating point and 95% prediction region are shown in *Appendix 9* (see *Figures 32* and *33*). The prediction region in the SROC plot is large, especially for specificity, indicating heterogeneity across studies.

Urine neutrophil gelatinase-associated lipocalin assays (ARCHITECT and BioPorto): across all settings

Figure 11 shows the forest plots of sensitivity and specificity estimates for all 14 studies assessing the urine NGAL assays (both ARCHITECT and BioPorto) across all clinical settings (5319 patients in total). Sensitivity values ranged from 0.46 to 0.90 and specificity values ranged from 0.48 to 1.00. Summary estimates for sensitivity and specificity were 0.71 (95% CI 0.64 to 0.76) and 0.78 (95% CI 0.67 to 0.87), respectively. *Figure 12* shows the SROC plot with 95% confidence region for the

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dupont[52]	22	45	13	61	0.63 (0.45 to 0.79)	0.58 (0.48 to 0.67)
Nickolas[74]	27	3	3	602	0.90 (0.73 to 0.98)	1.00 (0.99 to 1.00)
Parikh[37]	28	220	33	939	0.46 (0.33 to 0.59)	0.81 (0.79 to 0.83)
Kokkoris[54]	28	18	8	46	0.78 (0.61 to 0.90)	0.72 (0.59 to 0.82)
Nickolas[56]	65	292	31	1247	0.68 (0.57 to 0.77)	0.81 (0.79 to 0.83)
Cho[69]	40	27	14	64	0.74 (0.60 to 0.85)	0.70 (0.60 to 0.79)
Cho[66]	8	24	2	97	0.80 (0.44 to 0.97)	0.80 (0.72 to 0.87)
Barreto[68]	43	20	22	47	0.66 (0.53 to 0.77)	0.70 (0.58 to 0.81)
Thanakitcharu[48]	14	44	5	67	0.74 (0.49 to 0.91)	0.60 (0.51 to 0.70)
Matsa[73]	34	15	25	80	0.58 (0.44 to 0.70)	0.84 (0.75 to 0.91)
Treeprasertsuk[59]	27	23	8	63	0.77 (0.60 to 0.90)	0.73 (0.63 to 0.82)
Hjortrup[72]	24	23	8	77	0.75 (0.57 to 0.89)	0.77 (0.68 to 0.85)
Yang[65]	128	122	36	112	0.78 (0.71 to 0.84)	0.48 (0.41 to 0.54)
Tecson[78]	21	40	12	172	0.64 (0.45 to 0.80)	0.81 (0.75 to 0.86)

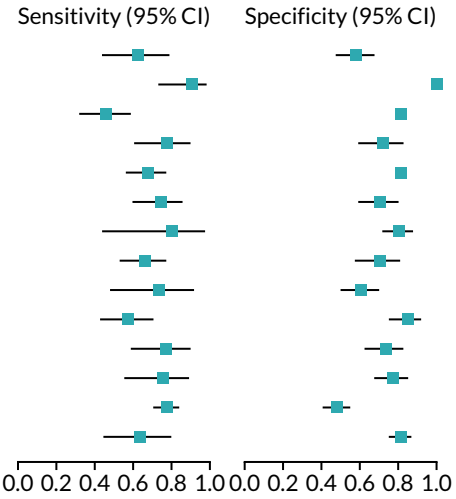

FIGURE 11 Forest plots of sensitivity and specificity for all urine NGAL assays (both ARCHITECT and BioPorto) for the detection of AKI in adults across all clinical settings. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

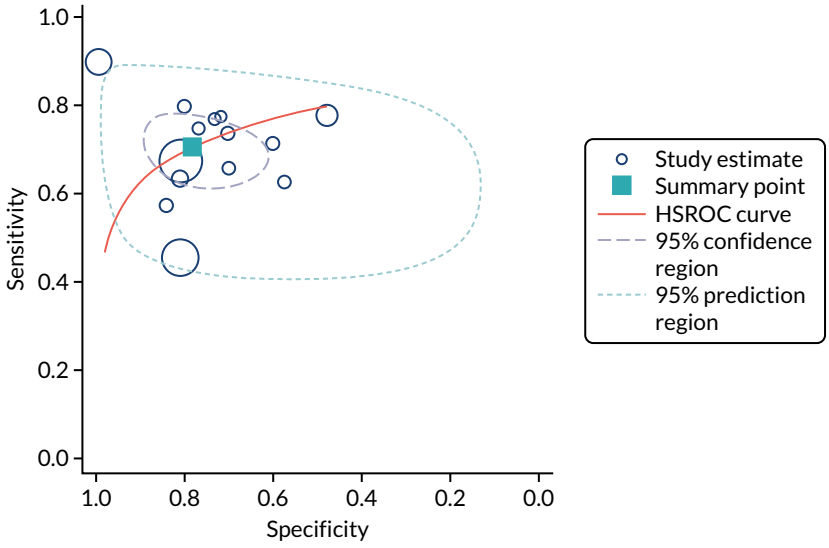

FIGURE 12 The SROC plot for all urine NGAL assays (both ARCHITECT and BioPorto) for the detection of AKI in adults: all clinical settings. HSROC, hierarchical summary receiver operating characteristic.

summary operating point and 95% prediction region. The prediction region is large, indicating heterogeneity across studies.

BioPorto plasma neutrophil gelatinase-associated lipocalin assay: adult population

No suitable data in any post-surgical setting (cardiac surgery or major non-cardiac surgery) were available from the included studies.

Critical care: mixed population

Four studies (771 patients in total) assessed the use of the BioPorto plasma NGAL assay for the detection of AKI in patients admitted to ICU or critical care for various clinical reasons (*Table 8*). Cut-off points varied across studies The prevalence of AKI ranged from 13% to 38% across studies. *Figure 13* shows the forest plots of sensitivity and specificity. Sensitivity values ranged from 0.58 to 0.93 and specificity values ranged from 0.23 to 0.85. The summary estimate of sensitivity was 0.76 (95% CI 0.56 to 0.89) and that of specificity was 0.67 (95% CI 0.40 to 0.86). *Figure 14* shows the SROC plot with 95% confidence region for the summary operating point and 95% prediction region. Confidence and prediction regions are large and are greater for sensitivity than for specificity. Although this indicates the presence of heterogeneity across studies, it is worth observing that all studies and their confidence and prediction regions are positioned in the left side of the graph, above the diagonal of no effect. It is worth paying attention to the Itenov *et al.*[81] study, which shows a high sensitivity estimate and a very low specificity estimate.

Table 9 presents a summary of the diagnostic data for the seven urine NGAL assay studies that assessed AKI in children. All but one study assessed children who underwent cardiac surgery. Across studies, the age of the paediatric population ranged from 1 day to 8 years.

ARCHITECT urine neutrophil gelatinase-associated lipocalin assay: child population

Cardiac surgery

Five studies (887 children in total) assessed the use of the ARCHITECT urine NGAL assay for the detection of AKI among children who had undergone cardiac surgery (see *Table 9*). The cut-off point used to define a positive test and the timing of biomarker measurements varied across studies. The prevalence of AKI ranged from 17% to 55% across studies. *Figure 15* shows the forest plots of sensitivity and specificity estimates across studies. Sensitivity values ranged from 0.42 to 0.83 and specificity values ranged from 0.43 to 0.92. The summary estimate of sensitivity was 0.68 (95% CI 0.53 to 0.80) and that of specificity was 0.79 (95% CI 0.63 to 0.89). *Figure 16* shows the SROC plot with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are very large, indicating considerable heterogeneity between studies.

Critical care: mixed population

One study[91] assessed the use of the ARCHITECT urine NGAL assay for the detection of AKI in 324 children admitted to ICU or critical care for various clinical reasons (see *Table 9*). The cut-off point was 126 ng/ml. The prevalence of AKI in the study was 35%. The sensitivity and specificity values for the urine sample collected at ICU admission were 0.77 (95% CI 0.60 to 0.90) and 0.85 (95% CI 0.74 to 0.92), respectively.

BioPorto urine neutrophil gelatinase-associated lipocalin assay: child population

Cardiac surgery

One study[65] assessed the use of the BioPorto urine NGAL assay for the detection of AKI in 323 children who underwent cardiac surgery (see *Table 9*). Urine NGAL was measured using a concentration normalised by units of creatinine. The sensitivity and specificity values for the urine sample collected 6 hours after surgery were 0.77 (95% CI 0.69 to 0.84) and 0.47 (95% CI 0.40 to 0.54), respectively. The prevalence of AKI in the study was 39%.

TABLE 8 Summary of diagnostic accuracy data for the BioPorto plasma NGAL assay for the detection of AKI in adults (critical care setting)

Study	Target population (setting)	Assay	Timing of test	Cut-off point (ng/ml)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Matsa 2014[73]	Critical care – mixed population (ICU/ITU)	BioPorto plasma NGAL	ICU admission	400	0.60 (0.47 to 0.73)	0.85 (0.77 to 0.92)	0.77	0.38
Hjortrup 2015[72]	Critical care – mixed population (sepsis)	BioPorto plasma NGAL	ICU admission	558	0.58	0.76	0.66 (0.54 to 0.77)	0.24
Tecson 2017[78]	Critical care – mixed population (ICU/ITU)	BioPorto plasma NGAL	Within 48 hours of ICU admission	142	0.79 (0.61 to 0.91)	0.73 (0.67 to 0.79)	0.76 (0.64 to 0.87)	0.13
Itenov 2017[81]	Critical care – mixed population (ICU/ITU)	BioPorto plasma NGAL	ICU admission	185	0.93	0.23	NR	0.36

ITU, intensive treatment unit; NR, not reported.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Matsa[73]	35	14	23	81	0.60 (0.47 to 0.73)	0.85 (0.77 to 0.92)
Hjortrup[72]	18	24	13	76	0.58 (0.39 to 0.75)	0.76 (0.66 to 0.84)
Tecson[78]	26	57	7	155	0.79 (0.61 to 0.91)	0.73 (0.67 to 0.79)
Itenov[81]	80	119	6	36	0.93 (0.85 to 0.97)	0.23 (0.17 to 0.31)

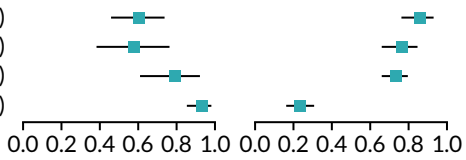

FIGURE 13 Forest plots of sensitivity and specificity for the BioPorto plasma NGAL assay for the detection of AKI in adults: critical care setting. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

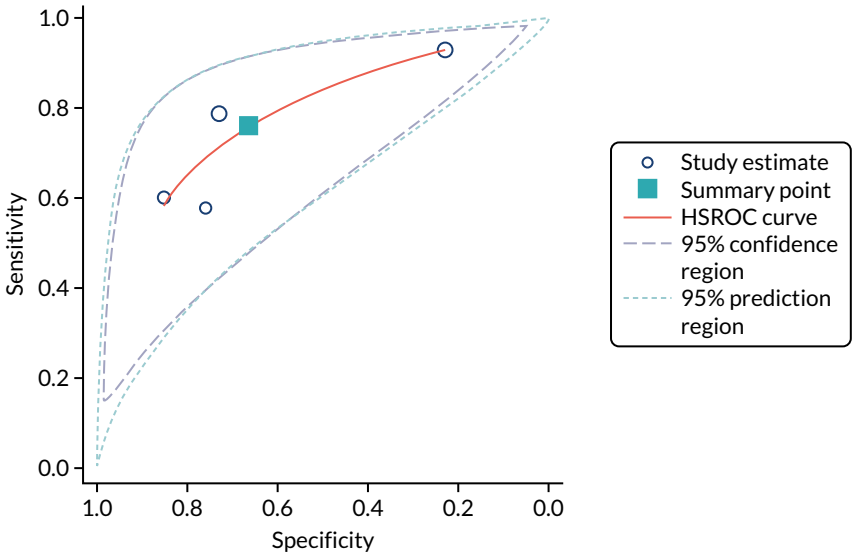

FIGURE 14 The SROC plot for the BioPorto plasma NGAL assay studies for the detection of AKI in adults: critical care setting. HSROC, hierarchical summary receiver operating characteristic.

Urine neutrophil gelatinase-associated lipocalin assays (both ATCHITECT and BioPorto) across all clinical settings: child population

Figure 17 shows the forest plots of sensitivity and specificity estimates for the seven studies (1310 children in total) assessing urine NGAL assays (both ARCHITECT and BioPorto) for the detection of AKI among children across all clinical settings. Sensitivity values ranged from 0.42 to 0.83; specificity values ranged from 0.43 to 0.92. Summary estimates for sensitivity and specificity were 0.71 (95% CI 0.60 to 0.80) and 0.76 (95% CI 0.61 to 0.86), respectively. *Figure 18* shows the SROC plot with 95% confidence region for the summary operating point and 95% prediction region. The confidence and prediction regions are very large, indicating considerable heterogeneity between studies.

Accuracy of NephroCheck, ARCHITECT neutrophil gelatinase-associated lipocalin and BioPorto neutrophil gelatinase-associated lipocalin assays for the detection of acute kidney injury in critically ill patients

For both adults and children, the accuracy of NephroCheck, ARCHITECT urine NGAL and BioPorto urine and plasma NGAL assays for detection of AKI in each clinical setting is shown in *Table 10*. The table displays either the AUC estimates as reported by individual studies or the AUC summary estimates together with the corresponding prediction intervals when pooling of AUC estimates was feasible. Associated forest plots of the AUC meta-analyses are presented in *Appendix 10* (see *Figures 34–50*). For the adult population, the AUC summary estimates ranged from 0.62 for the BioPorto urine NGAL assay to 0.74 for the BioPorto plasma NGAL assay in the cardiac surgery setting, and from 0.72 for the

TABLE 9 Summary of diagnostic accuracy data for urine NGAL assays (both ARCHITECT and BioPorto) for the detection of AKI in children

Study	Target population (setting)	Assay	Timing of test	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Prevalence of AKI
Parikh 2011[84]	Cardiac surgery	ARCHITECT urine NGAL	ICU admission	> 72 ng/ml	0.42	0.85	0.71	0.17
Cantinotti 2012[88]	Cardiac surgery	ARCHITECT urine NGAL	2 hours after surgery	49.9 ng/ml	0.78	0.81	0.85 (0.77 to 0.91)	0.27
Bennett 2008[87]	Cardiac surgery	ARCHITECT urine NGAL	2 hours after surgery	> 150 ng/ml	0.79 (0.69 to 0.86)	0.92 (0.84 to 0.96)	0.93	0.50
Seitz 2013[90]	Cardiac surgery	ARCHITECT urine NGAL	2 hours after end of surgery	27.6 ng/ml	0.55	0.43	0.56	0.55
Alcaraz 2014[89]	Cardiac surgery	ARCHITECT urine NGAL	ICU admission	100 ng/ml	0.82	0.76	0.84 (0.76 to 0.92)	0.34
Yang 2017[65]	Cardiac surgery	BioPorto urine NGAL	6 hours after surgery	186 µg/g of creatinine	0.77	0.47	0.72 (0.64 to 0.80)	0.39
Zwiers 2015[91]	Critical care – mixed population (ICU/ITU)	ARCHITECT urine NGAL	ICU admission	126 ng/ml	0.76	0.84	0.81 (0.68 to 0.94)	0.35

ITU, intensive treatment unit.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Parikh[84]	22	39	31	219	0.42 (0.28 to 0.56)	0.85 (0.80 to 0.89)
Cantinotti[88]	41	15	11	68	0.79 (0.65 to 0.89)	0.82 (0.72 to 0.90)
Seitz[90]	41	36	35	27	0.54 (0.42 to 0.65)	0.43 (0.30 to 0.56)
Bennett[87]	78	8	21	89	0.79 (0.69 to 0.86)	0.92 (0.84 to 0.96)
Alcaraz[89]	30	17	6	53	0.83 (0.67 to 0.94)	0.76 (0.64 to 0.85)

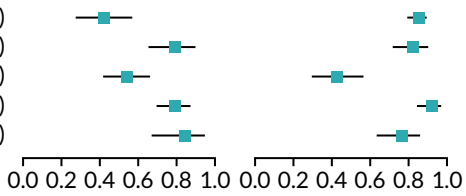

FIGURE 15 Forest plots of sensitivity and specificity for the ARCHITECT urine NGAL assay for the detection of AKI in children: cardiac surgery setting. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

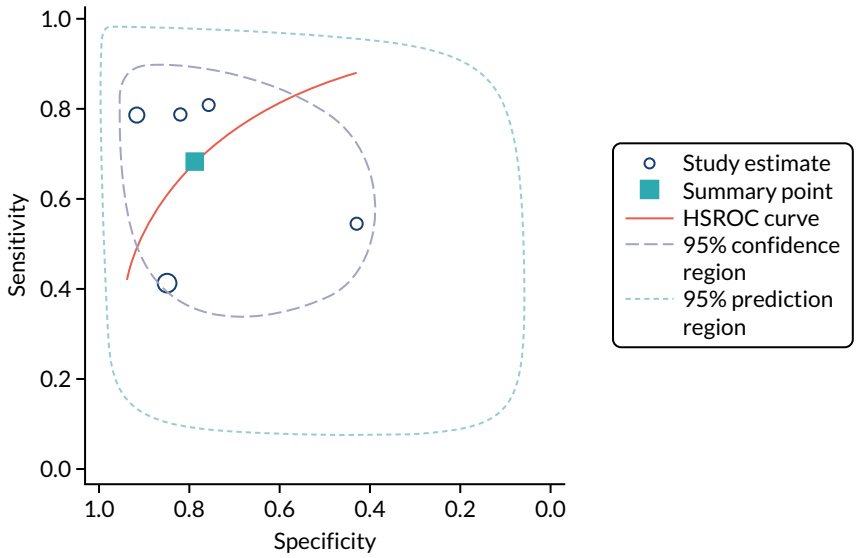

FIGURE 16 The SROC plot for the ARCHITECT urine NGAL assay studies for the detection of AKI in children: cardiac surgery setting. HSROC, hierarchical summary receiver operating characteristic.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Parikh[84]	22	39	31	219	0.42 (0.28 to 0.56)	0.85 (0.80 to 0.89)
Cantinotti[88]	41	15	11	68	0.79 (0.65 to 0.89)	0.82 (0.72 to 0.90)
Seitz[90]	41	36	35	27	0.54 (0.42 to 0.65)	0.43 (0.30 to 0.56)
Bennett[87]	78	8	21	89	0.79 (0.69 to 0.86)	0.92 (0.84 to 0.96)
Alcaraz[89]	30	17	6	53	0.83 (0.67 to 0.94)	0.76 (0.64 to 0.85)
Zwiers[91]	27	10	8	55	0.77 (0.60 to 0.90)	0.85 (0.74 to 0.92)
Yang[65]	97	104	29	93	0.77 (0.69 to 0.84)	0.47 (0.40 to 0.54)

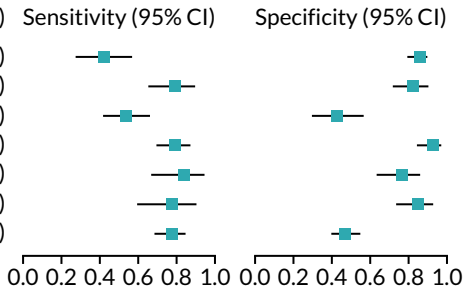

FIGURE 17 Forest plots of sensitivity and specificity for all urine NGAL assays (ARCHITECT and BioPorto) for the detection of AKI in children across all clinical settings. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

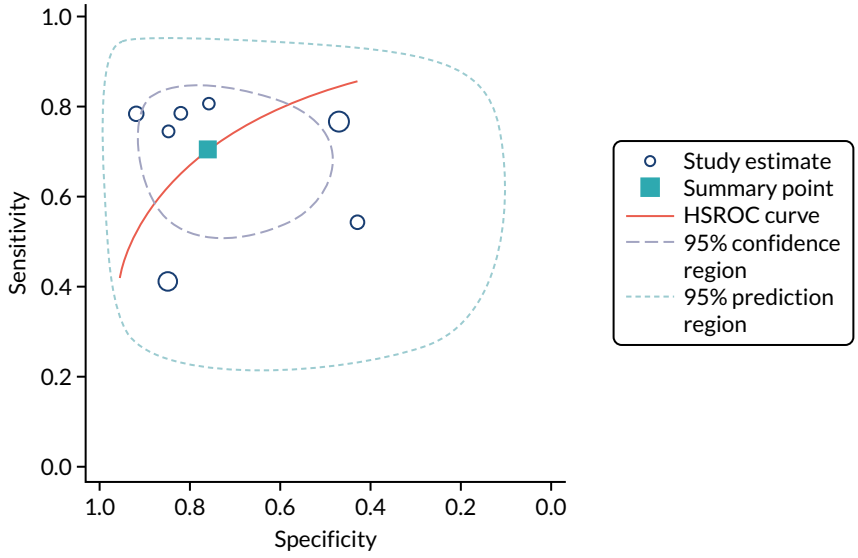

FIGURE 18 The SROC plot for all urine NGAL assay (ARCHITECT and BioPorto) studies for the detection of AKI in children: all clinical settings. HSROC, hierarchical summary receiver operating characteristic.

TABLE 10 The AUC estimates and AUC summary estimates for NephroCheck and NGAL studies for detection of AKI

Population, biomarker and setting	Studies (*n*)	AUC (95% CI)		95% prediction interval
		Estimate	Summary	
Adults, NephroCheck, across all settings	7	–	0.76 (0.50 to 0.91)	(0.47 to 0.90)
Adults, NephroCheck, cardiac surgery	1	0.68 (0.54 to 0.81)	–	–
Adults, NephroCheck, major non-cardiac surgery	–	–	–	–
Adults, NephroCheck, critical care	6	–	0.74 (0.67 to 0.81)	(0.44 to 0.91)
Adults, ARCHITECT urine NGAL, all settings	14	–	0.73 (0.68 to 0.78)	(0.53 to 0.87)
Adults, ARCHITECT urine NGAL, cardiac surgery	6	–	0.70 (0.65 to 0.74)	(0.58 to 0.79)
Adults, ARCHITECT urine NGAL, major non-cardiac surgery	1	0.50 (034 to 0.66)	–	–
Adults, ARCHITECT urine NGAL, critical care	7	–	0.76 (0.69 to 0.82)	(0.50 to 0.91)
Adults, BioPorto urine NGAL, across settings	15	–	0.70 (0.65 to 0.74)	(0.53 to 0.82)
Adults, BioPorto urine NGAL, cardiac surgery	4	–	0.62 (0.55 to 0.69)	(0.33 to 0.84)
Adults, BioPorto urine NGAL, major non-cardiac surgery	1	0.78 (0.66 to 0.90)	–	–
Adults, BioPorto urine NGAL, critical care	10	–	0.72 (0.67 to 0.77)	(0.54 to 0.85)
Adults, urine NGAL (ARCHITECT and BioPorto), cardiac surgery	10	–	0.67 (0.62 to 0.78)	(0.53 to 0.78)

continued

TABLE 10 The AUC estimates and AUC summary estimates for NephroCheck and NGAL studies for detection of AKI (*continued*)

Population, biomarker and setting	Studies (*n*)	AUC (95% CI)		95% prediction interval
		Estimate	Summary	
Adults, urine NGAL (ARCHITECT and BioPorto), major non-cardiac surgery	2	–	0.65 (0.35 to 0.86)	–
Adults, urine NGAL (ARCHITECT and BioPorto), critical care	17	–	0.74 (0.70 to 0.78)	(0.56 to 0.86)
Adults, urine NGAL (ARCHITECT and BioPorto), all settings	29	–	0.71 (0.68 to 0.74)	(0.55 to 0.84)
Adults, BioPorto plasma NGAL, across all settings	10	–	0.72 (0.66 to 0.77)	(0.52 to 0.86)
Adults, BioPorto plasma NGAL, cardiac surgery	3	–	0.74 (0.65 to 0.82)	(0.06 to 0.99)
Adults, BioPorto plasma NGAL, major non-cardiac surgery	1	0.78 (0.66 to 0.90)	–	–
Adults, BioPorto plasma NGAL, critical care	7	–	0.72 (0.65 to 0.78)	(0.47 to 0.88)
Children, urine NGAL (ARCHITECT and BioPorto), across settings	9	–	0.81 (0.71 to 0.88)	(0.37 to 0.97)
Children, ARCHITECT urine NGAL, cardiac surgery	5	–	0.80 (0.65 to 0.90)	(0.17 to 0.99)
Children, BioPorto urine NGAL, cardiac surgery	2	–	0.88 (0.47 to 0.98)	–
Children, urine NGAL (ARCHITECT and BioPorto), all cardiac surgery	7	–	0.82 (0.71 to 0.90)	(0.31 to 0.98)
Children, ARCHITECT urine NGAL, critical care	1	0.81 (0.69 to 0.94)	–	–
Children, BioPorto urine NGAL, critical care	1	0.68 (0.55 to 0.81)	–	–
Children, urine NGAL (ARCHITECT and BioPorto), critical care	2	–	0.73 (0.58 to 0.84)	–

BioPorto urine and plasma NGAL assays to 0.76 for the ARCHITECT urine NGAL assay in the critical care setting. For the child population in the cardiac surgery setting, the AUC summary estimates ranged from 0.80 for the ARCHITECT urine NGAL assay to 0.88 for the BioPorto urine NGAL assay. All AUC summary estimates had relatively large 95% prediction intervals, indicating heterogeneity between studies. The forest plots in *Appendix 10* (see *Figures 34–50*) show that variation is present both between and within studies.

For each biomarker, *Table 11* shows the AUC for the detection of AKI compared with that of serum creatinine or conventional clinical assessment, as reported by the individual studies that provided this information. AUC values varied across studies. In the majority of cases, the reported AUC indicated a slightly better performance of the biomarkers than that of serum creatinine or conventional clinical assessment for the detection of AKI. However, in a number of cases, serum creatinine or conventional clinical assessment appeared to perform better than the biomarkers under assessment.

TABLE 11 The AUC for NephroCheck, ARCHITECT urine NGAL and BioPorto urine and plasma NGAL assays for the detection of AKI, compared with the AUC for serum creatinine or conventional clinical assessment

Study ID, geographical location, patient population	Clinical setting	Biomarker	AUC (95% CI or SEM)	
			Creatinine or clinical model	Biomarker
Bihorac 2014,[29] USA, adult population	Critical care (mixed population)	NephroCheck	Serum creatinine 0.63 (0.56 to 0.70)	0.82 (0.76 to 0.88)
Kashani 2013,[34] North America and Europe, adult population	Critical care (mixed population)	NephroCheck	Serum creatinine 0.75 (0.70 to 0.80)	0.80 (0.75 to 0.84)
Kimmel 2016,[36] Germany, adult population	Critical care (mixed population)	NephroCheck	Serum creatinine 0.60 (0.53 to 0.66)	0.74 (0.66 to 0.81)
		BioPorto plasma NGAL	Serum creatinine 0.60 (0.53 to 0.66)	0.55 (0.5 to 0.66)
		BioPorto urine NGAL	Serum creatinine 0.60 (0.53 to 0.66)	0.66 (0.58 to 0.73)
Haase 2014,[60] Germany, adult population	Cardiac surgery	ARCHITECT urine NGAL	Serum creatinine 0.66 (0.51 to 0.76)	0.71 (0.6 to 0.83)
		BioPorto plasma NGAL	Serum creatinine 0.66 (0.51 to 0.76)	0.71 (0.58 to 0.83)
Kokkoris 2012,[54] Greece, adult population	Critical care (mixed population)	ARCHITECT urine NGAL	Serum creatinine 0.77 (0.67 to 0.84)	0.74 (0.64 to 0.82)
		BioPorto plasma NGAL	Serum creatinine 0.77 (0.67 to 0.84)	0.78 (0.68 to 0.85)
Liebetrau 2013,[47] Germany, adult population	Cardiac surgery	ARCHITECT urine NGAL	Serum creatinine 0.74 (0.58 to 0.91)	0.90 (0.811 to 0.99)
Parikh 2011,[37] North America, adult population	Cardiac surgery	ARCHITECT urine NGAL	Clinical model 0.69 (SEM 0.04)	0.67 (SEM 0.04)
Parikh 2011,[95] North America, adult population	Cardiac surgery	ARCHITECT urine NGAL	Serum creatinine 0.46 (SEM 0.04)	0.71 (SEM 0.04)
Nickolas 2012,[56] USA and Germany, adult population	Critical care (mixed population)	ARCHITECT urine NGAL	Serum creatinine 0.91 (0.87 to 0.94)	0.81 (NR)
Treeprasertsuk 2015,[59] Thailand, adult population	Critical care (mixed population)	ARCHITECT urine NGAL	Serum creatinine 0.58 (NR)	0.83 (0.76 to 0.91)
De Loor 2017,[63] Belgium, adult population	Cardiac surgery	BioPorto urine NGAL	Serum creatinine 0.78 (0.72 to 0.83)	0.65 (0.58 to 0.72)
Hjortrup 2015,[72] Denmark, adult population	Critical care (mixed population)	BioPorto urine NGAL	Plasma creatinine 0.66 (0.56 to 0.77)	0.71 (0.59 to 0.82)
		BioPorto plasma NGAL	Plasma creatinine 0.66 (0.56 to 0.77)	0.66 (0.54 to 0.77)
Nickolas 2008,[74] USA, adult population	Critical care (mixed population)	BioPorto urine NGAL	Serum creatinine 0.92 (0.87 to 0.98)	0.95 (0.88 to 1.00)
Verna 2014,[79] USA, adult population	Critical care (mixed population)	BioPorto urine NGAL	Serum creatinine 0.89	0.86 (NR)
Alcaraz 2014,[89] Spain, child population	Cardiac surgery	ARCHITECT urine NGAL	Clinical model 0.85 (0.78 to 0.93)	0.84 (0.76 to 0.92)

NR, not reported; SEM, standard error of the mean.

Role of biomarkers in predicting worsening of acute kidney injury mortality and need for renal replacement therapy

Table 12 displays the AUC and the pooled AUC estimates with corresponding 95% CIs for the NephroCheck, ARCHITECT urine NGAL and BioPorto urine and plasma NGAL assay studies for the prediction of worsening of AKI, mortality and RRT in each clinical setting for both adults and children.

TABLE 12 The AUC estimates for prediction of worsening of AKI, mortality and need for RRT

Population, biomarker and setting	Follow-up	Studies (*n*)	AUC (95% CI)	
			Estimate	Summary estimate
AKI				
Adults, ARCHITECT urine NGAL, critical care	During hospital stay	1	–	0.65 (0.43 to 0.82)
Adults, BioPorto urine NGAL, critical care	During ICU stay	1	0.71 (0.59 to 0.82)	–
Adults, BioPorto plasma NGAL, critical care	During ICU stay	1	0.66 (0.54 to 0.77)	–
Mortality				
Adults, ARCHITECT urine NGAL, cardiac surgery	During hospital stay (11/288 patients died)	1	0.70 (0.56 to 0.84)	–
Adults, ARCHITECT urine NGAL, major non-cardiac surgery	30 days (10/109 patients died)	1	0.65 (0.45 to 0.85)	–
Adults, ARCHITECT urine NGAL, critical care	30 days (17/121 patients died)	1	0.75 (0.66 to 0.85)	–
Adults, BioPorto urine NGAL, critical care	90 days	2	–	0.62 (0.58 to 0.66)
Adults, BioPorto plasma NGAL, critical care	In hospital	2	–	0.68 (0.63 to 0.73)
Adults, BioPorto plasma NGAL, critical care	30 days (7/105 patients died)	1	0.72 (0.49 to 0.87)	–
Adults, BioPorto plasma NGAL, critical care	90 days	1	0.55 (0.47 to 0.63)	–
Adults, urine NGAL (ARCHITECT and BioPorto) critical care	In hospital	2	–	0.76 (0.64 to 0.85)
Children, ARCHITECT urine NGAL, cardiac surgery	In hospital (3/196 patients died)	1	0.91 (0.55 to 0.99)	–
Need for RRT				
Adults, NephroCheck, cardiac surgery	NR	1	0.78 (0.71 to 0.84)	–
Adults, ARCHITECT urine NGAL, cardiac surgery	Up to 12 months (22/288 patients received RRT)	1	0.68 (0.57 to 0.79)	–
Adults, BioPorto urine NGAL, critical care	–	2	–	0.74 (0.49 to 0.89)
Adults, BioPorto plasma NGAL, critical care	During ICU stay (40/222 patients received RRT)	1	0.70 (0.61 to 0.78)	–
Children, ARCHITECT urine NGAL, cardiac surgery	During hospital stay (4/196 patients received RRT)	1	0.86 (0.57 to 0.97)	–

NR, not reported.

Only a limited number of studies were available for AUC meta-analyses. Associated forest plots are presented in *Appendix 11* (see *Figures 51–55*). In the critical care setting (adult population), the AUC values reported in individual studies ranged from 0.66 for the BioPorto plasma NGAL assay to 0.71 for the BioPorto urine NGAL assay for worsening of AKI, and from 0.55 for the BioPorto plasma NGAL assay for prediction of 90-day mortality to 0.75 for the ARCHITECT urine NGAL assay for prediction of 30-day mortality. One study reported an AUC of 0.70 for BioPorto plasma NGAL for prediction of need for RRT. The AUC summary estimate (pooling of 2 studies) for worsening of AKI in the critical care setting was 0.65 (95% CI 0.43 to 0.82) for ARCHITECT urine NGAL. AUC summary estimates ranged from 0.62 for BioPorto urine NGAL for 90-day mortality to 0.68 for the BioPorto plasma NGAL assay for in-hospital mortality, with a 95% CI of 0.58 to 0.73. The AUC summary estimate (two studies) for prediction of RRT in critical care for the BioPorto urine NGAL assay was 0.74 (95% CI 0.49 to 0.89).[72,75] In the cardiac surgery setting (adult population), AUC values from individual studies ranged from 0.68 for the ARCHITECT urine NGAL assay to 0.78 for NephroCheck for prediction of need for RRT, with a 95% CI of 0.57 to 0.84.

Appendix 12, *Table 30*, presents the AUC with 95% CI or the OR with 95% CI for the addition of the biomarkers to existing clinical models for the prediction of AKI, mortality and need for RRT. It is worth noting that the statistical models differed between studies and often were not sufficiently detailed. In particular, although most of the adjusting predictors were specified, information on the potential candidate variables was missing. In general, the number of events was small, given the number of predicting variables, even for AKI outcomes. Overall, the addition of biomarkers to the clinical models improved risk prediction of newly developed AKI or worsening of AKI, and mortality. However, only a limited amount of data were available for each biomarker in each clinical setting, thereby restricting any generalisable interpretation.

Interpretation of clinical effectiveness evidence

The results of the meta-analyses of sensitivity and specificity estimates suggest that the biomarkers under investigation (i.e. NephroCheck, ARCHITECT urine NGAL and BioPorto urine and plasma NGAL assays) may have a role in the detection of AKI in critically ill patients. However, owing to the considerable clinical and statistical heterogeneity observed across studies and the limited number of studies available for certain clinical settings and/or type of biomarker, these results should be interpreted with caution and require further evidence to substantiate them. Furthermore, the threshold level for NGAL varied considerably across studies. However, as optimal NGAL thresholds for detection of AKI in various clinical settings have yet to be established, we decided to pool results across studies with similar characteristics, despite this obvious limitation. For the adult population, we were able to conduct meta-analyses for studies that assessed patients in the critical care (mixed population) setting and for studies across all clinical settings. There were too few studies assessing patients after cardiac surgery or major non-cardiac surgery. The NephroCheck test had the highest pooled sensitivity (0.83), but the worst pooled specificity (0.51), whereas the ARCHITECT and BioPorto urine NGAL tests had slightly lower pooled sensitivity estimates (0.70 and 0.72, respectively), but better pooled specificity estimates (0.72 and 0.87, respectively). The BioPorto urine NGAL assay pooled sensitivity was similar to that of the BioPorto plasma NGAL assay (0.72 vs. 0.76, respectively), but the pooled specificity was better for the BioPorto urine NGAL assay than for the BioPorto plasma NGAL assay (0.87 vs. 0.67, respectively). The biomarkers had a similar performance across all clinical settings (the NephroCheck test pooled sensitivity and specificity were 0.75 and 0.61, respectively; the ARCHITECT urine NGAL assay pooled sensitivity and specificity were 0.67 and 0.72, respectively; the BioPorto urine NGAL assay pooled sensitivity and specificity were 0.73 and 0.83, respectively; and the BioPorto plasma NGAL assay pooled sensitivity and specificity were 0.76 and 0.67, respectively), with the BioPorto plasma NGAL assay showing the highest sensitivity (0.76) and the BioPorto urine NGAL assay showing the highest specificity (0.83).

With regard to the observed low specificity of the NephroCheck test, we do not know with certainty whether this is because of the relatively poor performance of the biomarker or the fact that serum creatinine is an imperfect reference standard for assessing kidney injury.

We also noted that, when a study had a small number of AKI events (low prevalence), the relationship observed between sensitivity and specificity estimates became quite different from that of studies for which prevalence was higher.

For the child population, we were able to conduct meta-analyses for the five ARCHITECT urine NGAL assay studies that assessed children who underwent cardiac surgery. The pooled sensitivity was 0.68 and the pooled specificity was 0.79. Too few studies were available for the other assays or clinical settings. When we combined all urine NGAL studies (ARCHITECT and BioPorto) across all settings (seven studies), we obtained similar estimates of accuracy (sensitivity 0.71; specificity 0.76).[65,84,87–91]

For the prediction of relevant clinical outcomes, only a limited number of studies were available for each biomarker in each clinical setting; this hampered the possibility of performing pooled analyses. Furthermore, the details of the methodology used for the statistical analyses were insufficient, especially for older studies. The more recent studies appeared to use some of the PROBAST[22] recommendations and terminology, but they were still far from satisfactory, as demonstrated by the results of the PROBAST assessment (see *Figures 3* and *4*). Moreover, although information on the adjustment strategies and the process of variables' selection was provided in individual studies, the original cohort of potential predictors, prior to the multivariable analysis, was never clearly specified, leading to potential risk of data-mining and, hence, methodological bias.

Similarly, although there was an indication that the addition of biomarkers to existing clinical models might improve the prediction of relevant clinical outcomes, studies varied substantially in terms of study characteristics and statistical methods used to assess prediction, thereby limiting any reliable conclusion.

On the whole, we observed considerable clinical and statistical heterogeneity in all analyses, especially with regard to clinical setting, NGAL threshold levels, time of sample collection, definition of AKI, time of AKI diagnosis, number of AKI events and assay platforms. Therefore, we have limited confidence in the validity and reliability of the observed results.

Chapter 4 Assessment of cost-effectiveness

This chapter assesses the cost-effectiveness of alternative biomarkers (NephroCheck, ARCHITECT urine NGAL and BioPorto urine and plasma NGAL assays) used in combination with standard clinical assessment (i.e. serum creatinine and urine output), compared with standard clinical assessment alone, for evaluating critically ill people who are at risk of developing AKI and are being considered for possible critical care admission in an NHS hospital setting. The specific objectives were to review the existing cost-effectiveness evidence base for these tests and to develop a de novo economic model to assess cost-effectiveness from an NHS and Personal Social Services perspective.

Systematic review of existing cost-effectiveness evidence

Objective

The aim of the review of economic evaluations was to identify, report and critically appraise existing economic evaluations of NephroCheck, ARCHITECT urine NGAL, and BioPorto urine and plasma NGAL assays for evaluating critically ill people (adults and children) at risk of developing AKI.

Search strategies

Comprehensive electronic searches were conducted to identify economic evaluations of the candidate tests. Highly sensitive search strategies were developed, including index terms, free-text words, abbreviations and synonyms. The following electronic databases were searched: Ovid MEDLINE, Ovid EMBASE, NHS Economic Evaluation Database, HTA Database, Research Papers in Economics, and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Presentations Database, with no restriction on date, language or publication type. The searches were undertaken on 27 May 2019, with additional searches on 11 September 2019.

Inclusion and exclusion criteria

Studies were deemed appropriate for inclusion in the review of economic evaluations if they (1) were full economic evaluations, defined as a comparative assessment of costs and outcomes in the framework of cost–utility, cost-effectiveness, cost–benefit or cost-minimisation analyses; (2) assessed the cost-effectiveness of the candidate tests within the population defined in the NICE scope (i.e. critically ill people, both adults and children, at risk of AKI who are being considered for admission to ICUs); and (3) provided sufficient information to judge the quality of the study and obtain any relevant data (i.e. conference abstracts alone were unlikely to meet this criterion). Economic evaluations conducted alongside single effectiveness studies (e.g. RCTs) and decision-analytic models were all deemed relevant for inclusion. Studies were excluded if they were methodological studies, systematic reviews of cost-effectiveness studies (although these were retained for reference) or cost-of-illness studies. Studies were also excluded if they assessed tests/biomarkers outside the NICE scope (e.g. cystatin C) only or used the candidate tests for a purpose other than determining risk of AKI.

Quality assessment of included studies

Included studies were appraised against the NICE reference case for the assessment of cost-effectiveness of diagnostic tests.[96]

Evidence synthesis of cost-effectiveness studies

The main findings are summarised in a narrative review, with key study characteristics and findings tabulated for ease of comparison.

Results

Figure 19 illustrates the PRISMA flow diagram for the review of economic evaluations. The searches identified 125 potentially relevant abstracts. After abstract screening, 99 (79.2%) studies were

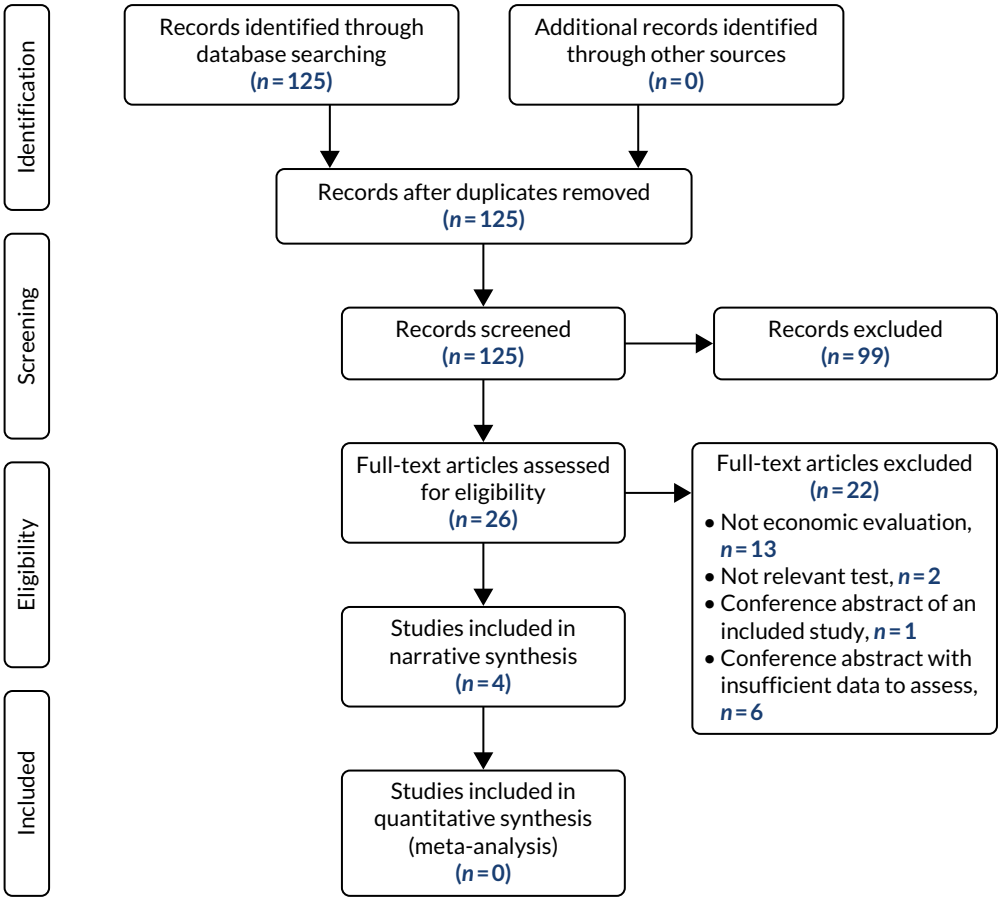

FIGURE 19 The PRISMA flow diagram for the review of cost-effectiveness studies. CA, conference abstract; EE, economic evaluation.

excluded because they did not meet the inclusion criteria. Full-text articles were sought for the remaining 26 (20.8%) studies for further assessment against the inclusion/exclusion criteria. Of those 26 studies, four studies were ultimately included in the review.[95,97–99] A tabulated summary of the study characteristics and results is provided in *Table 13*, and a quality assessment against the NICE reference case is provided in *Table 14*.

Relevance of the included studies for the current decision problem

Of the four studies identified in the review, three conducted cost-effectiveness analyses based on decision-analysis modelling.[97–99] Two of these studies included both a decision tree to capture the diagnostic phase of the model and a Markov cohort model to capture the long-term sequelae of diagnosis and possible prevention of AKI.[97,98] Both modelling strategies were similar and appropriate for the current decision problem in that they modelled the progression of AKI to CKD, end-stage renal disease (ESRD), transplantation and death. Although two studies[97,99] were conducted in the UK, only one study[97] was deemed directly relevant for informing the decision model developed as part of this assessment. Hall *et al.*[97] was also the only study to assess all of the candidate tests specified in the NICE scope. Although Hall *et al.*[97] provide a comprehensive and high-quality assessment of the cost-effectiveness of the relevant tests, the setting of the study relates to AKI occurring in people already admitted to ICUs and is therefore outside the scope of this assessment. Therefore, substantial revision of the Hall *et al.*[97] model is required, particularly for the early acute phase, to generate results that are appropriate for decision-making in critically ill patients who are at risk of AKI and are being considered for possible admission to ICU, but are not yet in the ICU setting.

TABLE 13 Summary of study characteristics and results from the review of economic evaluations

Characteristic	Study			
	Hall *et al.*[97] 2018	Parikh *et al.*[95] 2017	Petrovic *et al.*[98] 2015	Shaw *et al.*[99] 2011
Population	Adults, aged ≥ 18 years	Adults, aged ≥ 18 years, without ESRD or need for RRT	Paediatric, aged ≤ 18 years	Base case: 67-year-old male
Setting	Hospital critical care (all-comers) and post-cardiac surgery subgroup	Hospital (ED) setting, data from two sites	Post cardiac surgery, country unclear (assumed Serbia)	Post cardiac surgery
Objective(s)	• To assess the potential cost-effectiveness of AKI biomarkers • To determine the value of future research	To determine if NGAL can reduce hospital costs	To determine the cost-effectiveness of the candidate tests	To determine the cost-effectiveness of urine NGAL for AKI diagnosis
Country	UK	USA	Unclear (assumed Serbia)	UK
Intervention(s)	AKI biomarkers plus standard care: • NephroCheck • Cystatin C (plasma) • Cystatin C (urine) • Cystatin C (serum) • NGAL (plasma) • NGAL (urine) • NGAL (serum)	Serum creatinine plus NGAL (urine)	• Cystatin C (serum) • NGAL (urine) • uL-FABP	NGAL (urine) plus current practice (monitoring of creatinine, blood urea nitrogen, urine output)
Comparator(s)	Standard care (serum creatinine and urine output testing)	Serum creatinine alone	Serum creatinine alone	Current practice alone
Source of effectiveness/ diagnostic accuracy data	• No direct effectiveness data • Linked-evidence approach • Diagnostic accuracy data obtained from a meta-analysis of diagnostic accuracy studies	N/A (cost only)	• Linked-evidence approach • Selected literature	• Linked-evidence approach • Selected literature
Evaluation type (decision-analytic modelling/RCT)	Decision tree (diagnostic pathway) plus Markov cohort model [long-term outcomes, including CKD, ESRD (with or without dialysis), transplant]	Cost simulation	Decision tree (diagnostic pathway) plus Markov cohort model (long-term outcomes including CKD, ESRD, transplant and death)	Decision tree
Measure of benefit	QALYs	N/A	QALYs	QALYs
Perspective	NHS and PSS	Payer	Third-party payer	NHS perspective (although societal perspective stated)
Cost year	2015 prices	Unclear	Unclear	2008
Time horizon	• Decision tree: 90 days • Markov model: lifetime	Unclear, assume hospital admission duration	Lifetime (maximum age 100 years)	Lifetime

continued

TABLE 13 Summary of study characteristics and results from the review of economic evaluations (*continued*)

Characteristic	Study			
	Hall *et al.*[97] 2018	Parikh *et al.*[95] 2017	Petrovic *et al.*[98] 2015	Shaw *et al.*[99] 2011
Discount rate	• Costs: 3.5% per annum • QALYs: 3.5% per annum	NR	• Costs: 3% per annum • QALYs: 3% per annum	NR
Sensitivity analyses conducted?	Deterministic sensitivity analyses conducted around time horizon, test costs, AKI incidence, impact of early treatment, costs of AKI intervention, ICU utility, diagnostic accuracy, additional mortality risk for false-positive test results, impact of negative test results	Deterministic sensitivity analysis: varying hospital cost, LOS, proportion with baseline CKD, proportion developing a urinary tract infection, costs of further testing	Deterministic sensitivity analysis: incidence of AKI and associated mortality, sensitivity and specificity	Deterministic sensitivity analysis: mainly different treatment effects, also baseline AKI probability, probability of CKD, effect of early intervention on AKI, change in hospital costs, change in diagnostic accuracy, cost per NGAL test
	• PSA conducted: yes	PSA conducted: cost simulation	PSA conducted: yes	PSA conducted: yes
Base-case results (including summary of incremental analyses)	ICERs vs. standard care: • Cystatin C (serum): £11,476 • Cystatin C (urine): £13,449 • NGAL (urine): £13,742 • NGAL (plasma): £13,372 • Cystatin C (plasma): £13,504 • NGAL (serum): £13,828 • NephroCheck: £19,324	Costs vs. standard care: • NGAL urine (site 1): US$408 • NGAL urine (site 2): US$522	ICERs vs. standard care: • uL-FABP: US$5959 • Cystatin C (serum): US$7077 • Urine NGAL: US$9315	ICERs vs. standard care: • Urine NGAL (tx: 12.5% improvement) – dominant • Urine NGAL (tx: 25% improvement) – dominant • Urine NGAL (tx: 50% improvement) – dominant
Sensitivity analysis results	• All test results were sensitive to changes in assumptions around test-guided changes in patient management and associated outcomes resulting from tests driven by diagnostic accuracy. Hall *et al.*[97] discuss the full range of sensitivity analysis results • High degree of uncertainty and feasible assumptions could change conclusions	• Results were most sensitive to the costs in hospital and the assumptions about LOS, additional test requirements and the baseline proportion of the population with CKD • Urine NGAL remained cost-saving for all analyses undertaken	Significant variation in price was not found to affect overall conclusions	Under all conditions, NGAL in addition to current practice was the most cost-effective strategy when compared with current practice alone, even when the treatment effect was minimal. Results were driven by the impact of early intervention on hospital LOS

ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; LOS, length of stay; N/A, not applicable; NR, not reported; PSA, probabilistic sensitivity analysis; PSS, Personal Social Services; tx, clinical improvement in treatment effect; uL-FABP, urinary liver-type fatty acid-binding protein.

TABLE 14 Appraisal of included studies against the NICE reference case[96] and scope[100]

Attribute	Reference case and technology appraisal methods guidance	Study			
		Hall *et al.*[97] 2018	Parikh *et al.*[95] 2017	Petrovic *et al.*[98] 2015	Shaw *et al.*[99] 2011
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	Yes	Yes	Yes
Patient group	As per NICE scope (i.e. critically ill, pre ICU)	No: ICU group of patients outside the NICE scope, which is pre ICU	Partially: the NICE scope includes adults as well as children	Partially; however, the NICE scope is broader than post cardiac surgery only	Partially; however, the NICE scope is broader than post cardiac surgery only
Perspective costs	NHS and Personal Social Services	Yes	No	No	Partially
Perspective benefits	All health effects on individuals	Yes	No	Yes	Yes
Form of economic evaluation	Cost-effectiveness analysis (QALYs)	Yes	No	Yes	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	No	Yes	Unclear
Synthesis of evidence on outcomes	Systematic review	Yes	No	No	No
Outcome measure	QALYs	Yes	N/A	Yes	Yes
Health states for QALY	Described using a standardised and validated instrument (i.e. EQ-5D)	Yes, when possible	N/A	Unclear	Unclear
Benefit valuation	Time trade-off or standard gamble	Yes, when possible	N/A	Unclear	Unclear
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the public	Yes, when possible	N/A	Unclear	Unclear
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	No	No	No
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	N/A	Yes	Yes
Probabilistic modelling	Probabilistic modelling	Yes	Yes	Yes	Yes
Sensitivity analysis	Deterministic sensitivity analyses conducted	Yes	Yes	Yes	Yes

EQ-5D, EuroQol-5 Dimensions; N/A, not applicable.

Additional literature searches

Further searches were conducted to help develop the economic model. Broader searches were carried out to identify existing economic models in the area of AKI in addition to those identified for the candidate biomarker tests. A separate search was also developed for health-state utility data relevant to the health states included in the economic model. As searches for models and parameters were conducted by Hall *et al.*[97] up to 2016, our searches aimed to identify any relevant studies published after this date. Supplementary searches were carried out in MEDLINE, EMBASE, NHS Economic Evaluation Database, HTA Database, Research Papers in Economics, and ISPOR Scientific Presentations. The searches were undertaken on 11 September 2019, with no language restrictions. The relevant data are discussed in the subsections to follow.

Independent assessment of cost-effectiveness

A two-phase model was developed using TreeAge Pro 2018 (TreeAge Software, Inc., Williamstown, MA, USA) to assess the cost-effectiveness of using biomarker tests to help detect the risk of AKI development and to help initiate early preventative care.

As described in *Chapter 3*, there was no direct evidence regarding the clinical effectiveness of biomarker-guided preventative care, compared with standard monitoring-guided preventative care, on final health outcomes (e.g. AKI status, mortality, need for RRT). Therefore, a linked-evidence approach was required to determine the potential value of the tests. The model structure was therefore built to reflect hypothesised associative benefits of averting AKI or reducing its severity through biomarker-guided early intervention. The structure was informed by the review of cost-effectiveness studies and was based largely on Hall *et al.*,[97] who kindly provided access to their model [built in R (The R Foundation for Statistical Computing, Vienna, Austria)] under a Creative Commons licence. The appropriateness of the model structure was validated with the External Assessment Group's (EAG's) clinical experts. Data sources to populate the model are described in the sections that follow. The model was built and analysed following the guidelines stipulated in the NICE reference case for diagnostic test evaluation.[101]

Methods

Relevant population(s)

The baseline population and prevalence of CKD in hospital for the model were obtained from a Grampian population cohort (described in *Model structure: initial decision tree phase*). The model base-case analysis is therefore based on a mixed cohort of CKD and non-CKD patients, with an average age of 63 years, and a 54.3% female population.

Diagnostic biomarkers evaluated

The model aims to assess the cost-effectiveness of the NephroCheck test, the ARCHITECT urine NGAL assay and the BioPorto urine and plasma NGAL assays in combination with standard clinical assessment, compared with standard clinical assessment alone (including serum creatinine and urine output), for evaluating critically ill people at risk of developing AKI who are being assessed for possible critical care admission.

Model structure: initial decision tree phase

The systematic review did not identify any randomised trials providing causal evidence for the effect of biomarker-guided care versus standard monitoring (serum creatinine)-guided care on patient-relevant outcomes such as peak AKI severity, admission to ICU, need for RRT, CKD or mortality.

In the absence of such data, the initial decision tree phase of the model used a linked-evidence approach to capture the potential impact of diagnostic test accuracy (sensitivity and specificity) on the

probability of averting AKI or reducing its severity through earlier adoption of a KDIGO care bundle triggered by a positive biomarker test result. The model then captured possible effects on changes in health outcomes through associative links between AKI severity and the relevant outcomes [need for ICU care, length of stay (LOS), 90-day mortality, and development of CKD].

These associative links have been built up in the decision tree by reanalysis of observational data from Grampian.[102] The data set includes 17,630 adult patients admitted to hospital in Grampian in 2003 and is the complete population of all patients who had an abnormal kidney function blood test on hospital admission, including all patients who developed AKI. The study methodology is described in detail by Sawhney *et al.*,[103] but the data derived from the data set used to populate the model are unpublished. These observational, population-level data were used to define the starting age, sex and underlying proportion of prevalent CKD cases in the modelled cohort. The data were also used to populate the model with respect to the distribution of peak AKI severity, as well as LOS in hospital, probability of admission to ICU and 90-day mortality parameters (by KDIGO AKI stage) for the decision tree phase of the model.

In the decision tree, patients who are critically ill in hospital, are at risk of developing AKI and are having their kidney function monitored are divided into two cohorts, those with AKI and those without AKI, depending on the underlying prevalence.[102,103] The underlying prevalence of AKI was calculated directly from a more recent version of the Grampian data set,[102] describing all hospital admissions with at least one overnight stay in 2012 (for patients having their kidney function monitored). The base-case prevalence of AKI generated from these data was 9.2%, sampled probabilistically from a beta distribution in the model based on count data. A sensitivity analysis uses prevalence data directly from the systematic review studies used to generate the diagnostic test accuracy parameters.

Acute kidney injury is defined in the model as having, or being destined to develop, AKI while in hospital and is classified based on the peak severity of AKI. There is an assumption in the model that it is possible to avert AKI with early biomarker-guided treatment in people who would otherwise develop it under standard care. However, it should be noted that, in some circumstances, it may not be possible to avoid AKI by earlier detection, as AKI may not always be modifiable.[3] The probability of averting AKI is zero in the standard-care arm. AKI is split into four KDIGO-defined stages (stages 1–3), with stage 3 split by the proportion of patients receiving RRT or not. The initial phase of the model describes the associations between peak AKI classification and probability of admission to ICU, LOS in ICU, LOS in hospital and 90-day mortality. These associative effects are all derived from the Grampian population cohort described previously. At the end of the 90 days, costs and QALY payoffs are assigned based on the decision tree pathway followed, before surviving patients enter the Markov cohort model.

The standard-care cohort is assumed to be perfectly identified as having or not having AKI, based on a combination of serum creatinine levels, other diagnostic workup and clinical expert opinion, which represents clinical practice. The hypothesised advantage of the biomarkers is that they may help to detect AKI earlier, but will not detect additional cases of AKI not detected by current practice. *Figure 20* provides an illustration of the initial decision tree pathways for the standard-care arm of the model.

Participants in the intervention (test) arms of the model are similarly split into those with and without AKI, according to the same prevalence data, but all participants receive additional testing. It is assumed that the background diagnostic workup is similar for all arms of the model (i.e. all patients will continue to have their serum creatinine and urine output monitored). As the diagnostic accuracy test data are primarily based on single use of the test, it is assumed, in the base-case model, that each test will be administered only once. It is assumed that the test is administered as soon as possible after a patient has been determined to be at risk of AKI to enable early detection and preventative measures to be implemented. A sensitivity analysis explores the impact of more frequent multiple-use tests on the results.

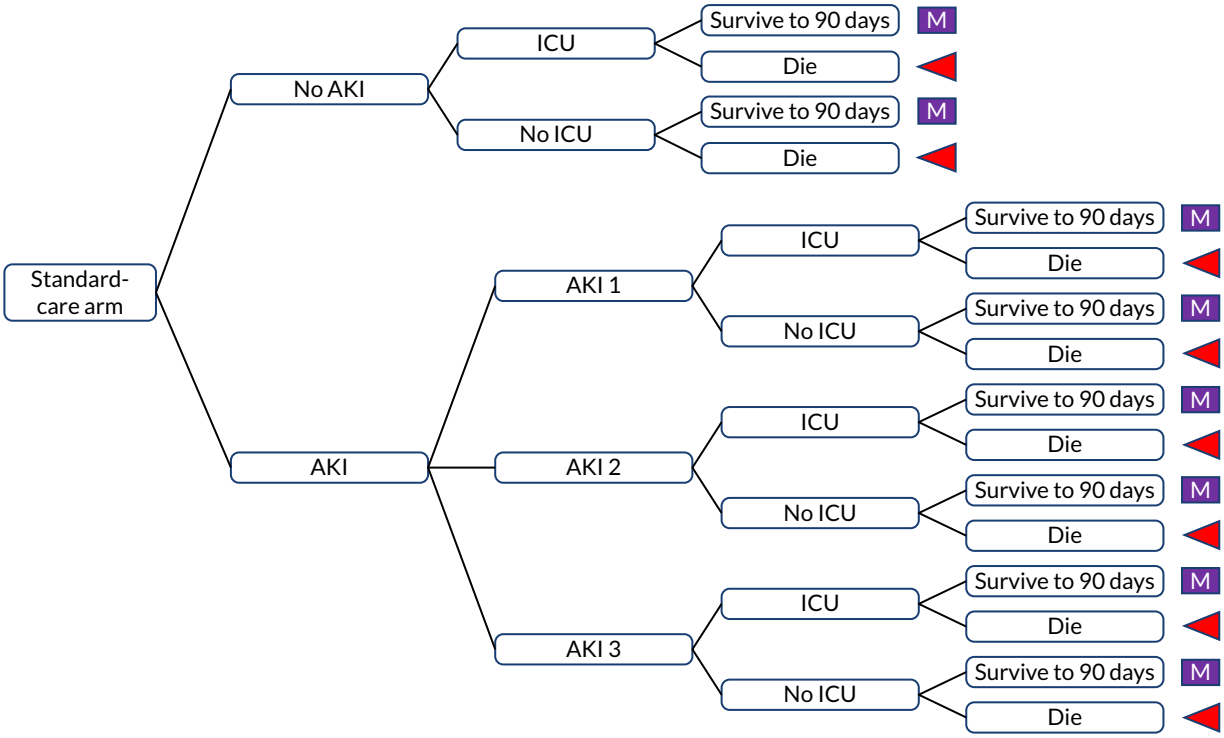

FIGURE 20 Simplified decision tree structure up to 90 days for the standard-care (serum creatinine) arm of the model. Note that the AKI 3 pathway in the model is replicated for the proportion of the cohort receiving acute RRT and those not receiving acute RRT. M, Markov model. Reproduced with permission from Jacobsen *et al.*[104] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

The diagnostic accuracy of the candidate tests in addition to serum creatinine, compared with serum creatinine alone, was obtained from the results of the systematic review and meta-analysis described in *Chapter 3*. *Table 15* describes the diagnostic accuracy parameters, namely sensitivity and specificity, used in the modelling. All diagnostic data are incorporated probabilistically in the model, accounting for the joint uncertainty in sensitivity and specificity for each biomarker test. The logit of the sensitivity/specificity for each of the biomarker tests was derived from the meta-analysis of diagnostic accuracy studies. The model specified the correlation between sensitivity and specificity parameters (on the logit scale). These parameters were converted to Cholesky decomposition matrices, with the decomposed data referenced by multinormal distributions, sampling from the mean and standard error (on the logit scale). The probabilistic draws were back-transformed from the logit scale for application in the model. It should be noted that diagnostic accuracy data obtained from the meta-analyses are based on heterogeneous studies with different thresholds; this is particularly true for the NGAL assays. Therefore, the results of the economic model, particularly for comparisons between different NGAL assays, should be interpreted cautiously. Further details have been provided in *Chapter 3*.

For each biomarker test group, the proportions of true AKI cases that are true positive and false negative are determined by test sensitivity, whereas the proportion of non-AKI cases that are true negatives or false positives are determined by test specificity.

Based on the EAG's own clinical expert opinion (Simon Sawhney and Callum Kaye, University of Aberdeen, 2019, personal communication), it is assumed in the base case that patients testing negative would not have any adaptions made to their care pathway. This is because it would be unlikely that care would be de-escalated based solely on a negative NephroCheck or NGAL result, as the conservative practitioner would wait to ensure that there was no rise in serum creatinine before concluding that no AKI was present and stepping down the patient's care.

TABLE 15 Sensitivity and specificity data used in the model

Test	Parameter	Mean (95% CI)	Mean (logit scale)	Standard error (logit scale)	Correlation for multivariate normal distribution (logit scale)	Source
NephroCheck	Sensitivity	0.75 (0.58 to 0.87)	1.1178	0.3967	−0.824	Meta-analysis (see *Chapter 3*)
	Specificity	0.61 (0.49 to 0.72)	0.4573	0.2567		
BioPorto plasma NGAL	Sensitivity	0.76 (0.56 to 0.89)	1.1563	0.4615	−1.000	Meta-analysis (see *Chapter 3*)
	Specificity	0.67 (0.40 to 0.86)	0.6863	0.5659		
ARCHITECT urine NGAL	Sensitivity	0.67 (0.58 to 0.76)	0.7273	0.2047	−0.5168	Meta-analysis (see *Chapter 3*)
	Specificity	0.72 (0.64 to 0.79)	0.9553	0.1909		
BioPorto urine NGAL	Sensitivity	0.73 (0.65 to 0.80)	1.017	0.195	0.526	Meta-analysis (see *Chapter 3*)
	Specificity	0.83 (0.64 to 0.93)	1.562	0.511		

The model assumes that all patients will receive the KDIGO care bundle once they are defined as AKI positive using current standard practice methods (i.e. monitoring serum creatinine and urine output), regardless of their NephroCheck or NGAL test result. The potential to benefit from use of the biomarkers, therefore, lies in the early adoption of a preventative care bundle. For patients testing positive, the model includes the functionality to reflect uncertainty in clinical decision-making, that is the probability that a positive test would be acted on. This parameter is assumed to take a value of 100%, in accordance with best practice guidance whereby positive biomarker tests should have a preventative KDIGO care bundle implemented, with the associated costs. Although all positive test results will trigger the KDIGO bundle, only those patients whose tests are true positive will accrue any potential benefits of having their AKI averted or having reduced severity (i.e. peak KDIGO stage) AKI. For exploratory scenarios in which a test might not be acted on in practice, the cohort would follow the standard-care pathways according to whether or not they had AKI, as measured using current clinical practice.

There is limited direct evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay, risk of 90-day mortality or development of new/progression of existing CKD). Therefore, a linked-evidence approach was required, whereby we relied on observational associations to infer how prevention or mitigation of AKI may affect changes in health outcomes. The associative effects are the benefits of averting or mitigating AKI that lead to better health outcomes (i.e. need for ICU care, CKD and mortality).

These associations necessitate causal assumptions, but, although a causal link between AKI and poor outcomes is plausible, the extent of this causal relationship is uncertain and controversial. It cannot necessarily be assumed that, by averting or changing the severity of AKI, a patient would have the exact same risks (associative effects from the Grampian observational data described previously) of ICU and mortality as a patient who was never going to develop AKI in the first place.

As the true causal relationship between AKI and health outcomes is unknown, the model includes the functionality to apply none, all or a proportion of the relative risk (RR) of health outcomes such as need for ICU care, mortality and CKD (AKI vs. none) to the AKI-averted proportion of the cohort. This is achieved while maintaining the observational associations in the standard-care arm of the model.

The base-case analysis assumes that there are no adverse health consequences of a false-positive test on either NephroCheck or NGAL. Clinical expert opinion (Simon Sawhney and Callum Kaye, personal communication) indicates that there may be a risk to a patient's health of inappropriate fluid resuscitation; delay of access to appropriate imaging because of concerns regarding contrast exposure; or removal of the most effective, but potentially nephrotoxic, treatments for a critically ill patient. However, the magnitude of this negative effect is difficult to quantify. Therefore, a sensitivity analysis explores scenarios in which an additional mortality risk is added for false-positive tests.

In summary, the early-stage (up to 90 days) costs and outcomes depend on (1) the diagnostic accuracy of the test, (2) clinical decision-making in the presence of positive or negative test results, (3) the initiation of a KDIGO care bundle to avert AKI and amend the distribution of peak AKI severity and (4) the degree to which the hypothesised associative effects between AKI and final health outcomes, such as length of hospital stay, admission to ICU, need for RRT, 90-day mortality and risk of CKD, can be modified simply by amending the AKI distribution.

Model structure: follow-up Markov model

One potential route to patient benefit is that avoiding AKI or reducing its severity may reduce the risk of later developing CKD. As CKD is defined as a minimum of 3 months of persistent reduced renal function,[105,106] progression from AKI to CKD is incorporated into the Markov phase of the model.

Figure 21 illustrates the long-term follow-up model structure.

After 90 days, the surviving cohort from each of the decision tree pathways enters a lifetime Markov model. The model follows a similar structure to those of Hall *et al.*[97] and Parikh *et al.*,[95] with six mutually exclusive health states: outpatient follow-up, CKD (stages 1–4), ESRD not requiring dialysis, ESRD requiring dialysis, post transplant and death. Members of the cohort enter the model either in the outpatient follow-up state, where they experience an annual baseline risk of developing CKD, or directly in the CKD state, with the proportion starting in the CKD state determined by the underlying CKD prevalence and the severity of AKI from the acute (decision tree) phase of the model.

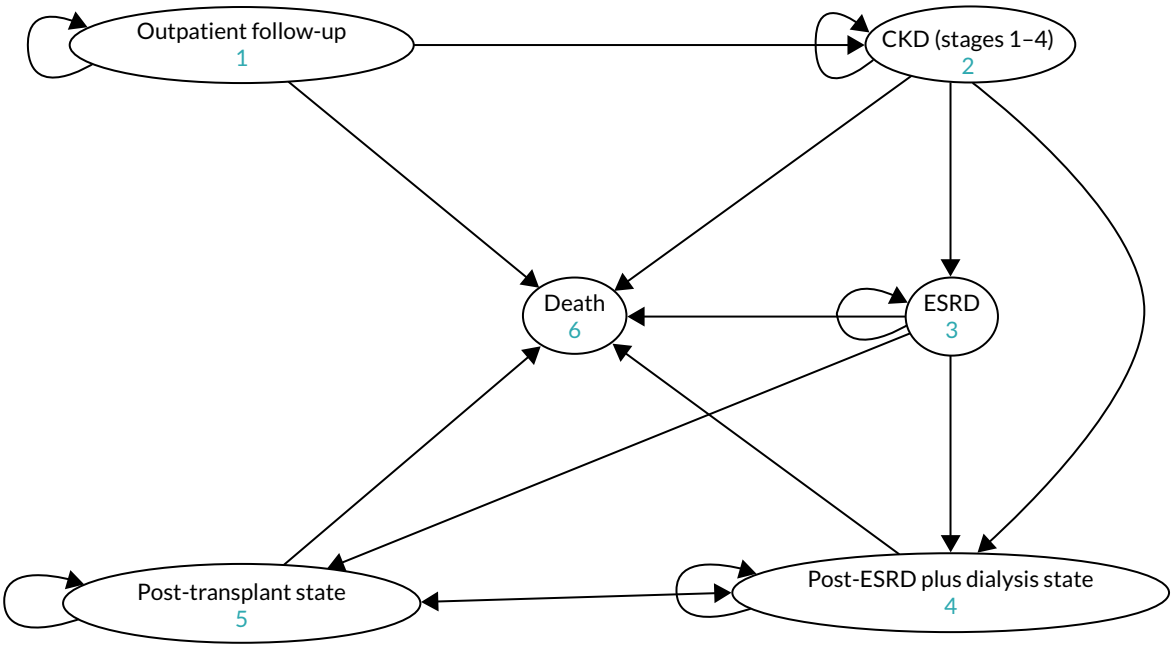

FIGURE 21 Markov model structure. Reproduced with permission from Jacobsen *et al.*[104] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

The base-case model assumes that the outpatient cohort have an increased risk of CKD in the first cycle that is dependent on their AKI experience, but, thereafter, the transition between the outpatient follow-up and CKD states is independent of whether or not a patient had AKI in the hospitalisation period. A sensitivity analysis explores the impact of an increased CKD risk applied for the full lifetime time horizon, as per Hall *et al.*[97]

The cohort is then modelled to transition through the disease pathway, starting with CKD stages 1–4 (defined as a single Markov state), to ESRD, with or without the requirement for dialysis, the need for transplant, the success or failure of that transplant, and, ultimately, progression to death, with state-specific mortality probabilities. Those members of the cohort who experience transplant failure are assumed to return to the dialysis health state, in which the probability of a second transplant is the same as the probability of a first transplant. The cohort is exposed to a probability of all-cause mortality from each model state and assigned mortality probabilities based on the higher value of age- and sex-adjusted all-cause mortality or the disease state-specific mortality obtained from the literature.

Model parameters: probabilities and duration of length of stay

Table 16 summarises the probability, LOS and relative effect size parameters used to populate the economic model. Further details and description are provided in the sections that follow.

TABLE 16 Probability, LOS and RR parameters used in the economic model

Parameter	Mean parameter value	SE	Distribution	Source
Incidence of AKI[a]				
No AKI	0.908		Remainder	Grampian data[107]
Any AKI	0.092	–	Beta (count) ($n = 4314$, $N = 46{,}884$)[b]	Grampian data[107]
AKI 1 (given AKI)	0.687	–	Dirichlet	Grampian data[107]
AKI 2 (given AKI)	0.194	–	Dirichlet	Grampian data[107]
AKI 3 (given AKI)	0.119	–	Dirichlet	Grampian data[107]
Probability of ICU admission				
No AKI	0.014	0.0038	Beta	Grampian data[102]
AKI 1	0.100	0.0254	Beta	Grampian data[102]
RR of ICU admission vs. AKI 1				
AKI 2	1.423	0.1082	LN vs. AKI 1	Grampian data[102]
AKI 3	1.930	0.1096	LN vs. AKI 1	Grampian data[102]
Probability of 90-day mortality				
No AKI	0.049	0.0069	Beta	Grampian data[102]
AKI 1	0.215	0.0347	Beta	Grampian data[102]
RR of 90-day mortality vs. AKI 1				
AKI 2	1.602	0.0640	LN vs. AKI 1	Grampian data[102]
AKI 3	2.151	0.0624	LN vs. AKI 1	Grampian data[102]
Probability of requiring RRT				
No AKI, AKI 1 and 2	0	–	–	Assumption
AKI 3	0.552	–	Beta (count) ($n = 885$, $N = 1603$)	Truche *et al.* 2018[108]

continued

TABLE 16 Probability, LOS and RR parameters used in the economic model (*continued*)

Parameter	Mean parameter value	SE	Distribution	Source
LOS parameters				
Hospital LOS	*Mean*	*Median*		
No AKI	8.1	3	LN	Grampian data[102]
AKI 1	26.3	14	LN	Grampian data[102]
AKI 2	32.4	18	LN	Grampian data[102]
AKI 3	28.4	17	LN	Grampian data[102]
ICU LOS[c]				
No AKI	2	1	LN	Bastin *et al.*[109]
AKI 1	4	2	LN	Bastin *et al.*[109]
AKI 2	8	4	LN	Bastin *et al.*[109]
AKI 3	26	13	LN	Bastin *et al.*[109]
The effects of early adoption of a KDIGO care bundle (RR)[d]				
	Mean RR[e]	*SE log RR*[e]		
Any AKI	0.768	0.094	LN	Meersch *et al.*[110]
AKI 1 (given AKI)	1.232	0.180	LN	Meersch *et al.*[110]
AKI 2 (given AKI)	0.868	0.180	LN	Meersch *et al.*[110]
AKI 3 (given AKI)	0.843	0.356	LN	Meersch *et al.*[110]
Parameters linking AKI and CKD				
	Mean	*SE*		
Prevalence of CKD (starting proportion)	0.1105	–	Beta (count) ($n = 5935$, $N = 53{,}691$)	Grampian data[102]
Baseline incidence of CKD	0.0044	0.0003	Beta	Rimes-Stigare *et al.*[111]
	Mean HR	*Log SE*		
HR of CKD (given AKI 1)	2.32	0.0363	LN	See *et al.*[112]
HR of CKD (given AKI 2)	4.00	0.5656	LN	See *et al.*[112]
HR of CKD (given AKI 3)	7.98	0.9675	LN	See *et al.*[112]
Markov model transition probabilities				
	Mean	*SE*		
Outpatient to CKD	0.0044	0.0003	Beta	Rimes-Stigare *et al.*[111]
CKD to death	0.03	0.002	Beta	Kent *et al.*[113]
CKD (survivors) to ESRD	0.01	0.001	Beta	
CKD (survivors) to ESRD plus dialysis	0.04	0.002	Beta	
Remain with CKD			Remainder	
ESRD to death	0.12	0.005	Beta	Kent *et al.*[113]
ESRD (survivors) to ESRD plus dialysis	0.18	0.006	Beta	
ESRD (survivors) to transplant	0.09	0.004	Beta	
Remain ESRD, no dialysis			Remainder	

TABLE 16 Probability, LOS and RR parameters used in the economic model (*continued*)

Parameter	Mean parameter value	SE	Distribution	Source
	Alpha	*Beta*		
Outpatient to death[f]	No ICU • Year 1: 391 • Years 2–5:[g] 748 ICU • Year 1: 564 • Year 2–5:[g] 964	No ICU • Year 1: 4824 • Years 2–5:[g] 3810 ICU • Year 1: 4651 • Years 2–5:[g] 3322	Beta (count)	Lone *et al.*[114]
ESRD plus dialysis to death	• Year 1: 951 • Year 3: 2116 • Year 5: 2990	• Year 1: 5178 • Year 3: 3988 • Year 5: 3254	Beta (count)	UK Renal Registry (table 1.17)[115]
ESRD plus dialysis to transplant	• Year 1: 417 • Year 3: 1056 • Year 5: 1305	• Year 1: 5712 • Year 3: 5048 • Year 5: 4939	Beta (count)	
Remain in ESRD plus dialysis			Remainder	
Transplant to ESRD plus dialysis	• Year 1: 4 • Year 3: 16 • Year 5: 26	• Year 1: 487 • Year 3: 475 • Year 5: 431	Beta (count)	UK Renal Registry (table 1.17)[115]
Transplant to death	• Year 1: 8 • Year 3: 16 • Year 5: 31	• Year 1: 483 • Year 3: 475 • Year 5: 426	Beta (count)	
Transplant successful			Remainder	

LN, log normal; SE, standard error.

a Note that incidence of AKI data are obtained from the 2012 Grampian cohort, whereas probabilities of ICU admission and 90-day mortality are obtained from an earlier (2003) data set.

b For beta (count) distributions, n = 'number of events' and N = 'total number of observations', with mean parameter estimate calculated as n/N.

c For LOS in ICU, only median LOS information was available. For the purposes of parameterising the LN distribution and to account for the likely skewed nature of the data, it was assumed that the mean was twice the median. This ratio was obtained by dividing the mean LOS reported in Hall *et al.*[97] by the median LOS for all AKI patients in the ICU setting.

d Base case assumes that the impact of NGAL assay-guided care on AKI is the same as that of NephroCheck-guided care. A sensitivity analysis explores a scenario in which a NGAL assay cannot avert AKI.

e Mean RR and SE log RR calculated by the EAG using data from Meersch *et al.*[110]

f Average of ICU and hospitalised (non-ICU) mortality applied in the model base-case analysis.

g Converted to annual cycle-specific probabilities for application in the model.

Early phase probabilities and length of stay

The potential associative links between AKI and ICU admission, ICU LOS, hospital LOS and 90-day mortality are all sourced from the Grampian data set.[102] For chance nodes in the decision tree with only two possible branches, probabilities are sampled from beta distributions. Where there are three or more branches, probabilities are incorporated using Dirichlet distributions.

The model assumes, based on expert opinion, and consistent with Hall *et al.*,[97] that RRT is provided in AKI stage 3 only; this is deemed reflective of most current clinical practice. Assuming no RRT for patients who have a peak AKI of stage 1 or 2 might be considered a favourable scenario for biomarker tests that can reduce AKI severity, thereby generating reductions in cost. In the absence of published UK data, the proportion of AKI stage 3 patients requiring RRT is taken from a retrospective analysis of 5242 ICU survivors with AKI across 23 French ICUs.[108] A total of 1603 of these survivors had KDIGO AKI stage 3, of whom 55.2% received RRT. It is assumed that the French ICU setting is broadly transferable to a UK pre-ICU setting for critically ill patients and is therefore appropriate for populating the model. Data reported from Hall *et al.*[97] are not used because they relate to only a single UK ICU setting with a small sample of patients with AKI 3 patients ($n = 18$). The EAG's clinical experts validated these data as relevant to the UK setting and noted that the probability was lower than that applied in Hall *et al.*,[97] which was consistent with clinical experience outside the ICU setting. Moreover, more detailed data on the need for RRT in England are currently being collected by the UK Renal Registry, but are not yet publicly available.

There are potentially strong associations between AKI status or severity of AKI and the probability of needing ICU care and of dying within 90 days of hospital admission. However, these data should not be interpreted as definitive causative effects and a sensitivity analysis explores the application of different assumptions around these highly uncertain associations.

Data for LOS in hospital are obtained from the Grampian data set,[102] but ICU LOS was unavailable by peak AKI status. ICU LOS data were therefore obtained from an alternative source, Bastin *et al.*,[109] a large cohort study of 1881 adults who had cardiac surgery (and who were, therefore, deemed critically ill and sufficiently matched the scope for this assessment). Bastin *et al.*[109] reported median LOS in ICU by AKI stage (according to AKIN and KDIGO criteria). Given the likely skewed distribution of LOS data, a log-normal distribution fitted to mean and median days' duration is used to generate the simulated draws for the probabilistic analysis. As mean LOS in ICU was not available to parameterise the log-normal distribution, it was assumed that the mean was twice the median, reflecting the ratio of mean to median days' stay as reported in Hall *et al.*,[97] who obtained the data from the Leeds Teaching Hospitals NHS Trust, AKI registry data, for ICU patients.

As the variable 'hospital LOS' also includes the time spent in ICU, the time on a hospital ward is obtained by subtracting the ICU LOS from the total hospital LOS for the application of costs and utilities in the model. As the probabilistic analysis samples independently from these distributions, an additional correction is added to the model to ensure that LOS in an ICU cannot exceed total hospital LOS in any of the sampled draws. The average LOS in hospital/ICU for those with a peak AKI of 3 is applied to both those requiring and those not requiring RRT. The assumption that requirement for RRT would not usually extend the hospital admission for this patient cohort has been validated by the EAG's clinical experts.

The relative effects of diagnostic biomarkers on acute kidney injury and clinical outcomes: the impact of early adoption of a Kidney Disease: Improving Global Outcomes care bundle

The impact of an early Kidney Disease: Improving Global Outcomes care bundle on acute kidney injury

National-level guidelines[16] indicate that, in a patient defined as being at risk of developing AKI through a positive biomarker result, all appropriate efforts should be made to ensure that AKI does not develop, and, if it does, it should be minimised in terms of severity (i.e. providing the maximum support possible

for the kidneys). The model therefore assumes that all AKI patients will receive a KDIGO care bundle; the only difference between the testing strategies is the duration for which that bundle is implemented, with earlier implementation assumed to incur additional resource use in terms of fluid management, nephrologist review and pharmacist review of medications, as well as the removal of any potentially nephrotoxic agents when necessary.[5]

There are two potential mechanisms by which early adoption of a KDIGO care bundle might lead to patient benefit. These are to (1) avert AKI in people in whom it would otherwise develop and (2) shift the distribution of AKI severity (between KDIGO AKI stages 1–3), if AKI occurs.

Hall *et al.*[97] conducted a review of the literature to identify studies testing the impact of early preventative intervention for AKI. Their searches identified eight studies relevant to early intervention in the UK setting (excluding early RRT, which was deemed contentious). Four studies explored the impact of early nephrologist involvement, which was deemed to be the most reflective proxy for the non-specific care bundles that a patient may access as part of the KDIGO care bundle recommendations.[5] The largest of these four studies, with a sample of 1096 participants, was used in the Hall *et al.*[97] economic model, and found that early nephrologist consultation reduced AKI incidence: adjusted odds ratio (early involvement vs. not) 0.71 (95% CI 0.53 to 0.95).

The EAG has conducted a supplementary targeted search of trials for the post-Hall *et al.*[97] period to identify any further potentially relevant studies exploring the impact of early preventative intervention or application of AKI care bundles on the probability of developing AKI and/or the severity of peak AKI. In brief, 39 additional titles and abstracts were identified from the targeted searches, of which 17 (44%) were full-text assessed. Based on the NICE scope,[100] KDIGO care guidelines[5] and clinical expert opinion (Simon Sawhney, University of Aberdeen, 2019, personal communication), it was decided that studies testing the impact of a KDIGO care bundle provided the most appropriate source of data to populate the economic model. Three trials[110,116,117] (18%) assessed the effect of NephroCheck-guided application of a KDIGO bundle compared with standard care where information about the NephroCheck test result was not available to a patient's hospital care team. No studies assessed the impact of NGAL-guided treatment.

All three studies reported results in terms of the probability of developing AKI.[110,116,117] However, only one study[110] described the impact on both the incidence and severity of AKI. Meersch *et al.*[110] reported the results of a single-centre trial, with a sample of 276 participants, in a German setting. All of the population had positive NephroCheck test results, using a 0.3 mg/dl threshold, consistent with the sources of diagnostic accuracy data obtained from the systematic review of diagnostic accuracy studies (see *Chapter 3*). Patients were then randomised to receive a strict implementation of the KDIGO guidelines or standard care. The intervention group included avoidance of nephrotoxic agents, discontinuation of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), close monitoring of urine output, close monitoring of serum creatinine levels, avoidance of hyperglycaemia (for 72 hours), consideration of alternatives to radiocontrast agents, and fluid optimisation. In the control (standard-care) group, Meersch *et al.*[110] state that the recommendations of the American College of Cardiology Foundation 2011 were followed, including keeping mean arterial pressure at > 65 mmHg and central venous pressure at between 8 and 10 mmHg. ACEIs and ARBs were used only when the haemodynamic situation stabilised and hypertension occurred. It is unclear whether or not knowledge of the NephroCheck test result was revealed to the treating hospital team for patients in the standard-care arm of the study. The primary outcome in Meersch *et al.*[110] was 72-hour AKI and the trial found an absolute risk reduction of 16.6% (95% CI 5.5% to 27.99%). The Meersch *et al.*[110] study was supported by the German Research Foundation (Bonn, Germany), the European Society of Intensive Care Medicine (Brussels, Belgium), the Innovative Medizinische Forschung (Münster, Germany) and an unrestricted research grant from Astute Medical, Inc.

A second, smaller study (121 participants),[116] also in a German setting, showed that NephroCheck-guided care demonstrated a trend towards a lower probability of AKI, although the results were not statistically significant, with an OR for standard care versus NephroCheck of 1.96 (95% CI 0.93 to 4.10). The study did,

however, find significantly greater odds of AKI (defined as stage 2 and 3 combined) in the standard care group than in the NephroCheck group: OR for standard care versus NephroCheck 3.43 (95% CI 1.04 to 11.32). A third study,[117] with only 100 participants, compared the effect of a NephroCheck-triggered consultation implementing KDIGO recommendations for AKI with the effect of standard care in an ED in Germany. AKI outcomes were similar in both groups. The probability of AKI stage 2 or 3 at day 1 post admission was 32.1% in the intervention group and 33.3% in the control group; at day 3, it was 38.9% in the intervention group and 39.1% in the control group. Neither the Gӧcze *et al.*[116] study nor the Schanz *et al.*[117] study reports any funding involvement from the test manufacturers.

As the Meersch *et al.*[110] study has a larger sample, and reports data for both the probability of AKI and the distribution of AKI severity, given that it occurs, these data were used for the model base-case analysis. Although the clinical context of the immediate postoperative period after cardiac surgery from Meersch *et al.*[110] is likely to be generalisable between the UK and other countries, the nature of the AKI insult (ischaemia/reperfusion, postoperative haemodynamic, oxidative stress, haemolysis, in people with cardiac comorbidity) is specific to this context, as is acknowledged by the authors. Accordingly, this study[110] may not be generalisable to AKI in the context of other acute or critical illness circumstances in which biomarker performance and the potential for AKI prevention/mitigation may be different.

The model describes the potential impacts of a biomarker-guided care bundle on (1) the chance that patients may develop AKI and (2) the severity of AKI given that it occurs. The assumption is that early biomarker-guided implementation of the KDIGO care bundle may reduce the proportion of people who develop AKI and help ensure that, if they do develop AKI, it will be of reduced severity. These effects are applied probabilistically as RRs in the model for those with true-positive test results only, using log-normal distributions.

In the absence of any data on the impact of NGAL-guided KDIGO care bundles on the probability of developing AKI or the severity of AKI, the base-case model assumes that the potential to avert AKI is similar for both biomarkers. However, based on clinical expert opinion (Simon Sawhney, personal communication) and the manufacturer-described role of the tests, NGAL measures injury and can be used to define AKI, whereas NephroCheck can identify stress, thereby enabling intervention before AKI develops. Therefore, a sensitivity analysis explores a scenario in which the RR of AKI for NGAL-guided care is equal to 1, while retaining the same effect on the AKI distribution, given that AKI occurs as for NephroCheck. It is acknowledged that these assumptions are uncertain, and the sensitivity analysis may present a bias against NGAL if data were to become available to suggest an effect on AKI prevention.

It was assumed that there are no negative health effects of early intervention for the proportion of each test group with false-positive results, but the additional costs of the bundle were still incurred. The model also includes the functionality to explore the impact of an additional mortality risk, for example because of excessive resuscitation as a result of fluid administration or removal of effective, but nephrotoxic, treatments in patients with a false-positive test result.

Although the model describes the impact of biomarker-guided early intervention on the distribution of AKI, it is unclear whether or not these effects translate into final clinical and patient-relevant health outcomes, such as need for ICU care, need for RRT, mortality or the development of CKD. The limited evidence that exists from Meersch *et al.*[110] suggests that, although there is a significant reduction in the primary study outcome of AKI within 72 hours for NephroCheck-guided implementation of a care bundle, compared with standard care (OR 0.483, 95% CI 0.293 to 0.796), this ability to avert AKI was not demonstrated to translate into improvements in a range of clinical and patient-relevant outcomes, including need for RRT therapy in hospital (OR 1.618, 95% CI 0.676 to 3.874), 90-day all-cause mortality (OR 1.213, 95% CI 0.486 to 3.028), ICU LOS (median difference 0 days, 95% CI −1 to 0 days) or hospital LOS (median difference 0 days, 95% CI −1 to 1 days). Although the study

was not powered to detect differences in these outcomes, there are no trends in the data that are suggestive of an effect size. Furthermore, the uncertainty regarding the link between increased resource use and clinical outcomes is emphasised by Wilson *et al.*,[118] who demonstrated in their RCT of an electronic alert system for AKI that an early warning system increases resource use (e.g. renal consultation), but with no evidence that this translates into measurable clinical or patient benefit in terms of mortality or LOS. Indeed, for a subgroup on a surgical ward, the mortality rate was significantly higher in the electronic alert group. As these causal links between AKI and changes in health outcomes are highly uncertain and hypothesised based on observational data in the model, extensive sensitivity analyses are conducted to test the impact of a range of plausible assumptions on cost-effectiveness.

Follow-up phase probabilities

Starting proportions applied in Markov cohorts

One plausible route to patient benefit from averting or reducing the severity of AKI is through the prevention of new CKD and the indirectly associated longer-term progression to ESRD and transplant. It should be noted that the model does not assume a direct effect of peak AKI on ESRD at 90 days; therefore, patients can enter the Markov model in either the outpatient follow-up or CKD (stages 1–4) health states only. A reanalysis of 2012 data from the Grampian cohort[102] indicated that only a very small proportion [13/4314 (≈ 0.03%)] of patients with AKI, almost all of whom had underlying CKD, progressed directly to ESRD at 90 days. Therefore, we assumed no direct transition from the decision tree to the ESRD state in the Markov model. The starting proportions (after 90 days) for each health state are dependent on the decision tree pathway through which the cohort has come, and the peak AKI severity the cohort experienced. The baseline prevalence of CKD in the UK general population has been estimated from Kerr[119] at 6.1%. However, in a group of critically ill, hospitalised patients, this prevalence may be substantially higher. For the base-case analysis, we use the underlying prevalence of CKD in the Grampian data set,[102] calculated as the prevalence of CKD in all hospitalised patients having their kidney function monitored. Multiplying through by the sampling fraction for no CKD (20%) and taking the proportion of CKD/full sample gives the baseline prevalence in this group, calculated as (5935/53,691) × 100% = 11.05%.

Health-state transition probabilities

The baseline incidence of new-onset CKD for the Markov model uses the same source as Hall *et al.*,[97] with an annual probability of progressing from the outpatient state to the CKD state of 0.0044 (95% CI 0.0039 to 0.0049) for patients in the no-AKI cohort.[111] The data are obtained from a large cohort study of 97,782 ICU patients enrolled on the Swedish intensive care register. The parameter value 0.0044 reflects the CKD incidence at 1 year post ICU admission for the proportion of patients with no AKI. The same baseline proportion of CKD was applied for those without AKI and for those modelled to have had AKI averted as a result of early preventative treatment. The proportion of the no-AKI cohort starting in the CKD state at day 90 was calculated as the underlying prevalence plus the new annual incidence, adjusted to the 90-day time horizon of the decision tree component of the model.

Hazard ratios for AKI 1, AKI 2 and AKI 3 on the development of CKD (defined as CKD stage ≥ 3) were obtained from a systematic review by See *et al.*[112] The review included a total of 82 studies quantifying the association between AKI and longer-term renal outcomes (including CKD) and mortality. However, only three studies reported the impact of each stage of AKI on CKD development.[120–122] One study (104,764 participants) in a US setting generated slightly counterintuitive results, with point estimates of the HR reducing as AKI stage increased.[120] However, two other studies in Asian settings (with 77[122] and 1363[121] participants) illustrated an increasing HR for more severe AKI stages. The systematic review has meta-analysed these three studies; the summary effects by AKI stage on CKD, defined as CKD stage 3, are used in the base-case analysis. The advantage of these studies is that they allow a demonstration of the impact of adapting the distribution of AKI severity on longer-term development of CKD. However, they are not conducted in a UK setting and may lack relevance. An alternative source, reporting the HR for the association between AKI and CKD that is constant across all AKI stages,

is reported by Sawhney *et al.*[102] for 9004 hospitalised patients with AKI in Grampian. The HR for development of stage 4 CKD (AKI vs. no AKI) was 2.55 (95% CI 1.41 to 4.64). This study has the advantage of relevance to the setting, but does not include risks by AKI severity. However, it should be noted that the definition of CKD is stage 4 in Sawhney *et al.*,[102] compared with stage 3 in the meta-analysed studies, which may limit the comparability of the reported HRs.

The HRs of CKD by AKI stage are applied to the new incidence over the first 90 days and to the first annual transition in the model. Thereafter, the transition probabilities from outpatient follow-up to CKD follow the baseline 0.0044 per year. This approach is based on expert opinion (Simon Sawhney, personal communication) that any longer-term effect of AKI on CKD development will become attenuated over time, particularly if it has not occurred in the first year following hospital discharge. A sensitivity analysis explores a scenario in which the HR of CKD is applied for the full duration of the model, reflecting the assumption applied in Hall *et al.*[97]

Prevalence of CKD and incidence of new-onset CKD are parameterised in the model using beta distributions, and the HRs for the effect of peak AKI severity on CKD incidence (i.e. transition probabilities to CKD state) are parameterised using log-normal distributions.

Progression from chronic kidney disease

The transition probability from outpatient follow-up to CKD is 0.0044, as described previously. The model cohort can then progress from CKD to ESRD, with or without dialysis, and from ESRD to transplant according to the modelled transition probabilities. It is assumed that AKI can influence only the number of people who get CKD and then has no further direct effect on how fast they progress through the CKD stages to ESRD, dialysis or transplant. The cohort is also exposed to an increasing mortality risk as it progresses through more severe disease states from CKD (stages 1–4) to ESRD without dialysis and ESRD with dialysis. Transitions from CKD (stages 1–4) to ESRD, from ESRD (no dialysis) to ESRD (with dialysis), and from CKD (stages 1–4)/ESRD to death are obtained from Kent *et al.*,[113] who reported data on progression of kidney disease from the large (7246 participants), international (Europe, North America and Australasia) Study of Heart and Renal Protection (SHARP) RCT. The median study follow-up was 4.9 years, participants had a mean age of 63 years and 64% of participants were male.

For those with ESRD on dialysis, the proportions transitioning to kidney transplant and mortality were obtained from 5-year data published in the 2018 UK Renal Registry report (table 1.17),[115] which provided information on transition from incident RRT in 2012 to transplant and mortality 1, 3 and 5 years later. The 3- and 5-year probabilities were annualised; the 3-year probability was applied to years 2 and 3, and the 5-year probability was applied to year 4 onwards. These probabilities were converted to the relevant annual cycle-specific probabilities and applied in the model using tunnel states to track time from entering a given health state. The UK Renal Registry also provided data on the probability of transition back to dialysis for failed transplants and the probability of death over 5 years following transplant. After 5 years post transplant, mortality is assumed to revert to the general population all-cause mortality probability and the annual probability of transplant failure remains at that reported from years 3–5 in the UK Renal Registry. It is further assumed that the proportion of the cohort with a transplant failure return to dialysis, and that their probability of progressing from ESRD on dialysis to a second transplant is the same as the probability of progression to the first transplant.

In the first 5 years of the follow-up phase of the model, mortality in all Markov states is modelled as the average mortality risk for patients discharged from hospital and ICU, unless health state-specific (ESRD, dialysis or transplant) mortality is higher, in which case the latter is applied. If, at any point, mortality falls below all-cause mortality, all-cause mortality is applied in the model. The 5-year post-discharge mortality data were based on Lone *et al.*,[114] a matched UK cohort study (mean age of 60 years) using national registries: the Scottish Intensive Care Society Audit Group, the Scottish

Morbidity Record (SMR) of acute hospital admissions (SMR01) and the Scottish death records. The model base case used an average of the ICU and non-ICU cohorts. Beyond 5 years, patients in the outpatient follow-up health state had the age- and sex-adjusted all-cause mortality probability applied,[123] and those with CKD, ESRD, chronic dialysis or a transplant would be assigned the health state-specific mortality probability, unless the age- and sex-adjusted all-cause mortality was higher than the health state-specific mortality. A sensitivity analysis explores the impact of assigning long-term mortality risks that are dependent on whether or not the cohort had been admitted to ICU during the index hospitalisation.

Transition probabilities are incorporated into the model probabilistically using beta distributions. As the cycle lengths for the model in Hall *et al.*[97] are the same as the current assessment (annual), it was not necessary to provide any further adjustment of the published transition probabilities.

Model parameters: costs

The health-care costs included are as follows: (1) the costs of conducting the tests, including equipment and staff resource use; (2) the costs of acute care in the first 90 days post hospital admission, including the additional cost of early application of a KDIGO care bundle, the cost of hospital/ICU LOS, and the cost of acute RRT; and (3) the annual, cycle-specific costs associated with Markov health states (CKD, ESRD, dialysis and transplant) over the longer-term follow-up phase. All costs are included from an NHS perspective and are reported in 2017/18 Great British pound values. When possible, resource use has been costed directly using 2017/18 UK national unit cost sources [the Personal Social Services Research Unit (PSSRU) for staff time,[124] NHS reference costs for secondary care procedures[125] and the *British National Formulary* for drugs[126]]. When this has not been possible, for example if total costs are reported in the literature without enough data regarding the underlying resource use to enable re-costing, these costs are inflated from their base year to 2017–18 values using the Campbell and Cochrane Economics Methods Group online inflation calculation tool.[127] *Table 17* details the cost parameters used in the economic model. Full details of the costing approach and associated assumptions are provided in the following sections.

TABLE 17 Cost parameters used in the economic model

Parameter	Mean parameter value (£)	Standard error (£)	Distribution	Source
Test costs				
NephroCheck	92.26	–	Applied deterministically	See *Appendix 13*, *Table 31*
BioPorto (urine and plasma) NGAL	59.55	–	Applied deterministically	See *Appendix 13*, *Table 31*
ARCHITECT urine NGAL	66.87	–	Applied deterministically	See *Appendix 13*, *Table 31*
Costs incurred up to 90 days (acute decision tree phase of the model)				
Three days of KDIGO care bundle	106.36	10.64 (mean × 10%)	Gamma	See *Appendix 13*, *Table 32*
Hospital ward setting – daily cost	313	38.27	Gamma	NHS reference costs 2017/18[125]
ICU setting – daily cost	1395	251.38	Gamma	NHS reference costs 2017/18.[125] SD calculated using quartiles published from 2015/16 reference costs inflated to 2018 values[a]

continued

TABLE 17 Cost parameters used in the economic model (*continued*)

Parameter	Mean parameter value (£)	Standard error (£)	Distribution	Source
Excess daily cost of AKI[b]	298	65.65	Gamma	NHS reference costs 2017/18.[125] SD calculated using quartiles published from 2016/17 reference costs inflated to 2018 values[a] (applied in sensitivity analysis only)
Estimated daily cost of RRT[c]	197		Applied deterministically	NHS reference costs 2017/18;[125] assumes 48% on intermittent haemodialysis/52% on continuous haemodialysis, from the 2009 National Confidential Enquiry into Patient Outcome and Death report[3]
Follow-up costs applied in the Markov model (day 90 +)				
Annual follow-up costs for the proportion of the cohort that were not admitted to an ICU during the acute phase[d]				
Year 1	3954	158	Gamma	Lone *et al.*[114]
Year 2	2864	139	Gamma	
Year 3	2547	140	Gamma	
Year 4	2277	129	Gamma	
Year 5	2090	125	Gamma	
Year 6	1794	125 (assumption)	Gamma	Calculation based on Lone *et al.*[114] Costs from year 6 onwards applied in sensitivity analysis only
Year 7	1618	125 (assumption)	Gamma	
Year 8	1465	125 (assumption)	Gamma	
Year 9	1331	125 (assumption)	Gamma	
Year 10	1210	125 (assumption)	Gamma	
Years 11 +	1102	125 (assumption)	Gamma	
Annual follow-up costs for the proportion of the cohort that were admitted to an ICU during the acute phase[d]				
Year 1	6500	198	Gamma	Lone *et al.*[114]
Year 2	4183	163	Gamma	
Year 3	3975	176	Gamma	
Year 4	3774	190	Gamma	
Year 5	3315	172	Gamma	
Year 6	2806	172 (assumption)	Gamma	Calculation based on Lone *et al.*[114] Costs from year 6 onwards applied in sensitivity analysis only
Year 7	2521	172 (assumption)	Gamma	
Year 8	2274	172 (assumption)	Gamma	
Year 9	2056	172 (assumption)	Gamma	
Year 10	1861	172 (assumption)	Gamma	
Years 11 +	1685	172 (assumption)	Gamma	
Health state-specific costs applied in the Markov model				
CKD stages 1–3	453	33.53	Gamma	Kent *et al.*[113]
CKD stage 4	441	14.61	Gamma	Kent *et al.*[113]

TABLE 17 Cost parameters used in the economic model (*continued*)

Parameter	Mean parameter value (£)	Standard error (£)	Distribution	Source
Weighted average (CKD stages 1–4)	446	–	–	–
ESRD (no dialysis)[e]	590	43.84	Gamma	Kent *et al.*[113]
ESRD year 1 (with dialysis)	21,328	209.77	Gamma	Kent *et al.*[113]
ESRD year 2 onwards (with dialysis)	26,203	54.45	Gamma	Kent *et al.*[113]
Functioning transplant year 1	27,636	329.84	Gamma	Kent *et al.*[113]
Transplant follow-up	1290	97.43	Gamma	Kent *et al.*[113]
Additional medication costs applied to health states				
ESRD year 1 (with dialysis)	2601[f]	–	Applied deterministically	NICE guidance 2015[128] and BNF 2019[126]
ESRD year 2 onwards (with dialysis)	2601[f]	–	Applied deterministically	NICE guidance 2015[128] and BNF 2019[126]
Functioning transplant year 1	10,623	–	Applied deterministically	NICE guidance 2015[128] and BNF 2019[126]
Transplant follow-up	9063	–	Applied deterministically	NICE guidance 2015[128] and BNF 2019[126]

BNF, *British National Formulary*.

a Note that it has been necessary to obtain standard errors from older data, as variability in costs are not reported in the 2017/18 NHS reference costs;[125] standard errors are calculated as $SD/\sqrt{N}$.

b Applied in sensitivity analysis as an additional cost over and above the ward/ICU daily cost.

c Assumed three sessions per week for intermittent haemodialysis and one session per day for continuous haemodialysis. Per-day cost calculated as (cost per session × proportion on intermittent haemodialysis × 3 days per week) + (cost per session × proportion on continuous haemodialysis × daily) = [£271 × 0.48 × (3/7)] + (£271 × 0.52 × 1) = £196.67 per day, on average.

d Note that the base-case analysis applies costs averaged for the ICU and hospital (non-ICU) patient cohorts. A sensitivity analysis explores the impact of applying follow-up costs separately for the proportion that require ICU care and hospital care in the initial 90-day phase.

e ESRD reported as CKD stage 5 in Kent *et al.*[113]

f This cost is based on the total annual cost of both erythropoiesis-stimulating agent medication and blood pressure medication (see calculation in *Appendix 13*, *Tables 35* and *36*.

Diagnostic test costs

NephroCheck testing is usually conducted on an Astute140 Meter, costing £3000, and an additional meter would need to be purchased. This cost was converted to an annuity, assuming that the platform's lifetime is 5 years and an annual depreciation rate of 3.5%. The test could also be conducted on a VITROS Immunodiagnostic System, although, currently, there is a limited installed base of these in UK hospitals,[97] which was confirmed at a NICE scoping workshop. The NGAL tests would not require a new platform for NGAL only, because it would be performed on platforms already available at the hospital laboratories. The capital costs of the laboratory analyser apportioned to each NGAL test are assumed to be negligible. The sensitivity analysis excludes capital and training costs to explore the impact on cost-effectiveness of scenarios in which a hospital might already have the required analyser in place and all staff are fully trained in its use.

The process of taking the sample for analysis, sending samples to the laboratory, processing at the laboratory and interpretation of test results would require the involvement of several members of the hospital team. A urine sample is first collected by a nurse, and then picked up by a porter, who takes it to the laboratory. It is assumed that, because the tests are classified as urgent samples, the porter would generally prioritise single test collection for the laboratory. A biomedical scientist conducts the diagnostic test in the laboratory. After completion of the test, the results from the laboratory would be authorised by a biochemist and released for review on the hospital information management system, where they can be interpreted by a nephrologist, an intensive care specialist or a junior doctor. The base-case analysis assumes an average of the three health-care professional costs for interpretation. Under some criteria (such as very abnormal results), a laboratory team might directly contact the care provider, but we assume that this approach would not be used routinely. For the purposes of test cost calculation, it is assumed that, on average, the role of interpreting the tests is equally split across the three specialist team members. The unit costs per hour for each of the staff resources involved in the testing process were obtained from PSSRU 2018:[124] to conduct the test – band 5 nurse (£37.00), porter costed as health-care assistant (£27.26) and band 6 biomedical scientist (£44.00); to interpret the test – medical consultant/nephrologist (£108) and junior doctor foundation year 2 (£32.00). It is assumed that a hospital consultant, nephrologist and junior doctor are all equally likely to be the health-care professional interpreting the test.

The duration of resource use for each member of the team is based on a combination of information provided by the manufacturer and clinical expert opinion (Simon Sawhney and Callum Kaye, personal communication) regarding the flow from obtaining the test sample to result interpretation. The staff time to process the test in the laboratory was based on the NICE request for information documents to the different test manufacturers and the final scope (NICE technical team, 2019, personal communication). Estimates of the time taken to prepare the urine sample and interpret the test were based on the EAG's clinical expert opinion (Simon Sawhney and Callum Kaye, personal communication).

Four test strategies were compared in the economic model: NephroCheck, BioPorto urine NGAL, ARCHITECT urine NGAL and BioPorto plasma NGAL. The NGAL test manufacturer BioPorto has not identified costs separately by sample type (plasma or urine). It is therefore assumed that these tests incur equal costs. The cost of the Alinity i urine NGAL test was not considered in the base-case economic evaluation because the review identified no diagnostic accuracy data for the test. Full costing of each test is provided in *Appendix 13*, *Table 31*. Further details of maintenance costs and consumables for each test can be found in *Appendix 13*, *Table 34*.

Cost of early treatment

The additional cost of early treatment with the KDIGO care bundle was calculated as £106.36 per patient treated, assuming an additional 3 days' application of the care bundle in test-positive patients. An additional 3 days of treatment was assumed in line with the primary outcome from Meersch *et al.*[110] (i.e. AKI at 72 hours) and based on clinical expert opinion (Simon Sawhney and Callum Kaye, personal communication) that a care bundle could be implemented for up to an extra 3 days. The care bundle cost is based on the NICE guidelines for preventing AKI,[16] which state that measures to prevent AKI are avoidance of nephrotoxic agents, discontinuation of medication (ACEIs and ARBs), close monitoring of serum creatinine and urine output, avoidance of hyperglycaemia, alternatives to radiocontrast and close haemodynamic monitoring. The NICE recommendations for preventing AKI[16] include seeking advice from a nephrology team with regard to giving 'iodinated contrast agent to adults with contraindications to intravenous fluids' (© NICE 2013 *Acute Kidney Injury: Prevention, Detection and Management. Clinical Guideline [CG169].*[16] Available from www.nice.org.uk/Guidance/CG169. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication) and from a pharmacist with regards to medications (ACEIs, ARBs). Therefore, both nephrologist and pharmacist time are included in the cost of the care bundle. Further details of the cost

calculation approach can be found in *Appendix 13*, *Table 32*. The additional cost of early adoption of the care bundle was applied to the proportion of the cohort with a positive biomarker test result, reflecting an assumption that care would be delivered for an additional 3 days over and above the cohort monitored using serum creatinine alone. The cost was applied using a gamma distribution with a standard deviation of 10% of the mean.

Acute phase costs

The base-case total cost in the acute phase (90 days) of the model depends on the number of days spent in hospital and the ICU. It also depends on the duration of acute RRT delivered to the proportion of AKI stage 3 patients receiving RRT. For the base-case analysis, data from the Adding Insult to Injury report show that 52% of RRT patients receive continuous RRT (daily) and 48% receive intermittent dialysis (an average of three sessions per week).[3] The duration of RRT delivery is obtained from a randomised trial conducted in a US critical care setting[129] comparing intensive (6 days per week; $n = 563$) with less intensive (3 days per week; $n = 561$) RRT strategies. The mean duration of RRT per patient was similar in both groups: intensive, 13.4 days (SD 9.6 days); $n = 563$; and less intensive, 12.8 days (SD 9.3 days); $n = 561$. The base-case model conservatively assumes the less intensive duration for the application of costs in the economic model. To incorporate the uncertainty and to reflect the likely skewed nature of the distribution, the duration of RRT is incorporated probabilistically into the model using a log-normal distribution. Data available from an alternative source,[130] as used in NICE guidance for the comparison of early and late RRT, were not considered because median, rather than mean, durations were reported and the data were assessed as being of low quality in the NICE guidance.[16] An additional daily excess cost of AKI was applied in a sensitivity analysis to capture the potential excess cost per day in hospital or an ICU of an AKI patient. This excess cost was not applied in the base-case scenarios because it was assumed that the cost of having AKI is captured in the cost of being in hospital or an ICU. All other acute costs and follow-up costs have a gamma distribution applied.

Long-term follow-up costs

There are four ways in which long-term follow-up costs may be driven by the proportion of the cohort that progress through different pathways from the initial decision tree. These are (1) whether or not long-term follow-up costs depend on whether or not a patient received ICU care in the initial decision tree, (2) whether or not there are additional follow-up costs beyond 5 years' post index hospitalisation discharge, (3) whether or not an excess long-term cost is applied for the proportion of the cohort coming through AKI arms of the decision tree and (4) health state-specific costs incurred as the cohort progress through CKD stages to dialysis or transplant.

The outpatient follow-up costs in the Markov model post index hospitalisation discharge were obtained from Lone *et al.*,[114] who reported 5 years of follow-up costs post index ICU and hospital discharge, using a matched cohort obtained from registries in Scotland [Scottish Intensive Care Society Audit Group, the SMR of acute hospital admissions (SMR01) and Scottish mortality data]. The base-case analysis assumes that the average of post-ICU and post-non-ICU admissions is applied in the Markov model. This is because patients in the cohort for this assessment are already deemed to be critically ill and at risk of needing ICU care, so might all be expected to have significant resource use post discharge. A sensitivity analysis allows the application of differential long-term costs that depend on whether or not a patient had received ICU care in the first 90 days.

The annual costs beyond 5 years are unknown. Therefore, the base-case analysis assumes no additional costs beyond year 5. A sensitivity analysis explores the impact of these assumptions by applying further costs between years 6 and 11 that reduce annually following a logarithmic function, with year 11 costs applied for the remaining duration of the model.

The base-case analysis assumes that there are no long-term excess follow-up costs as a result of having had AKI in the initial 90 days post hospitalisation. However, a sensitivity analysis explores a scenario in which patients entering the Markov model having had AKI in hospital incur an additional

15% of the non-AKI cohort costs for the first 5 years. The additional AKI cost factor was based on a proxy using the RR reported in Lone *et al.*[114] on the number of admissions that patients on RRT had over 5 years, compared with those who were not on RRT. These additional costs are applied in the model as a sensitivity analysis, with a mean ratio of 1.15, log standard error 0.074, sampling from a log-normal distribution.

Annual cycle-specific health-state costs were applied to the proportion of the cohort transitioning through the CKD, ESRD, ESRD on dialysis and transplant health states. Costs were obtained from Kent *et al.*,[113] using data from the SHARP trial reporting outpatient, day case and inpatient admissions. The CKD (stages 1–4) health-state cost applied in the model was calculated as the weighted average of CKD stages 1–3 and CKD stage 4, as reported in Kent *et al.*[113] Therefore, the average weighted cost applied was £445.98 per cycle. The cost of medications (immunosuppressants for transplant patients, erythropoiesis-stimulating agents for dialysis patients and blood pressure medications for dialysis patients) were not captured in the study; therefore, these costs were added to the costs observed in Kent *et al.*[113] The added transplant costs (immunosuppressants) were based on the approach applied in Scotland *et al.*[131] for calculating the annual cost of immunosuppressants, using 2018 prices. The added costs to dialysis patients arising from blood pressure medications and erythropoiesis-stimulating agents are also based on the approach applied in Scotland *et al.*,[131] with 2018 prices.

Health measurement and valuation

Table 18 summarises the utilities used throughout the economic model. These are described in more detail in the sections that follow. A full list of studies and utility values considered for population of the economic model can be found in *Appendix 13*, *Tables 33*, *37* and *38*.

Acute (decision tree) phase of the model

We have updated the searches from Hall *et al.*[97] to identify studies that report utilities for the initial decision tree phase of the model. Our post-Hall *et al.*[97] review identified four further potentially relevant studies. However, the only utilities that meet the NICE reference case are those proposed by Hall *et al.*[97] All other studies identified from the literature review use non-UK value sets, so are not appropriate for UK decision-making. Given that there are no appropriate utility studies for AKI stage, the analysis uses the utilities identified in Hall *et al.*[97] applied to the model based on LOS in hospital, LOS in ICU and duration discharged prior to 90 days following hospital admission. Owing to a lack of appropriate data and to avoid double-counting the utility impact of time in hospital/ICU, we have not attempted to apply any additional utility decrements by AKI stage (other than those on acute RRT). The application of utilities is consistent with that used by Hall *et al.*,[97] with utilities age- and sex-adjusted when possible, with normal and beta distributions used to incorporate the data probabilistically in the model. It is difficult to find utility values for patients in an ICU. Two systematic reviews were consulted: one by Dritsaki *et al.*[139] and one by Gerth *et al.*[140] Both reviews focused on a population admitted to an ICU; however, no studies identified in the reviews were deemed suitable. Therefore, the utility value of an unconscious patient has been applied for the duration of ICU stay, using data sourced from Kind *et al.*[132] and following the same approach as Hall *et al.*[97] As a sensitivity analysis, we consider an alternative approach to calculate ICU utility to explore the substantial uncertainty in this parameter. The alternative value takes the average of the unconscious state (−0.402 from Kind *et al.*[132]) and the average post-ICU discharge from Hernández *et al.*[133] from the Pragmatic Randomised, Controlled Trial of Intensive Care follow up programmes in improving Longer-term outcomes from critical illness (PRaCTICaL) (0.44), which followed up a cohort of ICU survivors reporting their quality of life using the EuroQol-5 Dimensions (EQ-5D) instrument. The calculated utility value applied in the sensitivity analysis was $[(-0.402 + 0.44)/2] = 0.019$.

TABLE 18 Health-state utility values used in the economic model

Parameter	Mean parameter value from source	Standard error	Age-adjusted utility applied in the model	Distribution	Source
Utilities applied in the acute (decision tree) phase of the model					
ICU[a]	−0.402	0.02	−0.402	Normal	Kind *et al.*[132] (appendix B)
Ward	0.44	0.0259	0.432	Beta	Hernández *et al.*[133]
Discharge	0.62	0.0268	0.608	Beta	Hernández *et al.*[133]
Acute dialysis decrement[b]	−0.11	0.02	−0.11	Beta	Wyld *et al.*[134]
Death	0	–	0	–	
Utilities applied in the chronic (Markov) phase of the model					
Post discharge (year 1)	0.666	0.016	0.655	Beta	Cuthbertson *et al.*[135]
Post discharge (years 2–4)	0.701	0.016	0.689	Beta	Cuthbertson *et al.*[135]
Post discharge (year 5 onwards)	0.677	0.017	0.665	Beta	Cuthbertson *et al.*[135]
CKD (stages 1–4)[c,d]	–	–	0.575	Beta	Nguyen *et al.*[136]
ESRD[d]	–	–	0.396	Beta	Nguyen *et al.*[136]
ESRD: haemodialysis[e]	0.560	0.033	0.551	Beta	Liem *et al.*;[137] Ara and Brazier[138]
ESRD: peritoneal dialysis[e]	0.580	0.043	0.564	Beta	Liem *et al.*[137]; Ara and Brazier[138]

a Assumed standard error equal to 5% of the mean utility for an unconscious patient.
b Decrement applied to utility in ward only.
c A weighted average utility value (with proportions based on Nguyen *et al.*[136]) across the CKD stages 1–4.
d The study reports utility decrements only; the mean utility applied in the model is back-calculated using the utility decrement from Nguyen *et al.*[136] applied to age- and sex-adjusted UK general population norms.
e For application in the model, the ESRD (dialysis) utility is applied as the weighted average utility based on the proportion of long-term dialysis delivered as haemodialysis and peritoneal dialysis, obtained from the UK Renal Registry report.[115]

Utility values for the chronic phase of the model

First, the Hall *et al.*[97] HTA programme assessment and economic model for long-term follow-up post AKI and the Scotland *et al.*[131] assessment for NICE of multiple-frequency bioimpedance devices to guide fluid management in people with CKD undergoing dialysis were consulted to obtain appropriate health-state utility values for application in the model. Hall *et al.*[97] conducted a thorough review of the literature prior to 2016 for utility parameters. The authors identified two systematic reviews of utility data that provided data that could be used in the economic model. The first, a systematic review and meta-regression published by Wyld *et al.*,[134] predicted utility according to treatment (transplant, dialysis, pre treatment, conservative management). This model predicted an EQ-5D utility value of 0.64 for patients on dialysis and an EQ-5D utility value of 0.75 for transplant patients. The utilities from Wyld *et al.*[134] were used in the Hall *et al.*[97] model.

However, a limitation of Wyld *et al.*[134] is that some of the EQ-5D scores were calculated from mapping algorithms and the age to which the mean utility estimates applied was not reported. The earlier systematic review by Liem *et al.*[137] restricted a meta-analysis to those studies using the EQ-5D index directly for each modality of chronic RRT, and reported the pooled mean age and sex distribution for the corresponding pooled EQ-5D values.

In addition to the two reviews identified by Hall *et al.*,[97] a further structured literature search was conducted to obtain any more recent utility studies that match the NICE DAP reference case (i.e. studies that included EuroQol-5 Dimensions, three-level version, data for UK patients, valued using UK general population tariffs). A range of databases were searched for English language, full-text publications, published between 2016 (end data of Hall *et al.*[97] searches) and 2019. Seven publications were identified that were deemed to meet the NICE reference case for the DAP; specifically, they reported EQ-5D-based utilities valued in accordance with the UK general population preference-based value sets. Studies in which the EQ-5D was administered to a non-UK population but the results were valued according to the UK tariff were also included.

The age- and sex-matched EQ-5D UK population norms were calculated using an equation published by Ara and Brazier[141] and used to derive age-/sex-adjusted utility multipliers from the raw pooled estimates, based on the age and sex distribution of the source studies.[138] The utility of the proportion of the cohort having a successful transplant is assumed to revert to that of the outpatient follow-up state. All utility data were incorporated into the model probabilistically using beta distributions.

Time horizon and discounting

The model was run over a lifetime time horizon, up to age 100 years (for a cohort with a starting age of 63 years in the model). The lifetime time horizon was chosen to ensure that all of the long-term costs and consequences of AKI-induced CKD were captured, including the long-term health effects of ultimate progression to ESRD, transplant and death. The cycle length for the model was annual, and half-cycle corrections have been applied to costs and utilities. All costs and outcomes accruing beyond the first yearly cycle of the model were discounted at a rate of 3.5% per annum, in line with the NICE reference case. The discount rate was varied between 0% and 6% in deterministic sensitivity analyses.

Analyses

The model calculated the expected costs and expected QALYs over the lifetime of each cohort. This includes the costs and QALYs incurred in the first 90-day acute phase of the model, based on diagnostic test accuracy, preventative action to avert AKI, resultant peak AKI status and requirement for admission to an ICU. It also includes the longer-term extrapolations from the Markov cohort model, simulating the long-term transitions between progressive stages of CKD for those who develop it.

The model is fully probabilistic to simultaneously describe the impact of all parameter uncertainty on the model results. All model parameter estimates are sampled from their assigned distributions, as described in the preceding sections, using 1000 simulations. When it was not possible to derive a distribution, for example when insufficient information existed to determine the SD of the distribution, it was assumed that the SD of a parameter was equal to 10% of its mean, unless otherwise stated.

Results are reported as cost–utility analyses, in terms of incremental cost per QALY, expressed as the incremental cost-effectiveness ratio (ICER). Test strategies are plotted on the cost-effectiveness frontier. Tests are ranked in ascending order of benefit (QALYs), with results reported for all tests incrementally against each other to enable the exclusion of strictly dominated (less beneficial and more costly) alternatives from the ICER calculations. ICERs versus standard care are also reported. Results from the probabilistic analysis simulations are plotted using cost-effectiveness acceptability curves based on the net benefit calculation to identify the optimal diagnostic testing strategy at different threshold values of willingness to pay for a QALY.

Model validation

The economic model was checked for errors using the approach suggested by Tappenden and Chilcott,[142] which specified verification tests. Components of the model tested were the estimation of the costs and QALYs, distributions of model parameters and other general tests for accuracy of the implementation of input parameters. No specific issues were identified through the verification tests.

Results

The model was developed and configured to assess the cost-effectiveness of the NephroCheck test, the ARCHITECT urine NGAL assay, the BioPorto urine NGAL test and the BioPorto plasma NGAL test in combination with standard clinical assessment, compared with standard clinical assessment alone.

There is no direct evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay, risk of 90-day mortality or development of new/progression of existing CKD). Accordingly, the cost-effectiveness results are based on a linked-evidence approach whereby we have relied on observational associations to infer how prevention or mitigation of AKI may affect changes in health outcomes. These associations necessitate causal assumptions, but, although a causal link between AKI and poor outcomes is plausible, the extent of this causal relationship is uncertain and controversial. The cost-effectiveness results are therefore presented for a range of alternative, but potentially plausible, scenario analyses, ranging from a set of optimistic assumptions whereby biomarker-guided care bundles may lead to substantial improvements in health outcomes (need for ICU, CKD, mortality) to a set of more conservative assumptions where change in AKI status has no effect on health outcomes. It is likely that the true estimate of cost-effectiveness lies somewhere between these two extremes.

Furthermore, the model includes the following key assumptions:

- The model base-case analysis is run for a mixed cohort of CKD and non-CKD patients, average age 63 years, 54.3% female, based on the characteristics of hospitalised patients in Grampian, Scotland, who have at least a one-night hospital stay and are having their kidney function monitored, and so are deemed to be at risk of AKI.
- It is assumed that NephroCheck and NGAL can rise at similar time points; in the absence of any evidence to suggest otherwise, it is assumed that the time gain, relative to serum creatinine, in terms of early implementation of a KDIGO care bundle is equal for both.
- The base-case analyses assume that there are no adverse consequences, in terms of health effects, of false-positive or false-negative test results compared with standard care. False-positive results would incur the additional futile application of the care bundle costs, and clinical expert opinion (Simon Sawhney and Callum Kaye, personal communication) indicates that false negatives will be monitored until the negative test result is confirmed and would represent current practice without biomarkers. However, there is some concern that a false-positive test may lead to unnecessary fluid resuscitation, especially if encountered by inexperienced clinicians, which could lead to an increased mortality risk, although the magnitude of that risk is unknown. A sensitivity analysis explores this.
- For the Markov models, it is assumed that a patient can develop CKD linked to the index AKI event for the first cycle of the model only, reflecting a total exposure time to increased CKD risk of 1 year + 90 days. Thereafter, the background risk of developing CKD in the population is applied.
- It is assumed that the proportion of the cohort that experience graft failure post transplant return to the 'ESRD on dialysis' health state, where they are exposed to the same risks of transition to transplant/death as when they first entered the dialysis state.
- For the proportion of the cohort that do not develop long-term CKD, the base-case models assume that the longer-term follow-up costs and mortality risks are not dependent on events in the acute phase of the model (i.e. AKI severity and associated ICU admission). A sensitivity analysis explores the impact of applying additional costs and mortality risks for those admitted to ICU in the acute phase of the model.
- The model is run for a lifetime time horizon or 100 years, whichever comes first, with costs and QALYs discounted at an annual rate of 3.5% per annum.

Evidence from Meersch *et al.*[110] shows that NephroCheck-guided early implementation of a KDIGO care bundle can avert AKI. However, the impact of NGAL-guided implementation of a care bundle is unknown. Therefore, two alternative base-case assumptions are considered. The first assumes that

NGAL and NephroCheck have the same potential to avert AKI (based on Meersch *et al.*[110]). The second assumes that NGAL can reduce the severity of AKI (also from Meersch *et al.*[110]), but cannot prevent it from occurring. The rationale for the latter analysis is that NGAL detects injury to the kidneys, whereas NephroCheck can potentially detect stresses on the kidneys and may offer an earlier warning of impending AKI. The two base-case models and a range of scenario analyses conducted around important model assumptions are described in *Table 19*. A total of 15 scenario analyses are reported on each of these two plausible base-case configurations to illustrate the significant uncertainty in the cost-effectiveness findings. *Table 20* reports the results for scenarios in which NGAL can avert AKI, and *Table 21* reports results of scenarios in which NGAL cannot avert AKI. The results of additional scenario analyses requested by NICE are provided in *Appendix 14* for completeness.

TABLE 19 Base-case model configuration and scenario analyses

Parameter/ assumptions	Value	Base-case justification/source	Sensitivity/scenario analyses	Scenario analysis reference
Alternative base-case assumptions				
Potential for biomarker tests to avert AKI (vs. standard care)	RR AKI 0.77	Based on Meersch *et al.*[110]	• Base case 1: applied to all tests • Base case 2: applied to NephroCheck only	• Base case 1: NGAL and NephroCheck can both avert AKI • Base case 2: only NephroCheck can avert AKI
Scenario analyses applied to base case 1 and base case 2				
Proportion of the RR of ICU admission (AKI vs. none) that can be achieved by averting AKI	0.5	Based on clinical expert opinion[a]	Varied between 0 and 1	• Scenario B: averting AKI leads to no improvement in health outcomes; reducing AKI severity leads to full associative effects on health outcomes • Scenario C: averting or reducing severity of AKI leads to no improvement in health outcomes • Scenario D: averting or reducing severity of AKI leads to full improvement in health outcomes
Proportion of the HR of CKD (AKI vs. none) that can be achieved by averting AKI	1	Based on clinical expert opinion[a]/ See *et al.*[112]	Varied between 0 and 1	
Proportion of the RR of 90-day mortality (AKI vs. none) that can be achieved by averting AKI	0	Based on Meersch *et al.*,[110] who show effects on AKI, but not on mortality. Similar data from Wilson *et al.*[118]	Varied between 0 and 1	
Proportion of the difference in hospital and ICU LOS (AKI vs. none) that can be achieved by averting AKI	0.5	Based on clinical expert opinion[a]	Varied between 0 and 1	
Impact of AKI stage on hospital and ICU LOS	Duration applied by AKI stage	Based on observational data from Grampian[102]	Duration assumed not to vary by stage, with same durations applied to all AKI stages based on average from Grampian observational data[102]	

TABLE 19 Base-case model configuration and scenario analyses (*continued*)

Parameter/ assumptions	Value	Base-case justification/source	Sensitivity/scenario analyses	Scenario analysis reference
Impact of AKI stage on the probability of ICU admission	Probability applied by AKI stage	Based on observational data from Grampian[102]	Probability assumed not to vary by stage, with same probability applied to all AKI stages based on average from Grampian observational data[102]	
Impact of AKI stage on the probability of developing CKD	HR applied by AKI stage	Based on systematic review and meta-analysis from See *et al.*[112]	HR assumed not to vary by stage, with same HR applied to all AKI stages, based on Sawhney *et al.*[102]	
Impact of AKI stage on the probability of 90-day mortality	Average probability applied for all AKI stages	Based on a lack of evidence that changing AKI severity can affect mortality directly, as per Meersch *et al.*[110]	Probabilities applied by AKI stage to explore uncertainty in this assumption	
AKI excess cost per day in hospital/ICU	No excess cost applied	Conservative approach to ensure avoidance of double-counting	Additional hospital excess bed-day cost applied as per Hall *et al.*[97] to all patients	Scenario E: as per scenario D with additional AKI costs
The following analyses are applied to the base-case configuration (scenario A)				
Additional costs per day on RRT	Yes	Based on HRG costs	No additional costs of RRT	Scenario F
Impact of AKI on long-term follow-up costs beyond 90 days	None (ratio = 1)	Conservative assumption	All long-term Markov model costs multiplied by 1.15, as per Hall *et al.*[97]	Scenario G: differential long-term outpatient cost and mortality applied according to whether or not patient entered ICU
Long-term outpatient follow-up costs, up to 5 years	Average of hospitalised and ICU patients	Based on average of two cohorts from Lone *et al.*[114]	Differential cost streams applied for 5 years according to whether or not cohort was admitted to ICU in first 90 days, based on Lone *et al.*[114]	
Long-term outpatient follow-up costs, after 5 years	No additional costs applied	Assumption that patients surviving post ICU to 5 years will incur no further excess costs	Additional annual costs applied for full lifetime, based on extrapolation of Lone *et al.*[114] data, applied separately to those who had an ICU admission and those who had no ICU admission at index hospitalisation	
Impact of ICU admission on long-term mortality	Average of hospitalised and ICU patients	Lone *et al.*[114]	Differential mortality applied according to whether or not cohort was admitted to ICU	

continued

TABLE 19 Base-case model configuration and scenario analyses (*continued*)

Parameter/ assumptions	Value	Base-case justification/source	Sensitivity/scenario analyses	Scenario analysis reference
Duration by which AKI event can affect excess CKD risk	1 year + 90 days	Assumption	Assume additional risk of CKD development over full lifetime time horizon	Scenario H
Discount rate (cost)	3.5%	NICE methods guide[96]	Varied 0–6%	• Scenario I (0%) • Scenario J (6%)
Discount rate (QALY)	3.5%	NICE methods guide[96]	Varied 0–6%	
Source of AKI prevalence data	9.2%	Grampian data[102] for hospitalised patients at risk of AKI	Alternative source: obtained directly from systematic review studies	Scenario K
Number of times test is used	1	Based on NICE scope	All tests conducted twice	Scenario L
RR of 90-day mortality for false-positive test results	1	Assumes no additional risk of unnecessary fluid resuscitation	Apply an additional RR of 1.5 to explore impact on results	Scenario M
Test capital and training costs in test cost	Included	As per company advice	Exclude in sensitivity analysis, assuming all capital equipment required is available for all tests (including NephroCheck)	Scenario N
Source of ICU utility data	–0.402	Kind *et al.*[132] (unconscious patient)	Average of unconscious patient (–0.402) and utility at discharge from ICU reported in the PRaCTICaL trial (Hernandez *et al.*[133])	Scenario O
Long-term outpatient utility	Varies by year	Long-term utility implication of hospitalisation/ICU, based on Hall *et al.*[97]	General population norms, assuming quicker recovery	Scenario P
Source of diagnostic accuracy data	All comers	All	Exploratory analysis applying available test accuracy data for children to the adult model	Scenario Q

HRG, Healthcare Resource Group.
a Simon Sawhney, personal communication.

TABLE 20 Scenario analyses assuming that the NGAL tests can avert AKI

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Scenario 1A: preferred base case assuming an associative effect of averting and mitigating AKI								
Test 3 (BioPorto urine NGAL)	22,887	–	6.07332	–	–	Dominant	43.5	54.6
Test 2 (BioPorto plasma NGAL)	22,900	£14	6.07332	0.00001	£2,694,918	Dominant	11.1	47.6
Standard care (serum creatinine)	22,901	Dominated	6.07296	Dominated	Dominated	–	45.1	–
Test 4 (ARCHITECT urine NGAL)	22,912	Dominated	6.07328	Dominated	Dominated	£32,131	0.1	41.4
Test 1 (NephroCheck)	22,938	Dominated	6.07332	Dominated	Dominated	£101,456	0.2	31.9
Scenario 1B: applying the full associative effect on the redistributed cohort only and assuming that the test affects the probability of dying at 90 days								
Standard care (serum creatinine)	22,829	–	6.08377	–	–	–	57.5	–
Test 3 (BioPorto urine NGAL)	22,937	£108	6.08602	0.00226	£47,877	£47,877	30.4	42.5
Test 4 (ARCHITECT urine NGAL)	22,951	Dominated	6.08584	Dominated	Dominated	£58,813	0.0	37.3
Test 2 (BioPorto plasma NGAL)	22,951	£14	6.08608	0.00006	£228,616	£52,816	11.9	39.5
Test 1 (NephroCheck)	22,988	Dominated	6.08604	Dominated	Dominated	£70,141	0.2	31.0
Scenario 1C: no associative effect								
Standard care (serum creatinine)	23,340	–	6.07257	–	–	–	100.0	–
Test 3 (BioPorto urine NGAL)	23,420	Dominated	6.07257	Dominated	Dominated	Dominated	0.0	0.0
Test 2 (BioPorto plasma NGAL)	23,436	Dominated	6.07257	Dominated	Dominated	Dominated	0.0	0.0
Test 4 (ARCHITECT urine NGAL)	23,437	Dominated	6.07257	Dominated	Dominated	Dominated	0.0	0.0
Test 1 (NephroCheck)	23,473	Dominated	6.07257	Dominated	Dominated	Dominated	0.0	0.0

continued

TABLE 20 Scenario analyses assuming that the NGAL tests can avert AKI (*continued*)

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Scenario 1D: full associative effect								
Standard care (serum creatinine)	22,959	–	6.08383	–	–	–	0.7	–
Test 3 (BioPorto urine NGAL)	23,013	£54	6.11006	0.02623	£2052	£2052	40.7	99.3
Test 2 (BioPorto plasma NGAL)	23,028	£15	6.11091	0.00084	£17,702	£2538	47.5	99.1
Test 4 (ARCHITECT urine NGAL)	23,031	Dominated	6.10799	Dominated	Dominated	£2981	1.1	98.8
Test 1 (NephroCheck)	23,065	Dominated	6.11064	Dominated	Dominated	£3955	10.0	97.7
Scenario 1E: as per scenario 1D, but applying a daily excess AKI cost to patients in hospital/ICU								
Test 3 (BioPorto urine NGAL)	23,638	–	6.11049	–	–	Dominant	38.6	99.2
Test 2 (BioPorto plasma NGAL)	23,650	£12	6.11104	0.00055	£21,968	Dominant	43.8	98.9
Test 4 (ARCHITECT urine NGAL)	23,664	Dominated	6.10823	Dominated	Dominated	Dominant	2.0	98.9
Standard care (serum creatinine)	23,681	Dominated	6.08377	Dominated	Dominated	–	0.8	–
Test 1 (NephroCheck)	23,687	Dominated	6.11102	Dominated	Dominated	£210	14.8	98.7
Scenario 1F: exclude RRT cost								
Test 3 (BioPorto urine NGAL)	23,258	–	6.07092	–	–	Dominant	39.5	49.9
Standard care (serum creatinine)	23,266	Dominated	6.07060	Dominated	Dominated	–	49.8	–
Test 2 (BioPorto plasma NGAL)	23,271	£14	6.07093	0.00001	£1,403,330	£17,694	10.0	44.9
Test 4 (ARCHITECT urine NGAL)	23,282	Dominated	6.07089	Dominated	Dominated	£54,497	0.3	39.0
Test 1 (NephroCheck)	23,309	Dominated	6.07092	Dominated	Dominated	£132,748	0.4	29.5

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at £20,000	Probability (%) of being cost-effective at £20,000 vs. standard care
Scenario 1G: apply the differential long-term follow-up costs and mortality according to whether or not a patient entered an ICU								
Test 3 (BioPorto urine NGAL)	30,290	–	6.56602	–	–	Dominant	50.2	99.5
Test 2 (BioPorto plasma NGAL)	30,296	£7	6.56605	0.00003	£227,069	Dominant	39.7	99.1
Test 1 (NephroCheck)	30,335	Dominated	6.56605	Dominated	Dominated	Dominant	8.1	97.2
Test 4 (ARCHITECT urine NGAL)	30,337	Dominated	6.56591	Dominated	Dominated	Dominant	1.4	98.6
Standard care (serum creatinine)	30,606	Dominated	6.56457	Dominated	Dominated	–	0.5	–
Scenario 1H: apply an excess CKD risk for those who experienced an AKI event over the full lifetime time horizon								
Test 3 (BioPorto urine NGAL)	23,201	–	6.07247	–	–	Dominant	54.8	76.5
Test 2 (BioPorto plasma NGAL)	23,212	£12	6.07251	0.00005	£254,012	Dominant	20.3	73.0
Test 4 (ARCHITECT urine NGAL)	23,228	Dominated	6.07234	Dominated	Dominated	Dominant	0.6	68.4
Test 1 (NephroCheck)	23,251	Dominated	6.07250	Dominated	Dominated	Dominant	1.0	58.2
Standard care (serum creatinine)	23,254	Dominated	6.07086	Dominated	Dominated	–	23.3	–
Scenario 1I: 0% discount rate applied to both costs and QALYs								
Test 3 (BioPorto urine NGAL)	27,644	–	8.20147	–	–	Dominant	44.3	57.9
Test 2 (BioPorto plasma NGAL)	27,657	£13	8.20149	0.00001	£996,593	Dominant	13.5	51.4
Standard care (serum creatinine)	27,664	Dominated	8.20095	Dominated	Dominated	–	41.6	–
Test 4 (ARCHITECT urine NGAL)	27,668	Dominated	8.20143	Dominated	Dominated	£9262	0.2	47.4
Test 1 (NephroCheck)	27,694	£37	8.20149	0.00000	£48,020,759	£56,351	0.3	37.4

continued

TABLE 20 Scenario analyses assuming that the NGAL tests can avert AKI (*continued*)

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Scenario 1J: 6% discount rate applied to both costs and QALYs								
Test 3 (BioPorto urine NGAL)	20,961	–	5.11682	–	–	Dominant	39.7	49.9
Standard care (serum creatinine)	20,969	Dominated	5.11654	Dominated	Dominated	–	49.4	–
Test 2 (BioPorto plasma NGAL)	20,974	£13	5.11683	0.00001	£1,295,058	£16,259	10.4	44.2
Test 4 (ARCHITECT urine NGAL)	20,984	Dominated	5.11680	Dominated	Dominated	£55,509	0.3	39.5
Test 1 (NephroCheck)	21,011	Dominated	5.11683	Dominated	Dominated	£145,369	0.1	30.6
Scenario 1K: apply alternative source for AKI prevalence (average prevalence of 0.2332 across systematic review studies)								
Test 3 (BioPorto urine NGAL)	23,050	–	5.85835	–	–	Dominant	42.3	79.0
Test 2 (BioPorto plasma NGAL)	23,055	£5	5.85837	0.00002	£256,153	Dominant	30.7	77.3
Test 4 (ARCHITECT urine NGAL)	23,084	Dominated	5.85827	Dominated	Dominated	Dominant	1.2	75.2
Test 1 (NephroCheck)	23,093	£39	5.85837	0.00000	£20,956,862	Dominant	5.0	69.3
Standard care (serum creatinine)	23,225	Dominated	5.85742	Dominated	Dominated	–	20.7	–
Scenario 1L: increase the number of times test is conducted to two								
Standard care (serum creatinine)	22,811	–	6.07532	–	–	–	70.3	–
Test 3 (BioPorto urine NGAL)	22,853	£41	6.07567	0.00035	£118,796	£118,796	19.9	28.9
Test 2 (BioPorto plasma NGAL)	22,865	£13	6.07567	0.00001	£2,201,973	£152,384	9.7	25.4
Test 4 (ARCHITECT urine NGAL)	22,884	Dominated	6.07564	Dominated	Dominated	£227,155	0.1	19.2
Test 1 (NephroCheck)	22,936	£71	6.07567	0.00000	£69,489,954	£350,812	0.0	12.4

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at £20,000	Probability (%) of being cost-effective at £20,000 vs. standard care
Scenario 1M: apply an additional risk of mortality to those with a false-positive test (RR 1.5)								
Test 1 (NephroCheck)	22,522	–	5.93563	–	–	£3072	0.0	0.0
Test 2 (BioPorto plasma NGAL)	22,545	£22	5.95376	0.01813	£1240	£3344	0.0	0.0
Test 4 (ARCHITECT urine NGAL)	22,630	£86	5.97629	0.02253	£3814	£3238	0.0	0.0
Test 3 (BioPorto urine NGAL)	22,718	£88	6.01026	0.03397	£2582	£3576	0.1	0.10
Standard care (serum creatinine)	22,954	£235	6.07608	0.06582	£3576	–	99.9	–
Scenario 1N: exclude capital and training costs in test costs								
Test 3 (BioPorto urine NGAL)	22,952	–	6.07161	–	–	Dominant	39.6	51.7
Standard care (serum creatinine)	22,964	Dominated	6.07126	Dominated	Dominated	–	47.9	–
Test 2 (BioPorto plasma NGAL)	22,965	£13	6.07163	0.00001	£999,957	£2229	12.2	45.6
Test 4 (ARCHITECT urine NGAL)	22,975	Dominated	6.07159	Dominated	Dominated	£35,302	0.0	40.5
Test 1 (NephroCheck)	23,002	Dominated	6.07162	Dominated	Dominated	£105,799	0.3	31.4
Scenario 1O: apply alternative ICU utility value (average of −0.402 and 0.44)								
Test 3 (BioPorto urine NGAL)	23,020	–	6.07328	–	–	Dominant	42.4	53.9
Standard care (serum creatinine)	23,032	Dominated	6.07296	Dominated	Dominated	–	45.9	–
Test 2 (BioPorto plasma NGAL)	23,033	£13	6.07329	0.00001	£1,565,836	£1487	11.0	47.4
Test 4 (ARCHITECT urine NGAL)	23,044	Dominated	6.07326	Dominated	Dominated	£39,666	0.2	41.3
Test 1 (NephroCheck)	23,071	Dominated	6.07329	Dominated	Dominated	£118,201	0.5	30.2

continued

TABLE 20 Scenario analyses assuming that the NGAL tests can avert AKI (*continued*)

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Scenario 1P: alternative outpatient utility source in the long term (apply general population norms)								
Test 3 (BioPorto urine NGAL)	23,149	–	7.05770	–	–	Dominant	41.8	53.5
Standard care (serum creatinine)	23,161	Dominated	7.05712	Dominated	Dominated	–	45.8	–
Test 2 (BioPorto plasma NGAL)	23,161	£12	7.05771	0.00002	£779,444	£1133	11.3	47.1
Test 4 (ARCHITECT urine NGAL)	23,172	Dominated	7.05765	Dominated	Dominated	£22,019	0.4	41.1
Test 1 (NephroCheck)	23,199	Dominated	7.05771	Dominated	Dominated	£65,271	0.5	33.6
Scenario 1Q: applying diagnostic test accuracy data for children to the adult AKI model (exploratory only)[a]								
Standard care (serum creatinine)	22,952		6.07678				55.1	
Test 4 (ARCHITECT urine NGAL)	22,957	£5	6.07709	0.00031	£15,835	£15,835	24.2	43.3
Test 3 (BioPorto urine NGAL)	22,968	£11	6.07713	0.00004	£260,525	£45,510	20.6	40.4

a Diagnostic accuracy data were not available for NephroCheck and BioPorto plasma NGAL.

Note
Tests were ranked in ascending order of costs. Strictly dominated tests (i.e. those that generate higher costs for lower QALYs) were then excluded from ICER calculations.

TABLE 21 Scenario analyses assuming that the NGAL tests cannot avert AKI

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Scenario 2A: alternative base case assuming that NephroCheck is the only test that can lead to averted AKI								
Standard care (serum creatinine)	22,978	–	6.07277	–	–	–	64.5	–
Test 1 (NephroCheck)	23,016	£38	6.07313	0.00036	£105,965	£105,965	29.7	32.0
Test 3 (BioPorto urine NGAL)	23,049	Dominated	6.07290	Dominated	Dominated	£539,041	5.3	11.0
Test 2 (BioPorto plasma NGAL)	23,064	Dominated	6.07290	Dominated	Dominated	£633,846	0.3	7.3
Test 4 (ARCHITECT urine NGAL)	23,065	Dominated	6.07289	Dominated	Dominated	£725,061	0.0	6.3
Scenario 2B: applying the full associative effect on the redistributed cohort only and assuming that the test affects the probability of dying at 90 days								
Standard care (serum creatinine)	22,947	–	6.08411	–	–	–	36.8	–
Test 3 (BioPorto urine NGAL)	23,033	£87	6.08912	0.00502	£17,290	£17,290	34.4	53.7
Test 4 (ARCHITECT urine NGAL)	23,049	Dominated	6.08875	Dominated	Dominated	£22,071	0.4	43.7
Test 2 (BioPorto plasma NGAL)	23,050	£17	6.08934	0.00022	£75,026	£19,717	11.1	48.9
Test 1 (NephroCheck)	23,101	Dominated	6.08615	Dominated	Dominated	£75,634	17.3	31.4
Scenario 2C: no associative effect								
Standard care (serum creatinine)	23,012	–	6.07534	–	–	–	100.0	–
Test 3 (BioPorto urine NGAL)	23,094	£82	6.07534	Dominated	Dominated	Dominated	0.0	0.0
Test 2 (BioPorto plasma NGAL)	23,110	£16	6.07534	Dominated	Dominated	Dominated	0.0	0.0
Test 4 (ARCHITECT urine NGAL)	23,110	Dominated	6.07534	Dominated	Dominated	Dominated	0.0	0.0
Test 1 (NephroCheck)	23,145	Dominated	6.07534	Dominated	Dominated	Dominated	0.0	0.0

continued

TABLE 21 Scenario analyses assuming that the NGAL tests cannot avert AKI (*continued*)

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Scenario 2D: full associative effect								
Standard care (serum creatinine)	23,114	–	6.08592	–	–	–	0.7	–
Test 3 (BioPorto urine NGAL)	23,199	Extendedly dominated	6.09125	Extendedly dominated	Extendedly dominated	£15,974	0.5	55.8
Test 2 (BioPorto plasma NGAL)	23,214	Extendedly dominated	6.09137	Extendedly dominated	Extendedly dominated	£18,364	0.3	50.3
Test 4 (ARCHITECT urine NGAL)	23,215	Dominated	6.09080	Dominated	Dominated	£20,721	0.0	46.0
Test 1 (NephroCheck)	23,223	£109	6.11360	0.02768	£3941	£3941	98.5	99.1
Scenario 2E: as per scenario 2D, but applying a daily excess AKI cost to patients in hospital/ICU								
Standard care (serum creatinine)	23,729	–	6.08549	–	–	–	0.7	–
Test 1 (NephroCheck)	23,730	£1	6.11261	0.02712	£29	£29	98.8	99.1
Test 3 (BioPorto urine NGAL)	23,815	Dominated	6.09063	Dominated	Dominated	£16,615	0.5	54.0
Test 4 (ARCHITECT urine NGAL)	23,830	Dominated	6.09020	Dominated	Dominated	£21,436	0.0	45.1
Test 2 (BioPorto plasma NGAL)	23,831	Dominated	6.09079	Dominated	Dominated	£19,153	0.0	49.9
Scenario 2F: exclude RRT cost								
Standard care (serum creatinine)	22,779	–	6.07846	–	–	–	68.1	–
Test 1 (NephroCheck)	22,823	£43	6.07882	0.00036	£119,317	£119,317	27.7	29.6
Test 3 (BioPorto urine NGAL)	22,850	Dominated	6.07859	Dominated	Dominated	£533,230	3.8	9.0
Test 2 (BioPorto plasma NGAL)	22,865	Dominated	6.07859	Dominated	Dominated	£633,002	0.4	6.8
Test 4 (ARCHITECT urine NGAL)	22,867	Dominated	6.07858	Dominated	Dominated	£730,093	0.0	5.6

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at £20,000	Probability (%) of being cost-effective at £20,000 vs. standard care
Scenario 2G: apply the differential long-term follow-up costs and mortality according to whether or not patient entered an ICU								
Test 1 (NephroCheck)	30,438	–	6.55843	–	–	Dominant	97.2	97.2
Standard care (serum creatinine)	30,712	Dominated	6.55697	Dominated	Dominated	–	2.8	–
Test 3 (BioPorto urine NGAL)	30,776	Dominated	6.55733	Dominated	Dominated	£181,324	0.0	15.4
Test 2 (BioPorto plasma NGAL)	30,790	Dominated	6.55733	Dominated	Dominated	£217,350	0.0	11.8
Test 4 (ARCHITECT urine NGAL)	30,793	Dominated	6.55730	Dominated	Dominated	£249,264	0.0	9.3
Scenario 2H: apply an excess CKD risk for those who experienced an AKI event over the full lifetime time horizon								
Test 1 (NephroCheck)	23,172	–	6.07060	–	–	Dominant	55.5	57.7
Standard care (serum creatinine)	23,174	Dominated	6.06893	Dominated	Dominated	–	39.9	–
Test 3 (BioPorto urine NGAL)	23,231	Dominated	6.06947	Dominated	Dominated	£106,920	3.6	21.2
Test 2 (BioPorto plasma NGAL)	23,246	Dominated	6.06948	Dominated	Dominated	£132,282	1.0	16.6
Test 4 (ARCHITECT urine NGAL)	23,250	Dominated	6.06942	Dominated	Dominated	£154,900	0.0	12.7
Scenario 2I: 0% discount rate applied to both costs and QALYs								
Standard care (serum creatinine)	27,689	–	8.20138	–	–	–	60.5	–
Test 1 (NephroCheck)	27,717	£28	8.20191	0.00053	£52,565	£52,565	34.1	36.6
Test 3 (BioPorto urine NGAL)	27,757	Dominated	8.20157	Dominated	Dominated	£371,108	4.9	12.7
Test 2 (BioPorto plasma NGAL)	27,771	Dominated	8.20157	Dominated	Dominated	£439,959	0.4	9.5
Test 4 (ARCHITECT urine NGAL)	27,774	Dominated	8.20155	Dominated	Dominated	£500,966	0.1	7.0

continued

TABLE 21 Scenario analyses assuming that the NGAL tests cannot avert AKI (*continued*)

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Scenario 2J: 6% discount rate applied to both costs and QALYs								
Standard care (serum creatinine)	21,153	–	5.11027	–	–	–	67.1	–
Test 1 (NephroCheck)	21,192	£40	5.11055	0.00028	£140,771	£140,771	27.4	30.7
Test 3 (BioPorto urine NGAL)	21,221	Dominated	5.11037	Dominated	Dominated	£686,941	4.7	10.8
Test 2 (BioPorto plasma NGAL)	21,235	Dominated	5.11038	Dominated	Dominated	£808,828	0.8	8.0
Test 4 (ARCHITECT urine NGAL)	21,238	Dominated	5.11036	Dominated	Dominated	£937,507	0.0	6.3
Scenario 2K: apply alternative source for AKI prevalence (average prevalence 0.2332 across systematic review studies)								
Test 1 (NephroCheck)	23,014	–	5.85682	–	–	Dominant	63.1	67.0
Standard care (serum creatinine)	23,122	Dominated	5.85589	Dominated	Dominated	–	28.4	–
Test 3 (BioPorto urine NGAL)	23,171	Dominated	5.85623	Dominated	Dominated	£142,617	6.7	33.2
Test 2 (BioPorto plasma NGAL)	23,183	Dominated	5.85624	Dominated	Dominated	£174,191	1.8	30.1
Test 4 (ARCHITECT urine NGAL)	23,188	Dominated	5.85620	Dominated	Dominated	£211,691	0.0	26.1
Scenario 2L: increase the number of times test is conducted to two								
Standard care (serum creatinine)	22,746	–	6.07904	–	–	–	88.8	–
Test 3 (BioPorto urine NGAL)	22,873	Extendedly dominated	6.07916	Extendedly dominated	Extendedly dominated	£1,053,861	1.9	2.6
Test 1 (NephroCheck)	22,875	£129	6.07939	0.00035	£369,737	£369,737	9.0	9.4
Test 2 (BioPorto plasma NGAL)	22,888	Dominated	6.07916	Dominated	Dominated	£1,167,690	0.3	1.5
Test 4 (ARCHITECT urine NGAL)	22,898	Dominated	6.07915	Dominated	Dominated	£1,370,281	0.0	0.7

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at £20,000	Probability (%) of being cost-effective at £20,000 vs. standard care
Scenario 2M: apply an additional risk of mortality to those with a false-positive test (RR 1.5)								
Test 1 (NephroCheck)	22,533	–	5.93052	0.00000	–	£3062	0.0	0.0
Test 2 (BioPorto plasma NGAL)	22,632	£99	5.94584	0.01532	£6478	£2644	0.0	0.0
Test 4 (ARCHITECT urine NGAL)	22,715	£83	5.97024	0.02440	£3389	£2464	0.0	0.0
Test 3 (BioPorto urine NGAL)	22,809	£94	6.00383	0.03360	£2801	£2297	0.0	0.0
Standard care (serum creatinine)	22,963	£155	6.07124	0.06740	£2297	–	100.0	–
Scenario 2N: exclude capital and training costs in test costs								
Standard care (serum creatinine)	22,987	–	6.08128	–	–	–	65.1	–
Test 1 (NephroCheck)	23,025	£39	6.08162	0.00035	£111,620	£111,620	29.4	32.2
Test 3 (BioPorto urine NGAL)	23,051	Dominated	6.08139	Dominated	Dominated	£546,618	4.5	12.6
Test 2 (BioPorto plasma NGAL)	23,066	Dominated	6.08140	Dominated	Dominated	£663,328	1.0	9.3
Test 4 (ARCHITECT urine NGAL)	23,069	Dominated	6.08138	Dominated	Dominated	£766,927	0.0	6.1
Scenario 2O: apply alternative ICU utility value (average of −0.402 and 0.44)								
Standard care (serum creatinine)	23,234	–	6.07749	–	–	–	67.2	–
Test 1 (NephroCheck)	23,274	£41	6.07783	0.00034	£120,580	£120,580	28.0	29.9
Test 3 (BioPorto urine NGAL)	23,302	Dominated	6.07761	Dominated	Dominated	£586,840	4.4	11.0
Test 2 (BioPorto plasma NGAL)	23,317	Dominated	6.07761	Dominated	Dominated	£696,184	0.4	8.1
Test 4 (ARCHITECT urine NGAL)	23,319	Dominated	6.07760	Dominated	Dominated	£796,431	0.0	6.2

continued

TABLE 21 Scenario analyses assuming that the NGAL tests cannot avert AKI (*continued*)

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Scenario 2P: alternative outpatient utility source in the long term (apply general population norms)								
Standard care (serum creatinine)	22,867	–	7.05869	–	–	–	63.5	–
Test 1 (NephroCheck)	22,904	£36	7.05928	0.00059	£61,809	£61,809	32.0	34.1
Test 3 (BioPorto urine NGAL)	22,938	Dominated	7.05889	Dominated	Dominated	£360,613	4.3	9.9
Test 2 (BioPorto plasma NGAL)	22,954	Dominated	7.05889	Dominated	Dominated	£431,098	0.2	7.8
Test 4 (ARCHITECT urine NGAL)	22,955	Dominated	7.05887	Dominated	Dominated	£483,707	0.0	5.7
Scenario 2Q: applying diagnostic test accuracy data for children to the adult AKI model (exploratory only)[a]								
Standard care (serum creatinine)	23,012		6.07121				91.0	
Test 4 (ARCHITECT urine NGAL)	23,093	£80	6.07132	0.00011	£713,879	£713,879	6.5	8.8
Test 3 (BioPorto urine NGAL)	23,114	£21	6.07134	0.00001	£1,477,906	£801,274	2.5	7.0

a Diagnostic accuracy data were not available for NephroCheck and BioPorto plasma NGAL.
Tests were ranked in ascending order of costs. Strictly dominated tests (i.e. those that generate higher costs for lower QALYs) were then excluded from ICER calculations.

Scenarios 1A and 2A describe two potential base-case analyses on which all the sensitivity analyses are conducted. These scenarios assume that there is a potential benefit of averting or having less severe AKI, in terms of improved outcomes (need for ICU care, risk of CKD and LOS), but the magnitude of that benefit may be less than that observed in observational data. Given the lack of direct evidence demonstrating the impact of biomarker tests on mortality, the base case assumes that there is no impact on 90-day mortality of averting AKI.

Scenarios B–E illustrate the impact of assumptions around the magnitude of the associative benefits of averting/experiencing less severe AKI on health outcomes. Scenarios F–P explore the impact of applying alternative follow-up costs and mortality, CKD projection, discount rate, alternative source data for AKI prevalence, test costs, excess mortality risk because of a false-positive result, and alternative utility sources.

The results are highly uncertain, with no clear optimal biomarker strategy. The findings are highly sensitive to each of the associative links applied between AKI and health outcomes, namely probability of ICU admission, LOS in hospital, probability of dying at 90 days and the risk of developing CKD.

In scenarios in which NGAL tests are assumed to be equally as effective as NephroCheck at averting AKI, the BioPorto urine NGAL test generally has the greatest probability of cost-effectiveness. This is because the main drivers of the relative cost-effectiveness of each of the biomarker tests against each other are the cost of the test and the diagnostic accuracy. The BioPorto urine NGAL test is slightly cheaper and the meta-analysis shows it as having slightly better diagnostic accuracy in the all-comers cohort. However, these findings should be interpreted cautiously because of the heterogeneity in the diagnostic test accuracy studies, which leads to further uncertainty in the cost-effectiveness results.

Conversely, the NephroCheck and ARCHITECT urine NGAL test are never the most cost-effective strategy when assuming that all tests are equally efficacious in averting AKI, because they are more costly tests, with comparatively poorer diagnostic accuracy. NephroCheck is estimated to have poorer specificity than the NGAL urine tests, thereby generating additional costs of treating false-positive test cases, who unnecessarily receive a KDIGO care bundle. However, under the alternative base-case assumptions, in which the NGAL tests are assumed to have no effect on averting AKI, the probability of NephroCheck being the most cost-effective test rises considerably. In the most optimistic scenario, NephroCheck is 100% cost-effective. In the most pessimistic scenario, standard care is the most cost-effective strategy.

Applying a daily excess cost of AKI in hospital or ICU (i.e. if the cost incurred by patients with AKI is not fully captured in the hospital/ICU daily cost) results in the tests being even more favourable than in the base case because more costs are offset by averting AKI or having less severe AKI in the test arms. This results in the NGAL tests being dominant and NephroCheck being cost-effective (ICER of $< £20{,}000$) compared with standard care.

The ARCHITECT urine NGAL test is generally less likely to be cost-effective in all scenarios because of the test accuracy and cost. The ARCHITECT urine NGAL test is estimated to have lower sensitivity and specificity than the other tests, and costs more than the other NGAL tests.

In general, the results are also sensitive to the assumptions on having hospital-/ICU-specific follow-up costs and mortality (instead of an average of the two); increased long-term cost of AKI, including the linked effect between AKI and probability of CKD for the whole duration of the model (instead of for one cycle, as in the base-case); and using an alternative source of AKI prevalence data (with higher prevalence), with all scenarios favouring the test strategies, making them increasingly more cost-effective than standard care. In most of these cases, the BioPorto urine NGAL test is the most cost-effective test strategy; however, in the most optimistic scenario, the BioPorto plasma NGAL test is the most cost-effective choice of test. On the other hand, assuming that a false-positive test result can lead

to an increased risk of mortality at 90 days (i.e. RR 1.5) favours standard care, which becomes the strategy with the highest probability of cost-effectiveness.

We have included an exploratory analysis in which the limited available diagnostic accuracy data for children are applied in the adult model. Diagnostic accuracy data were available for only two biomarkers (ARCHITECT urine NGAL and BioPorto urine NGAL). The following diagnostic accuracy estimates were included in this run of the model: BioPorto urine NGAL – sensitivity 0.77 (95% CI 0.70 to 0.84) and specificity 0.47 (95% CI 0.40 to 0.54); ARCHITECT urine NGAL – sensitivity 0.68 (95% CI 0.53 to 0.80) and specificity 0.79 (95% CI 0.63 to 0.89).

This analysis should be considered as speculative only, as to ensure a robust assessment of cost-effectiveness among children would require the reconfiguration of the model for a paediatric cohort, with appropriate care pathways and age-specific risks of transition between health states.

In summary, the results are highly uncertain and it is impossible to ascertain the most likely ICER given the available evidence. The range of ICERs across different plausible sets of assumptions is substantial and the probabilistic analyses indicate substantial uncertainties regarding the optimal test strategy. Any of the scenarios explored might be feasible, so it is important to consider these findings in the light of the substantial uncertainty underlying the impact of the tests on AKI and the causative links between AKI and changes in health outcomes. The substantial heterogeneity in the study populations for the diagnostic accuracy data for the candidate tests raises further concerns about the relative cost-effectiveness of the comparators in the absence of head-to-head trial comparisons across multiple candidate tests.

Cohort traces from the base-case Markov models

Figure 22 shows the Markov traces for the standard-care arm of the model under base case 1 assumptions. In the standard-care arm, at 10 years, the mortality for the cohort aged 63 years was 45% for the no-AKI cohort and 59% for the average of the AKI 1, 2 and 3 cohorts. The mortality for the no-AKI group is consistent with the observed 10-year mortality in the Grampian data.[102] However, the mortality observed for the AKI cohorts at 10 years is lower than in the observational data from Grampian. This is because we did not apply an additional AKI-specific excess mortality risk beyond the first year of follow-up in the model, as to assume that such an additional risk is directly caused by AKI is questionable, based on existing evidence (e.g. Meersch *et al.*[110]).

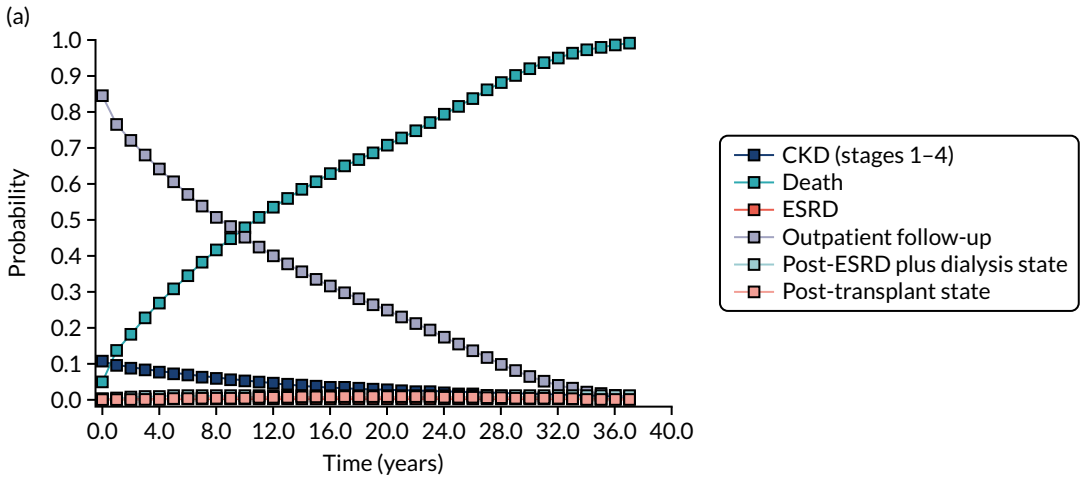

FIGURE 22 Markov cohort traces for base-case model configuration. (a) No AKI; (b) AKI 1; (c) AKI 2; and (d) AKI 3. (*continued*)

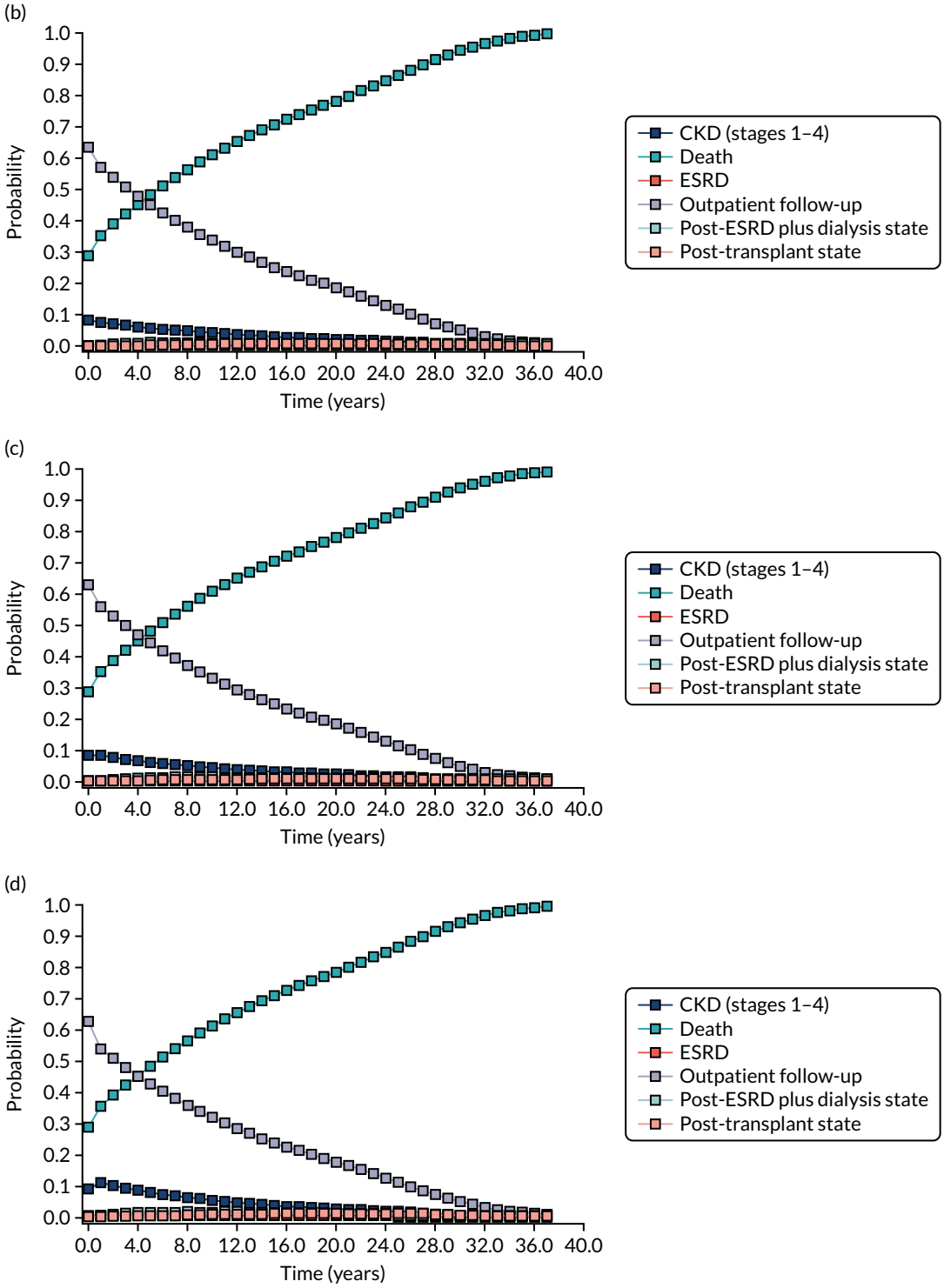

FIGURE 22 Markov cohort traces for base-case model configuration. (a) No AKI; (b) AKI 1; (c) AKI 2; and (d) AKI 3.

Cost-effectiveness acceptability curves

Figures 23 and *24* report cost-effectiveness acceptability curves for the two potential base-case scenarios.

Three subgroup analyses have been carried out on the two EAG-suggested base-case strategies (based on whether or not NGAL is assumed to be capable of averting AKI). The subgroups considered are adult critical care and adult post cardiac surgery. As there was an insufficient amount of data to populate a robust model for a children subgroup, this was considered as an exploratory analysis only (as per *Tables 20* and *21*).

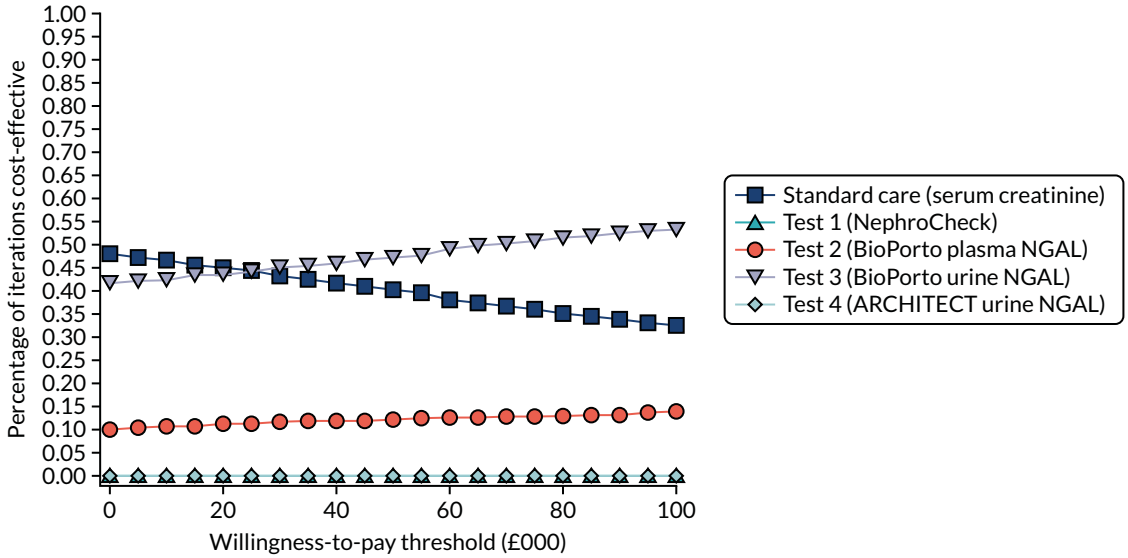

FIGURE 23 Cost-effectiveness acceptability curve: base case 1.

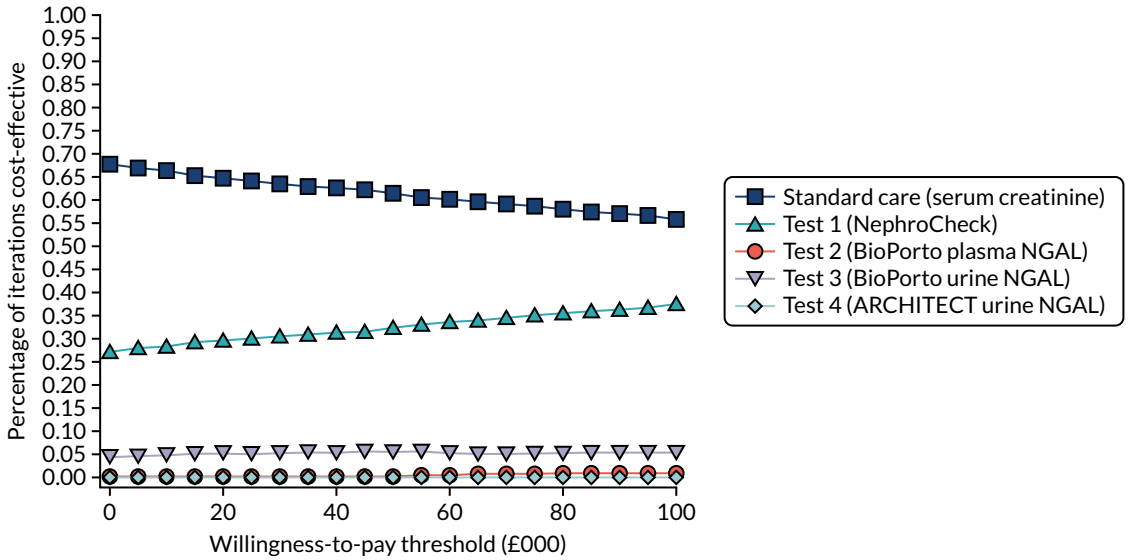

FIGURE 24 Cost-effectiveness acceptability curve: base case 2 – subgroup analyses.

Critical care subgroup

For the critical care subgroup, the same parameter values as the all-comers are used for the downstream model probabilities, costs and utilities. This subgroup may be useful for decision-making as it could be considered as an alternative, potentially more seriously ill, definition of the population in the NICE scope. Although the group is defined as 'critical care', the populations described in the source diagnostic accuracy studies are often more reflective of a seriously ill patient group that would not yet be in ICU in the UK setting. The diagnostic accuracy data used for this subgroup are described in *Table 22*.

The results of the critical care subgroup analysis are provided in *Table 23*.

Cardiac surgery subgroup

Diagnostic accuracy data were not available from the systematic review for all biomarker strategies for the cardiac surgery group, and were available from only single studies for some tests. When data were not available from the review, we used pooled estimates from Hall *et al.*,[97] but note that this analysis

TABLE 22 Diagnostic accuracy data used for the critical care subgroup analysis

Test	Parameter	Mean (95% CI)	Mean (logit scale)	SE (logit scale)	Correlation for multivariate normal distribution (logit scale)	Source
NephroCheck	Sensitivity	0.83 (0.72 to 0.91)	1.615	0.336	−1.000	Meta analysis (see *Chapter 3*)
	Specificity	0.51 (0.48 to 0.54)	0.040	0.064		
BioPorto urine NGAL	Sensitivity	0.72 (0.61 to 0.80)	0.926	0.247	0.905	Meta analysis (see *Chapter 3*)
	Specificity	0.87 (0.66 to 0.96)	1.876	0.617		
ARCHITECT urine NGAL	Sensitivity	0.70 (0.63 to 0.76)	0.855	0.165	1.000	Meta analysis (see *Chapter 3*)
	Specificity	0.72 (0.63 to 0.80)	0.958	0.226		
BioPorto plasma NGAL	Sensitivity	0.76 (0.56 to 0.89)	1.156	0.462	−1.000	Meta analysis (see *Chapter 3*)
	Specificity	0.67 (0.40 to 0.86)	0.686	0.566		

SE, standard error.

should be considered with caution as it includes test manufacturers outside the scope of the NICE assessment. The diagnostic accuracy data for the cardiac surgery subgroup are provided in *Table 24* and are included probabilistically in the model when possible.

Again, these results should be interpreted cautiously because of the lack of/limitations with the diagnostic accuracy data, and the questionable relevance of the downstream parameters/model structure for a cohort of post-cardiac patients only.

The results of the post-cardiac surgery subgroup analysis are provided in *Table 25*.

Interpretation of the results

Published data show that NephroCheck-guided implementation of a KDIGO care bundle has the potential to avert AKI. However, no such data exist for the NGAL tests. Therefore, two base-case analyses are considered. Base case 1 can be considered an optimistic scenario for the NGAL assays and assumes that all NGAL tests are equally as effective as NephroCheck in terms of the potential to avert AKI. Base case 2 can be considered a more conservative approach, in the absence of evidence, and assumes that only NephroCheck can avert AKI, but that all tests have the potential to reduce AKI severity if AKI occurs.

Fifteen scenario analyses are provided for each potential base case, ranging from a set of optimistic assumptions whereby biomarker-guided care bundles may lead to substantial improvements in health outcomes (need for ICU, hospital LOS, CKD, mortality) to a set of more conservative assumptions whereby changing of AKI status has no effects on health outcomes.

Incremental cost-effectiveness ratios are highly uncertain and subject to wide variation depending on the set of scenarios chosen. The probability of cost-effectiveness at an ICER of < £20,000 per QALY gained for scenarios in which NGAL is assumed to be equally as effective as NephroCheck in preventing AKI ranged from 0% to 15% (NephroCheck), 0% to 55% (BioPorto urine NGAL), 0% to 2% (ARCHITECT urine NGAL) and 0% to 48% (BioPorto plasma NGAL). BioPorto urine NGAL was

TABLE 23 Results of the critical care subgroup analysis

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Critical care subgroup, applied to base case 1								
Test 3 (BioPorto urine NGAL)	23,008	–	6.07439	–	–	Dominant	37.0	51.5
Test 2 (BioPorto plasma NGAL)	23,022	£14	6.07440	0.00002	£900,179	Dominant	12.1	45.7
Standard care (serum creatinine)	23,024	Dominated	6.07406	Dominated	Dominated	–	47.9	–
Test 4 (ARCHITECT urine NGAL)	23,029	Dominated	6.07438	Dominated	Dominated	£15,046	1.8	42.3
Test 1 (NephroCheck)	23,057	£36	6.07444	0.00004	£905,334	£87,368	1.2	34.2
Critical care subgroup, applied to base case 2								
Standard care (serum creatinine)	22,904		6.07716				65.0	–
Test 1 (NephroCheck)	22,937	£32	6.07755	0.00039	£82,079	£82,079	31.4	32.8
Test 3 (BioPorto urine NGAL)	22,971	Dominated	6.07728	Dominated	Dominated	£555,173	3.0	11.1
Test 2 (BioPorto plasma NGAL)	22,991	Dominated	6.07729	Dominated	Dominated	£676,218	0.5	8.3
Test 4 (ARCHITECT urine NGAL)	22,991	Dominated	6.07728	Dominated	Dominated	£732,572	0.1	7.9

TABLE 24 Diagnostic accuracy data used for cardiac surgery subgroup

Test	Measure	Mean (95% CI)	Mean logit	SE logit	Correlation for multivariate normal distribution[a]	Source
NephroCheck	Sensitivity	0.31 (0.09 to 0.61)	−0.800	0.704	−0.824	Cummings *et al.*[26] 2019
	Specificity	0.78 (0.74 to 0.82)	1.266	0.120		
BioPorto urine NGAL	Sensitivity	0.78 (0.72 to 0.84)	1.266	0.182	0.526	Yang *et al.*[65] 2017
	Specificity	0.48 (0.42 to 0.54)	−0.080	0.123		
ARCHITECT urine NGAL	Sensitivity	0.46 (0.33 to 0.59)	−0.160	0.274	−0.517	Parikh *et al.*[95] 2017
	Specificity	0.81 (0.79 to 0.83)	1.450	0.067		
BioPorto plasma NGAL	Sensitivity	0.62 (0.49 to 0.74)	0.490	0.277	−1.000	Hall *et al.*[97] 2018
	Specificity	0.78 (0.75 to 0.81)	1.266	0.090		

SE, standard error.
a Note that, in the absence of meta-analysed studies for this subgroup, all correlations are assumed equal to the all-comers' base-case analysis.
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generally the test associated with the greatest probability of cost-effectiveness, albeit this was highly uncertain, when compared with standard care. This is because BioPorto urine NGAL had slightly better diagnostic test accuracy data and slightly lower test costs than the comparator tests. However, there is substantial uncertainty in the diagnostic test accuracy, driven by study heterogeneity; therefore, results should be interpreted cautiously.

When it is assumed that NGAL tests cannot avert AKI, but can only reduce its severity, the cost-effectiveness case for NephroCheck improves substantially. However, cost-effectiveness remains highly uncertain, with a probability of cost-effectiveness ranging from 0% to 99% across the explored scenarios.

Given the significant uncertainties across the range of scenario analyses undertaken, it is not possible to draw robust conclusions on the cost-effectiveness of the respective biomarkers.

TABLE 25 Results of the post cardiac surgery subgroup analysis

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at £20,000	Probability (%) of being cost-effective at £20,000 vs. standard care
Post-cardiac surgery subgroup (applied to scenario 1)								
Standard care (serum creatinine)	22,912		6.07358				54.2	
Test 2 (BioPorto plasma NGAL)	22,914	£2	6.07387	0.00029	£7822	£7822	17.8	45.5
Test 3 (BioPorto urine NGAL)	22,922	£8	6.07394	0.00007	£112,645	£29,127	28.0	41.9
Test 4 (ARCHITECT urine NGAL)	22,938	Dominated	6.07380	Dominated	Dominated	£120,552	0.0	30.1
Test 1 (NephroCheck)	22,984	Dominated	6.07373	Dominated	Dominated	£484,944	0.0	9.6
Post cardiac surgery subgroup (applied to scenario 6)								
Standard care (serum creatinine)	22,983		6.07043				85.6	
Test 2 (BioPorto plasma NGAL)	23,055	Extendedly dominated	6.07054	Extendedly dominated	Extendedly dominated	£679,042	3.8	8.4
Test 1 (NephroCheck)	23,057	£74	6.07059	0.00016	£465,544	£465,544	6.5	8.1
Test 4 (ARCHITECT urine NGAL)	23,062	Dominated	6.07051	Dominated	Dominated	£996,121	0.1	4.0
Test 3 (BioPorto urine NGAL)	23,082	Dominated	6.07056	Dominated	Dominated	£737,663	4.0	7.5

Chapter 5 Discussion

Statement of principal findings

In current clinical practice, identification of patients at risk of developing AKI poses a significant challenge to clinicians. Markers of kidney stress and/or injury are hoped to be a useful adjunct to current clinical care, as they may facilitate patient management and informed decisions about treatment. Nevertheless, pathways of presentation and care for AKI are complex, and the potential for modifiability and clinical benefit is uncertain. This assessment looked at the performance of NephroCheck, ARCHITECT and Alinity i urine NGAL assays and BioPorto urine and plasma NGAL assays to assess the risk of AKI in critically ill patients considered for admission to critical care. We included 56 studies with a total of 17,967 participants.

Clinical effectiveness

The main clinical effectiveness findings suggest that these biomarkers may have a role in AKI risk assessment in patients admitted to critical care. Evidence for other clinical settings (cardiac surgery, major non-cardiac surgery) was limited.

The results of meta-analyses indicate that the use of biomarkers may be useful for identifying AKI. However, because of substantial clinical and statistical heterogeneity between studies, and large 95% confidence and prediction regions, there is considerable uncertainty surrounding the validity and reliability of these findings. Moreover, the overall performance of the biomarkers for the detection of AKI, as seen by the meta-analyses of AUC estimates, appears to be modest, rather than excellent, with large boundaries of uncertainty. For example, for the adult population, the highest AUC value for detection of AKI was 0.76, but prediction intervals ranged from 0.33 to 0.99.

For prediction of relevant clinical outcomes, only a small number of studies were available for each biomarker in each clinical setting; this limited the possibility to perform pooled analyses.

Similarly, although there was an indication that addition of biomarkers to existing clinical models might improve the prediction of relevant clinical outcomes, studies varied considerably in terms of study characteristics and statistical methods used to assess prediction, thereby limiting any reliable conclusion.

Overall, as studies varied considerably in terms of clinical setting, timing of sample collection, optimal threshold level, assay platforms, definition of AKI, number of AKI events, time of AKI diagnosis and inclusion/exclusion criteria, the reliability and generalisability of the observed findings are highly uncertain.

We did not find any study that used the Alinity i urine NGAL test or assessed the performance of the biomarkers for prediction of CKD. Similarly, we did not identify any study that assessed the impact of the routine use of the biomarkers on specific clinical outcomes in critically ill patients compared with current standard care.

Cost-effectiveness

A probabilistic decision tree and Markov model were developed (adapted from the model used by Hall *et al.*[97]) to describe the care pathway for a mixed prevalence cohort of CKD/no-CKD patients in a hospital setting for patients at risk of developing AKI. The decision tree part of the model captured the acute phase, up to the first 90 days, and modelled the risk of AKI and the potential for the use of biomarkers to prevent AKI or reduce its severity. We used a linked-evidence approach to derive hypothesised links between the presence/absence of AKI and AKI severity on changes in health

outcomes (need for ICU care, LOS in hospital, need for acute RRT, 90-day mortality and development of CKD). In the absence of robust trial data, we derived these associations from a large, existing observational data set.[102] The Markov model describes the progression of four cohorts (no AKI, AKI 1, AKI 2 and AKI 3) through a set of mutually exclusive health states capturing CKD, ESRD, long-term dialysis, kidney transplant and mortality. Progression through these states depends on an individual's AKI status in hospital, which influences the starting proportions in the Markov model CKD state.

The model includes health service perspective costs of biomarkers, early application of a KDIGO care bundle, hospitalisation (including ICU and ward costs), acute and long-term dialysis costs, long-term outpatient follow-up costs, and transplant and immunosuppressant costs. Health-state utility values and modelled mortality risk were combined to generate estimates of QALYs gained for each test. The model included the functionality to apply additional follow-up costs and mortality risk over the longer term for patients admitted to the ICU in their index admission.

The cumulative expected value of costs and QALYs were simulated over a lifetime time horizon for each cohort under standard care and each of the biomarker strategies; all results were reported as probabilistic ICERs. We found no trial data that could provide effect estimates for the extent to which biomarkers could both mitigate AKI and improve outcomes. Therefore, the model was built around a series of plausible proportional effects of averting/reducing the severity of AKI on changes in health outcomes. These ranged from optimistic scenarios in which patients who had AKI averted as a result of a biomarker-guided early implementation of a care bundle experienced the same risk of ICU, mortality and CKD as if they were in the no-AKI cohort, to more pessimistic scenarios in which the prevention of AKI or reduction of its severity had no impact on health outcomes.

The costs and QALYs for standard care and for each biomarker test strategy were ranked in ascending order of costs, whereby strategies that were more costly and less effective than an alternative were dominated and excluded from the calculation of the ICERs. In this scenario, the highest ICER under the threshold represents the strategy with the best value for money. All scenarios were also compared directly with standard care. In all cases, the probability of cost-effectiveness from the probabilistic simulation was reported.

Cost-effectiveness results were highly uncertain and ICERs were subject to wide variation depending on the set of scenarios chosen. The probability of cost-effectiveness at an ICER of < £20,000 per QALY gained for scenarios in which NGAL is assumed to be equally as effective as NephroCheck in preventing AKI ranged from 0% to 15% (NephroCheck), 0% to 55% (BioPorto urine NGAL), 0% to 2% (ARCHITECT urine NGAL) and 0% to 48% (BioPorto plasma NGAL). BioPorto urine NGAL was generally the test associated with the greatest probability of cost-effectiveness, albeit this was highly uncertain, when compared with standard care. This is because BioPorto urine NGAL had slightly better diagnostic test accuracy data and slightly lower test costs than the comparator tests. However, there is substantial uncertainty in the diagnostic test accuracy, driven by study heterogeneity; therefore, the results should be interpreted cautiously.

When it is assumed that NGAL tests cannot avert AKI, but can only reduce its severity, the cost-effectiveness case for NephroCheck improves substantially. However, cost-effectiveness remains highly uncertain, with a probability of cost-effectiveness ranging from 0% to 99% across the explored scenarios.

In general, the model results generate a less favourable assessment of cost-effectiveness for the biomarker tests than that of Hall *et al.*[97] There are five reasons for this. First, the prevalence of AKI in the Hall *et al.*[97] study was much higher (31.7%) than in our prevalent AKI population (9.2%). The higher prevalence might be explained by AKI being more common in the ICU setting (starting cohort in Hall *et al.*[97]) than in a hospital ward (the starting cohort in our economic model).

Second, the settings are different. Hall *et al.*[97] evaluated the cost-effectiveness of biomarkers for detecting AKI in a critical care setting, whereas our assessment evaluated the cost-effectiveness of AKI biomarkers in a critically ill hospitalised cohort considered for admission to critical care. The data sources used to populate the acute phase of the model are different. Hall *et al.*[97] relied on daily transitions between ICU, hospital and discharge up to 90 days, whereas we have relied on a large observational data set to populate the potential link between changes in AKI status and health outcomes. Therefore, the costs and utilities applied in the acute phase of the base-case models differ between the two analyses.

Third, both models produce estimates of cost-effectiveness that are sensitive to the data used for the diagnostic accuracy of the tests. The diagnostic accuracy data applied in Hall *et al.*[97] are different from those obtained in our meta-analyses, probably because of new studies becoming available since the Hall *et al.*[97] publication and the wider setting for our model. For example, the sensitivity of NephroCheck was 0.90 in Hall *et al.*[97] and 0.75 in our meta-analysis. Consequently, NephroCheck identified more true-positive cases, which generated greater QALY gains in Hall *et al.*[97] than were generated in our model.

Fourth, we take a more conservative approach to the estimation of long-term follow-up costs for the base-case analysis and have not applied excess lifetime costs beyond the 5-year data reported in Lone *et al.*[114]

Fifth, we further assume that there is no impact of AKI on follow-up costs beyond the 90 days, whereas Hall *et al.*[97] assume excess costs applied for the full lifetime time horizon. We also assume that the causal impact of AKI on CKD development ceases beyond the first cycle of the Markov model (i.e. 1.25 years after the AKI event), whereas Hall *et al.*[97] assume additional risk of CKD for the full lifetime time horizon of the model.

Overall, both models conclude that there is substantial uncertainty in the results, albeit predicting different base-case ICERs. The results are highly sensitive to key parameters in the model and any combination of the presented scenarios may be plausible.

Strengths and limitations of the assessment

The methods used to conduct this assessment were detailed and thorough. We conducted comprehensive literature searches of major electronic databases and relevant websites and assessed > 1000 full-text studies for eligibility. The large number of screened and extracted articles was necessary because key information (e.g. information on biomarker assays) was not available from the abstracts. This resulted in a need for significant literature screening resources and for considering strict inclusion criteria to ensure that the assessment remained feasible and timely. We restricted inclusion to studies that enrolled at least 100 participants and excluded studies on low-birthweight and preterm babies. It is possible that inclusion of all existing studies, irrespective of the sample size, might produce relevant findings. However, we reached a consensus that small and niche studies would not provide clinically generalisable evidence for pooling and would be underpowered to provide reliable evidence in isolation. Low-birthweight and preterm babies were considered a category of patients with specific care needs that are not generalisable to the population included in this assessment.

The primary weakness of the systematic review of clinical effectiveness evidence was the substantial clinical heterogeneity observed between studies. There was considerable heterogeneity, especially with regard to NGAL threshold levels, time of sample collection, definition of AKI and prevalence of AKI, time of AKI diagnosis, and assay platforms. Consequently, the diagnostic accuracy of individual tests varied considerably and the confidence and prediction regions in the pooled analyses were notably large. Moreover, when the studies had smaller numbers of AKI events (low prevalence), the relationship observed between sensitivity and specificity estimates became quite different from that of studies for which prevalence was higher.

Indeed, the shape and size of the prediction regions in the SROC plots were influenced by studies that showed a different relationship between sensitivity and specificity, compared with other studies. Hence, we do not have much confidence in the pooled estimates.

In particular, the intrinsic complexity of this assessment (multiple research questions, multiple biomarkers and sample media, multiple clinical settings, broad patient population, differences in assay platforms, definition of AKI) means that the findings reported here are also complex, particularly given the absence of robust trial evidence to support economic model development. Although the original scope of this assessment was the assessment of hospitalised patients considered to be at risk of admission to critical care, no studies focused on this specific group of patients (pre admission to critical care). Most studies were conducted outside the UK and assessed patients already admitted to intensive or critical care after different surgical procedures or with different (or multiple) clinical conditions. Furthermore, the provision of intensive care resources across the world are heterogeneous, so many studies will not be representative of how intensive care is utilised in the UK. This means that it is unclear how well the findings of heterogeneous studies which are predominantly based in intensive care and conducted outside the UK can be applied to a UK clinical scenario of people not currently receiving critical care, but at risk of requiring it.

Criteria used for the definition of AKI were consistent with current KDIGO recommendations, but differed slightly across studies with respect to operationalisation. This means that the extent of bidirectional misclassification of AKI and CKD may vary between studies and setting, which may affect biomarker performance.[143] In some studies, it was unclear whether or not the reported associations between biomarkers and AKI were indeed attributed to kidney injury. The current definition of AKI is based on elevations in serum creatinine concentration, which poses the conundrum of using an imperfect standard to assess the performance of biomarkers. Serum creatinine is not always measured at the same frequency as biomarkers are measured, and to ascertain the exact time of creatinine rise is problematic. As a result, the 'ground truth' of AKI existence could not be established with a gold-standard reference in any of the studies. In addition, no studies considered alternative methods for early or incipient AKI detection, such as the use of machine learning algorithms.[144]

In some studies, we observed a very small number of AKI events, compared with other included studies. Interestingly, two studies conducted in the cardiac surgery setting [a medium-size single-centre study[26] with 400 participants and a large multicentre study,[38] the Translational Research Investigating Biomarker Endpoints (TRIBE) trial, with 1219 participants)] showed similar prevalence rates (4% and 5%, respectively) and a similar pattern of accuracy (poor sensitivity estimates and good specificity estimates). The number of AKI events are known to vary depending on both AKI definition and clinical setting, which underlies the heterogeneity of existing studies.

An unavoidable limitation of this evaluation is the variation in the use of NGAL tests. Threshold cut-off points to classify patients with and patients without AKI in each clinical setting were not consistent across studies. This means that differences between studies could relate to the chosen threshold, rather than NGAL performance. We selected one threshold per study, according to our inclusion criteria, and estimated the underlying SROC curve using a hierarchical model, which takes into account the within- and between-study variability. NGAL studies also varied with respect to analytic methods of measurement. Some studies used absolute urine concentrations, whereas others used NGAL concentrations normalised for urine creatinine concentrations. There were insufficient data available per type of biomarker and clinical setting to further investigate this source of variability, and determine the extent to which analytic methods influence estimates of diagnostic accuracy and whether or not it was sensible to pool results across studies. Nevertheless, we note that in the multicentre TRIBE prospective study[38] assessing 1219 adults undergoing cardiac surgery, the authors repeated the analyses using NGAL urine-creatinine corrected values and did not observe improvements in the AUC values, compared with uncorrected results.

Several studies did not provide sensitivity, specificity and AUC values for the biomarkers for the diagnostic or prognostic accuracy of AKI. In future studies, accuracy measures such as sensitivity and specificity must be considered and defined rigorously at transparent cut-off points for predictive biomarkers, as they may need to vary according to clinical setting.[145]

Notwithstanding analytic and threshold heterogeneity, the number of available studies for each type of assay in each clinical setting limited our ability to assess the role of the biomarkers for the prediction of relevant clinical outcomes. Furthermore, the number of events was small in many studies and the duration of follow-up was not consistent across studies, so mortality and RRT could not be reliably assessed at the same time points. Furthermore, details of the methods used for prediction analyses were insufficient in many studies. Although information on adjustment strategies and on the process of variable selection were usually provided, the original cohort of potential predictors, prior to the multivariable analysis, was never clearly specified, leading to potential risk of bias.

Finally, introduction of a biomarker would require evidence not just that it performs well as a predictor of modifiable and intervenable AKI, but also that there is incremental improvement of existing or alternative approaches to clinical care. There was insufficient information to determine with certainty whether or not the biomarkers had an incremental advantage over the traditional marker of serum creatinine and urine output, or had information available for clinical assessment. Only a limited number of studies compared the AUC of the biomarkers under investigation with that of serum creatinine for the detection of AKI, and fewer studies compared the performance of the biomarkers with that of clinical models for prediction of AKI or of relevant patient outcomes.

Uncertainties

Clinical effectiveness evidence

There is considerable uncertainty surrounding the generalisability of the studies to the UK population. Most of the studies were conducted outside the UK and assessed patients already admitted to critical care. Because no studies were identified for inclusion, we were not able to assess the impact that the routine use of these biomarkers may have on clinical outcomes of critically ill people considered for admission to critical care, compared with standard clinical assessment.

At present, in the literature, there is limited information on the benefits of incorporating biomarker results with those of current clinical criteria (serum creatinine and urine output) to improve the clinical management of patients with AKI. Recently, Zarbock *et al.*,[146] in a RCT of critically ill surgical patients with AKI, assessed the use of early versus delayed RRT. Plasma NGAL of > 150 ng/ml was one of the inclusion criteria, together with the KDIGO criteria. The trial results showed that early RRT, compared with delayed RRT, reduced mortality, duration of RRT and hospital stay, and that the combination of the KDIGO classification system with plasma NGAL was effective in identifying patients with deteriorating AKI. Subsequent negative results from the Artificial Kidney Initiation in Kidney Injury (AKIKI) RCT[147] for critically ill medical patients suggest that these findings may apply to targeted circumstances only.

More recently (in 2017), the Zarbock group conducted a biomarker-guided RCT of patients who underwent cardiac surgery.[110] They used a biomarker-based approach (NephroCheck test) to identify high-risk patients and implement a bundle of supportive measures recommended by the KDIGO guidelines to reduce the occurrence of AKI, as well as that of mortality and RRT. Their results showed that implementation of the KDIGO guidelines, compared with standard care, reduced the frequency of AKI in the 72 hours after cardiac surgery. However, the trial did not show a reduction in the need for RRT, an improvement in mortality or a positive effect measure on any hard clinical outcome. The authors concluded that future, adequately powered, multicentre trials are required. Similarly, Gögce *et al.*,[116] in a study of major non-cardiac surgery patients, showed that the early adoption of a

bundle of supportive measures according to the KDIGO guidelines in patients with NephroCheck concentrations of > 0.3 (ng/ml)^2/1000 resulted in a reduced occurrence of AKI, decreased hospital and ICU stay, and reduced costs, but, again, there was no evidence of improvement of hard outcomes (need for RRT, mortality, or major kidney events).

Overall, despite some evidence suggesting possible improvement of care processes and health care use when biomarker-guided care bundles are used alongside KDIGO criteria, there is still considerable uncertainty regarding effects on health outcomes, particularly when used in the pre-critical care setting. In addition, the optimal threshold for NGAL and how this changes according to different clinical settings have yet to be established. Future studies should evaluate the targeted use of the biomarkers within specific clinical populations and circumstances in which there is potential for benefit with a plausible and feasible intervention. In particular, they should focus on the assessment of the impact of routine biomarker use on a reduction in mortality, major clinical adverse events, modification of clinical care, and resource use. In other words, future research should evaluate the use of these biomarkers to improve patients' clinical outcomes and management.

Discrete urine and plasma NGAL cut-off points for differentiating between AKI and non-AKI patients in each clinical setting need to be identified and the timing of collection of biomarker concentrations should be set out more clearly according to each setting. In line with the recommendations from the 10th Acute Dialysis Quality Initiative consensus conference,[148] there is also a need to harmonise the methods and platforms for collection, handling and storage of urine and plasma samples. Furthermore, it would be useful to harmonise the reporting of biomarker concentrations (e.g. absolute concentrations, ratio to urine creatinine) and corroborate techniques for normalising urine biomarker concentrations to urine creatinine concentrations.

Finally, it is well recognised that AKI encompasses a range of clinical aetiologies, phenotypes and patterns of renal recovery. In addition, current measures of AKI may be insufficient to disentangle AKI that is predominantly functional without kidney damage from people with incipient subclinical damage, and people with both AKI and kidney damage. In this context, it remains unclear how phenotypic information on people with AKI should most usefully be combined to help target those most likely to benefit from earlier recognition and timely intervention, nor how such an intervention may differ between clinical phenotypes.[148]

Cost-effectiveness evidence

There are three key areas of uncertainty in the economic evaluation modelling that limit the robustness of the cost-effectiveness results: (1) the lack of evidence on the impact of the biomarkers on health outcomes, (2) the heterogeneity in the diagnostic accuracy data (including uncertainty in the prevalence of AKI in a broad, poorly defined population) and (3) the uncertainty around the impact of a NGAL-guided implementation of a KDIGO care bundle on the frequency and severity of AKI. Given these uncertainties, the choice of a preferred base-case scenario is challenging and the observed results should be considered cautiously. These are speculative analyses ranging from a set of pessimistic scenarios to a set of optimistic scenarios for the use of the biomarkers under assessment.

Specifically, there is no evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay, risk of 90-day mortality or development of new/progression of existing CKD). Accordingly, the cost-effectiveness results are based on a linked-evidence approach, whereby we have relied on observational associations to infer how prevention or mitigation of AKI may affect changes in health outcomes. These associations necessitate causal assumptions, but, although a causal link between AKI and poor outcomes is plausible, the extent of this causal relationship is uncertain and controversial.[149,150] The cost-effectiveness results are therefore presented for a range of alternative, but potentially plausible, scenario analyses ranging from a set of optimistic assumptions in which biomarker-guided care bundles may lead to substantial improvements in health outcomes (need for ICU care, CKD, mortality) to a set of more conservative assumptions in

which change in AKI status has no effect on health outcomes. It is likely that the true estimate of cost-effectiveness lies somewhere between these two extremes.

Furthermore, the diagnostic accuracy data used in the economic model are obtained from studies that are considerably heterogeneous in terms of baseline AKI prevalence, timing of sample collection, threshold values and definition of AKI. Given the difficulty in defining the population that fits within the scope of this assessment, it is unclear how generalisable the diagnostic accuracy data are to the UK population in which the biomarkers could be used.

Also of note are additional uncertainties in the model that make it difficult to come to conclusions about the relative cost-effectiveness of each biomarker. For example, although there is some evidence in the literature, from Meersch *et al.*,[110] that early NephroCheck-guided implementation of a KDIGO care bundle may improve AKI status at 72 hours, the potential for similar improvements using NGAL is unknown. Therefore, we have considered two scenarios for the cost-effectiveness analyses. The first assumes, optimistically, that all NGAL tests are equally as effective at preventing AKI or reducing its severity as NephroCheck; the second, based on the available data from Meersch *et al.*,[110] assumes that NGAL can reduce the severity of AKI once it occurs, but cannot prevent its occurrence.

Because of these uncertainties, the results of the cost-effectiveness modelling are largely speculative and should be interpreted with caution. Although extensive probabilistic analyses are carried out for scenario analyses, these may still not fully capture the uncertainty faced in the implementation of these biomarkers in clinical practice.

In summary, the current evidence base is insufficient to make a full appraisal of the economic value of the biomarkers under investigation to provide cost-effective improvements in clinical outcomes of AKI. Therefore, we have provided a range of scenarios that cannot answer the full remit of this evaluation. We believe that the scenarios illustrate what might be required for the biomarkers to be cost-effective, highlighting, through the assumptions involved, the current gaps where further research is required.

Chapter 6 Conclusions

Implications for clinical practice and future research

We found that novel biomarkers have the ability to predict the presence or onset of AKI, but additional research is required to understand the incremental value of using these biomarkers on top of existing standard care. In addition, research that considers the utility of biomarkers on top of other novel approaches such as machine learning approaches to recognise incipient AKI in different clinical environments would be valuable.

There was limited trial evidence that the course of AKI in critical care circumstances may be modifiable or avoidable with early biomarker-guided care bundle approaches. Future research is needed to understand whether or not this is dependent on a well-performing timely biomarker, a care bundle appropriate for clinical context, or both. Research is also required to further evaluate such approaches outside the critical care setting.

Current literature is inadequate to determine whether or not biomarker-guided intervention can lead to hard clinical and economic outcomes, in addition to amelioration of AKI severity. The specific clinical circumstances in which benefit exists, and whether or not such benefit is dependent on reduction of AKI severity or is mediated through other means, would also be informative for future evaluations.

Uncertainty remains around the process of renal recovery and non-recovery after AKI. Mechanistic work exploring the nature, timing and extent of the recovery process could inform the nature and circumstances in which a biomarker-guided intervention might be effective. Similarly, clinical research on the timing and extent of renal recovery with different AKI phenotypes would enhance the ability to model cost-effectiveness of biomarker-guided therapies in different subsets of AKI.

In brief, we have identified the following research priorities:

- further research in the form of adequately powered, well-designed RCTs to determine the incremental value of biomarkers on clinical outcomes (such as mortality and development of CKD), quality of life, resource use, costs and cost-effectiveness
- further research to determine the clinical effectiveness and cost-effectiveness of adopting an early care bundle for the prevention/treatment of AKI, compared with standard care
- further research to help understand the quality-of-life (utility) implications for patients admitted to ICU care
- Future research to consider the potential roles for biomarker use in niche clinical areas, such as to assist in the discrimination of high- and low-risk patients who are already receiving critical care immediately after major surgery.

In addition, in the nephrology clinical research community, there is a need for efforts to standardise definitions and methods for studying AKI, kidney disease, progression, operationalisation of biomarkers and their interpretation.

Acknowledgements

The authors are grateful to Shona Methven for her help in developing the research protocol for this assessment and to Lara Kemp for her secretarial support.

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All authors contributed to the writing of this report.

Publications

Jacobsen E, Sawhney S, Brazzelli M, Aucott L, Scotland G, Aceves-Martins M, *et al.* Cost-effectiveness and value of information analysis of NephroCheck and NGAL tests compared to standard care for the diagnosis of acute kidney injury. *BMC Nephrol* 2021;**22**:399.

Data-sharing statement

All technical data are included in the main text or as appendices to this report. All queries should be submitted to the corresponding author for consideration.

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Appendix 1 Literature search strategies

NephroCheck/neutrophil gelatinase-associated lipocalin clinical effectiveness search strategies

EMBASE and MEDLINE (via Ovid)

EMBASE
Date range searched: 1974–14 May 2019.

Date searched: 27 May 2019.

MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions
Date range searched: 1946–14 May 2019.

Date searched: 27 May 2019.

Search strategy

1. Acute Disease/and exp Kidney Diseases/use ppezv (8605)
2. exp acute disease/and exp *kidney disease/use oemezd (2443)
3. exp *acute kidney failure/use oemezd (31,083)
4. acute kidney injury/use ppezv (41,584)
5. exp *kidney injury/use oemezd (12,360)
6. kidney tubular necrosis, acute/use ppezv (2352)
7. exp *kidney tubule necrosis/use oemezd (1519)
8. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (50,969)
9. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (58,624)
10. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or "nephrotoxic injur*").tw. (9425)
11. aki.tw. (27,925)
12. exp *contrast induced nephropathy/use oemezd (2540)
13. "contrast induced nephropathy".tw. (5028)
14. or/1-13 (159,431)
15. *reperfusion injury/(47,279)
16. reperfusion/use ppezv (4705)
17. (reperfusion adj5 (injur* or isch?emi*)).tw. (129,126)
18. exp *Delayed Graft Function/(1612)
19. "delayed graft function*".tw. (9243)
20. or/15-19 (144,655)
21. (renal or kidney* or nephr* or "tubular necrosis" or aki).tw. (2,045,747)
22. (or/1-7) or 21 (2,056,977)
23. 20 and 22 (25,897)
24. 14 or 23 [All AKI] (177,838)
25. lipocalins/or lipocalin-2/use ppezv (6282)
26. neutrophil gelatinase associated lipocalin/or lipocalin/use oemezd (12,442)
27. (NGAL or uNGAL or sNGAL).tw,kw. (7409)
28. ("Neutrophil gelatinase-associated lipocalin" or "neutrophil gelatinase lipocalin" or "lipocalin 2" or lcn2 or Oncogene 24p3 or siderocalin).tw,kw,nm. use ppezv (4262)
29. ("Neutrophil gelatinase-associated lipocalin" or "neutrophil gelatinase lipocalin" or "lipocalin 2" or lcn2 or Oncogene 24p3 or siderocalin).tw,kw,tn. use oemezd (5997)

30. or/25-29 [NGAL] (16,697)
31. "Tissue Inhibitor of Metalloproteinase-2"/use ppezv (3445)
32. "tissue inhibitor of metalloproteinase 2"/use oemezd (6871)
33. Metalloproteinase inhibitor 2.tw,nm,kw. use ppezv (15)
34. Metalloproteinase inhibitor 2.tw,kw. use oemezd (28)
35. tissue inhibitor of metalloproteinase-2.tw,nm,kw. use ppezv (3699)
36. tissue inhibitor of metalloproteinase-2.tw,kw. use oemezd (883)
37. TIMP metallopeptidase inhibitor 2.tw,nm,kw. use ppezv (10)
38. TIMP metallopeptidase inhibitor 2.tw,kw. use oemezd (11)
39. (TIMP 2 or TIMP2 or DDC8 or CSC-21K).tw,nm,kw. use ppezv (4818)
40. (TIMP 2 or TIMP2 or DDC8 or CSC-21K).tw,kw. use oemezd (6114)
41. or/31-40 [TIMP2] (14,536)
42. (IGFBP7 or IBP-7 or IGFBP-rP1).tw,nm,kw. use ppezv (410)
43. (IGFBP7 or IBP-7 or IGFBP-rP1).tw,kw. use oemezd (614)
44. IGF-binding protein 7.tw,nm,kw. use ppezv (16)
45. IGF-binding protein 7.tw,kw. use oemezd (23)
46. Insulin-like growth factor-binding protein 7.tw,nm,kw. use ppezv (220)
47. Insulin-like growth factor-binding protein 7.tw,kw. use oemezd (326)
48. MAC25 protein.tw,nm,kw. use ppezv (5)
49. MAC25 protein.tw,kw. use oemezd (5)
50. PGI2-stimulating factor.tw,nm,kw. use ppezv (6)
51. PGI2-stimulating factor.tw,kw. use oemezd (9)
52. "Prostacyclin-stimulating factor".tw,nm,kw. use ppezv (29)
53. Prostacyclin-stimulating factor.tw,kw. use oemezd (31)
54. #32 or #33 or #34 or #35 or #36 or #37.tw,nm,kw. use ppezv (15)
55. Tumor-derived adhesion factor.tw,kw. use oemezd (7)
56. or/42-55 [IGFBP7] (1273)
57. 41 and 56 [TIMP2 AND IGFBP7] (278)
58. nephrocheck.tw,kw. use ppezv (24)
59. nephrocheck.tw,dv,kw. use oemezd (55)
60. 58 or 59 (79)
61. 30 or 57 or 60 (16,915)
62. 24 and 61 (5763)
63. remove duplicates from 62 (4053).

Cumulative Index to Nursing and Allied Health Literature (via EBSCOhost; EBSCO Information Services, Ipswich, MA, USA)

Date searched: 17 May 2019.

Search strategy

S1 (MH "Kidney Diseases") AND (MH "Acute Disease") (257)

S2 (MM "Kidney Failure, Acute") (5995)

S3 (MH "Kidney Tubular Necrosis, Acute") (190)

S4 TX Acute N3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction) (10,442)

S5 TX Acute N3 (renal disease* or renal injury or renal failure or renal dysfunction) (3651)

S6 TX (Acute N3 (Tubular Necrosis or nephrotoxic*)) OR TX "nephrotoxic injur*" (447)

S7 TX aki (3496)

S8 TX "contrast induced nephropathy". (677)

S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 (13,805)

S10 (MM "Reperfusion Injury") (1816)

S11 (MH "Reperfusion") (947)

S12 TX "delayed graft function*". (213)

S13 TX reperfusion N5 (injur* or isch?emi*) (4919)

S14 S10 OR S11 OR S12 OR S13 (5890)

S15 TX renal or kidney* or nephr* or "tubular necrosis" or aki (157,197)

S16 S1 OR S2 OR S3 OR S15 (157,197)

S17 S14 AND S16 (1057)

S18 S9 OR S17 (14,436)

S19 TX (NGAL or uNGAL or sNGAL). (558)

S20 TX "Neutrophil gelatinase-associated lipocalin" or "neutrophil gelatinase lipocalin" or "lipocalin 2" or lcn2 or Oncogene 24p3 or siderocalin (762)

S21 TX "Metalloproteinase inhibitor 2" OR TX "tissue inhibitor of metalloproteinase-2" OR TX "TIMP metallopeptidase inhibitor 2" OR TX ("TIMP 2 or TIMP2 or DDC8 or CSC-21K") (61)

S22 TX ((IGFBP7 or IBP-7 or IGFBP-rP1)) OR TX "IGF-binding protein 7" OR TX "Insulin-like growth factor-binding protein 7" (63)

S23 TX "MAC25 protein" OR TX "PGI2-stimulating factor" OR TX "Prostacyclin-stimulating factor" (0)

S24 S22 OR S23 (63)

S25 S21 AND S24 (12)

S26 S19 OR S20 OR S25 (853)

S27 S18 AND S26 (473).

Cochrane Central Register of Controlled Trials (via Wiley Online Library)

Date searched: 17 May 2019.

Search strategy

1. MeSH descriptor: [Acute Kidney Injury] explode all trees (1214)
2. MeSH descriptor: [Kidney Tubular Necrosis, Acute] explode all trees (37)
3. (Acute NEAR/3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)):ti,ab,kw (23,064)
4. (Acute NEAR/3 (renal disease* or renal injury or renal failure or renal dysfunction)):ti,ab,kw (23,415)
5. (Acute NEAR/3 (Tubular Necrosis or nephrotoxic*)):ti,ab,kw (312)

6. ("nephrotoxic injur*"):ti,ab,kw (0)
7. (aki):ti,ab,kw (1209)
8. ("contrast induced nephropathy"):ti,ab,kw (822)
9. MeSH descriptor: [Acute Disease] explode all trees (9276)
10. MeSH descriptor: [Kidney Diseases] explode all trees (14,389)
11. #9 and #10 (193)
12. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #11 (24,407)
13. MeSH descriptor: [Reperfusion Injury] explode all trees (1006)
14. (reperfusion NEAR/5 (injur* or ischemi* or ischaemi*)):ti,ab,kw (2932)
15. MeSH descriptor: [Delayed Graft Function] explode all trees (89)
16. ("delayed graft function*"):ti,ab,kw (597)
17. #13 or #14 or #15 or #16 (3470)
18. (renal or kidney* or nephr* or "tubular necrosis" or aki):ti,ab,kw (79,148)
19. #1 or #2 or #11 or #18 (79,196)
20. #17 and #19 (997)
21. MeSH descriptor: [Lipocalins] explode all trees (199)
22. MeSH descriptor: [Lipocalin-2] explode all trees (93)
23. (NGAL or uNGAL or sNGAL):ti,ab,kw (550)
24. ("Neutrophil gelatinase-associated lipocalin" or "neutrophil gelatinase lipocalin" or "lipocalin 2" or lcn2 or Oncogene 24p3 or siderocalin):ti,ab,kw (533)
25. #21 or #22 or #23 or #24 (816)
26. ("Metalloproteinase inhibitor 2"):ti,ab,kw (0)
27. ("tissue inhibitor of metalloproteinase-2"):ti,ab,kw (70)
28. ("TIMP metallopeptidase inhibitor 2"):ti,ab,kw (0)
29. (TIMP 2 or TIMP2 or DDC8 or CSC-21K):ti,ab,kw (303)
30. MeSH descriptor: [Tissue Inhibitor of Metalloproteinase-2] explode all trees (42)
31. #26 or #27 or #28 or #29 or #30 (315)
32. (IGFBP7 or IBP-7 or IGFBP-rP1):ti,ab,kw (26)
33. ("IGF-binding protein 7"):ti,ab,kw (1)
34. ("Insulin-like growth factor-binding protein 7"):ti,ab,kw (22)
35. (MAC25 protein):ti,ab,kw (0)
36. ("PGI2-stimulating factor"):ti,ab,kw (0)
37. ("Prostacyclin-stimulating factor"):ti,ab,kw (1)
38. ("Tumor-derived adhesion factor"):ti,ab,kw (0)
39. #32 or #33 or #34 or #35 or #36 or #37 (33)
40. #31 and #39 (21)
41. (nephrocheck):ti,ab,kw (4)
42. #25 or #40 or #41 (832)
43. #12 or #20 (25,125)
44. #42 and #43 (292).

Clarivate Analytics Web of Science

Indexes: Science Citation Index Expanded, Conference Proceedings Citation Index – Science, and Conference Proceedings Citation Index – Social Science & Humanities.

Timespan: all years.

Date searched: 22 May 2019.

Search strategy

1. TOPIC: ("acute kidney injury" OR "acute kidney failure") (24,763)
2. TOPIC: (kidney NEAR/2 necrosis) (715)

3. TOPIC: (Acute NEAR/3 ("kidney disease*" or "kidney injury" or "kidney failure" or "kidney dysfunction")) (25,532)
4. TOPIC: (Acute NEAR/3 ("renal disease*" or "renal injury" or "renal failure" or "renal dysfunction")) (32,865)
5. TOPIC: ("contrast induced nephropathy") (3029)
6. #5 OR #4 OR #3 OR #2 OR #1 (54,254)
7. TOPIC: (NGAL or sNGAL or uNGAL) (3258)
8. TOPIC: (neutrophil NEAR/2 lipocalin) (3078)
9. #8 OR #7 (4099)
10. TOPIC: (Inhibitor NEAR/2 Metalloproteinase) (10,021)
11. TOPIC: (TIMP) (12,633)
12. #11 OR #10 (18,219)
13. TOPIC: (IGFBP7 or IBP-7 or IGFBP-rP1) (470)
14. TOPIC: ("Insulin-like growth factor-binding protein 7") (242)
15. #14 OR #13 (539)
16. #15 AND #12 (108)
17. TOPIC: (nephrocheck) (29)
18. #17 OR #16 OR #9 (4192)
19. #18 AND #6 (1943)
20. TOPIC: (rat or rats or mouse or mice or murine or dog or dogs or canine or pig or pigs or porcine) (3,841,039)
21. #20 AND #19 (428)
22. #19 not #21 (1543).

Other resources

The following resources were searched using appropriate text terms in combination when allowed by the search interface:

- HTA Database [www.crd.york.ac.uk/PanHTA/ (accessed 10 June 2019)].
- WHO's Global Index Medicus [www.globalhealthlibrary.net/php/index.php?lang=en (accessed 10 June 2019)].
- EU Clinical Trials Register [www.clinicaltrialsregister.eu/ (accessed 10 June 2019)].
- ICTRP [www.isrctn.com/ (accessed 10 June 2019)].
- ClinicalTrials.gov (via the US National Institutes of Health; Advanced Search Interface).

Search terms used:

- Acute kidney/renal injury.
- Acute kidney/renal failure.
- Kidney Tubular Necrosis.
- contrast induced nephropathy.
- Nephrocheck.
- TIMP-2.
- Metalloproteinase.
- IGFBP7.
- Insulin-like growth factor-binding protein 7.
- NGAL or uNGAL or sNGAL.
- Neutrophil gelatinase-associated lipocalin.

Results retrieved: 86.

Appendix 2 Screening checklist

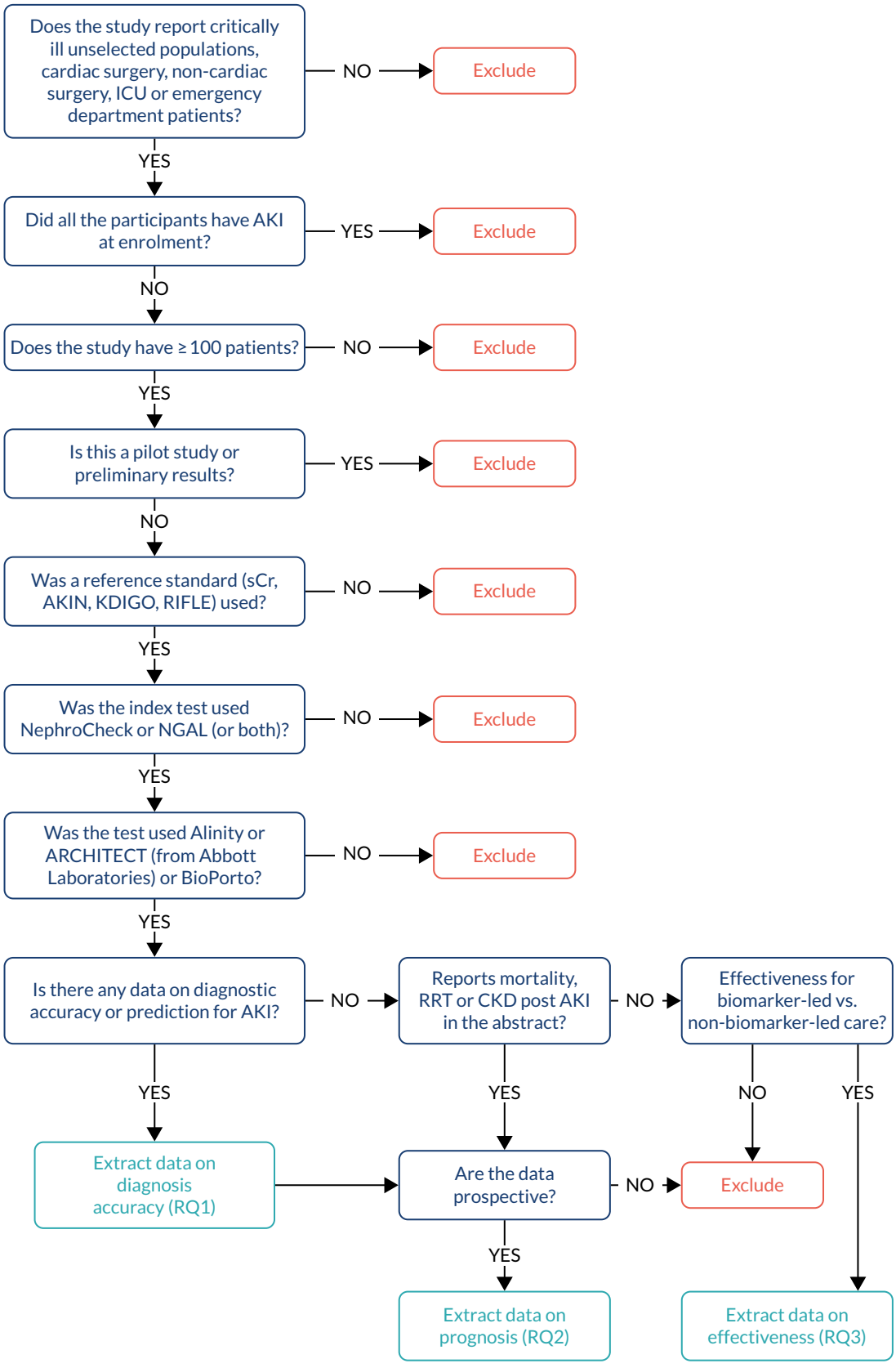

FIGURE 25 Screening checklist. RQ, research question; sCr, serum creatinine.

Appendix 3 Data extraction form

- Reference ID.
  - Study first author.
  - Year.
  - Project study name.
- Reviewer.

Baseline characteristics

- Population (adults/child/both).
- Target population.
- Recruitment period.
- Study centre (number of centres and names).
- Country.
- Funding.
- Index test 1 (urine NGAL, plasma NGAL or NephroCheck) and index test kit 1 (e.g. ARCHITECT or Alinity i from Abbott, or ELISA BioPorto).
- Age for whole sample.
- Sex.
- Serum creatinine.
- eGFR.
- Sequential Organ Failure Assessment score.
- CKD.
- Time point of measurement (non-surgical: closest to admission; surgical: immediately after surgery; prognosis studies: various time points).
- Threshold reported.
- Report cut-off point for NephroCheck or NGAL.
- True positive, false negative, false positive, true negative.
- *n* with AKI present (true positive plus false negative) confirmed by reference standard.
- *n* with AKI absent (false positive plus true negative) confirmed by reference standard.
- *n* with AKI present (true positive plus false positive) confirmed by test.
- *n* with AKI absent (false negative plus true positive) confirmed by test.

For each outcome (acute kidney injury diagnosis, mortality prognosis, renal replacement therapy prognosis and acute kidney injury prognosis)

- Sensitivity (lower and upper 95% CI).
- Specificity (lower and upper 95% CI).
- AUC (lower and upper 95% CI).
- Positive predictive value (lower and upper 95% CI).
- Negative predictive value (lower and upper 95% CI).
- Positive likelihood ratio (lower and upper 95% CI).
- Negative likelihood ratio (lower and upper 95% CI).
- Comment.

Appendix 4 List of included studies

The asterisk (*) denotes a primary reference.

Albert 2018[45]

Albert C, Albert A, Bellomo R, Kropf S, Devarajan P, Westphal S, *et al.* Urinary neutrophil gelatinase-associated lipocalin-guided risk assessment for major adverse kidney events after open-heart surgery. *Biomark Med* 2018;**12**:975–85. https://doi.org/10.2217/bmm-2018-0071

Alcaraz 2014[89]

Alcaraz AJ, Gil-Ruiz MA, Castillo A, López J, Romero C, Fernández SN, Carrillo A. Postoperative neutrophil gelatinase-associated lipocalin predicts acute kidney injury after pediatric cardiac surgery. *Pediatr Crit Care Med* 2014;**15**:121–30. https://doi.org/10.1097/PCC.0000000000000034

Ariza 2016[67]

*Ariza X, Graupera I, Coll M, Solà E, Barreto R, García E, *et al.* Neutrophil gelatinase-associated lipocalin is a biomarker of acute-on-chronic liver failure and prognosis in cirrhosis. *J Hepatol* 2016;**65**:57–65.

Markwardt D, Holdt L, Steib C, Benesic A, Bendtsen F, Bernardi M, *et al.* Plasma cystatin C is a predictor of renal dysfunction, acute-on-chronic liver failure, and mortality in patients with acutely decompensated liver cirrhosis. *Hepatology* 2017;**66**:1232–41. https://doi.org/10.1002/hep.29290

Asada 2016[50]

Asada T, Isshiki R, Hayase N, Sumida M, Inokuchi R, Noiri E, *et al.* Impact of clinical context on acute kidney injury biomarker performances: differences between neutrophil gelatinase-associated lipocalin and L-type fatty acid-binding protein. *Sci Rep* 2016;**6**:33077. https://doi.org/10.1038/srep33077

Barreto 2014[68]

Barreto R, Elia C, Solà E, Moreira R, Ariza X, Rodríguez E, *et al.* Urinary neutrophil gelatinase-associated lipocalin predicts kidney outcome and death in patients with cirrhosis and bacterial infections. *J Hepatol* 2014;**61**:35–42. https://doi.org/10.1016/j.jhep.2014.02.023

Beitland 2016[28]

Beitland S, Waldum-Grevbo BE, Nakstad ER, Berg JP, Trøseid AS, Brusletto BS, *et al.* Urine biomarkers give early prediction of acute kidney injury and outcome after out-of-hospital cardiac arrest. *Crit Care* 2016;**20**:314. https://doi.org/10.1186/s13054-016-1503-2

Bennett 2008[87]

Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, *et al.* Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. *Clin J Am Soc Nephrol* 2008;**3**:665–73. https://doi.org/10.2215/CJN.04010907

Bihorac 2014[29]

Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, *et al.* Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. *Am J Respir Crit Care Med* 2014;**189**:932–9. https://doi.org/10.1164/rccm.201401-0077OC

Bojan 2014[86]

Bojan M, Vicca S, Lopez-Lopez V, Mogenet A, Pouard P, Falissard B, Journois D. Predictive performance of urine neutrophil gelatinase-associated lipocalin for dialysis requirement and death following cardiac surgery in neonates and infants. *Clin J Am Soc Nephrol* 2014;**9**:285–94. https://doi.org/10.2215/CJN.04730513

Cantinotti 2012[88]

Cantinotti M, Storti S, Lorenzoni V, Arcieri L, Moschetti R, Murzi B, *et al.* The combined use of neutrophil gelatinase-associated lipocalin and brain natriuretic peptide improves risk stratification in pediatric cardiac surgery. *Clin Chem Lab Med* 2012;**50**:2009–17. https://doi.org/10.1515/cclm-2012-0125

Cho 2013[69]

Cho E, Yang HN, Jo SK, Cho WY, Kim HK. The role of urinary liver-type fatty acid-binding protein in critically ill patients. *J Korean Med Sci* 2013;**28**:100–5. https://doi.org/10.3346/jkms.2013.28.1.100

Cho 2014[66]

Cho E, Kim SC, Kim MG, Jo SK, Cho WY, Kim HK. The incidence and risk factors of acute kidney injury after hepatobiliary surgery: a prospective observational study. *BMC Nephrol* 2014;**15**:169. https://doi.org/10.1186/1471-2369-15-169

Collins 2012[51]

Collins SP, Hart KW, Lindsell CJ, Fermann GJ, Weintraub NL, Miller KF, *et al.* Elevated urinary neutrophil gelatinase-associated lipocalcin after acute heart failure treatment is associated with worsening renal function and adverse events. *Eur J Heart Fail* 2012;**14**:1020–9. https://doi.org/10.1093/eurjhf/hfs087

Cullen 2014[49]

Cullen MR, Jhanji S, Pearse RM, Fitzgibbon MC. Neutrophil gelatinase-associated lipocalin and albuminuria as predictors of acute kidney injury in patients treated with goal-directed haemodynamic therapy after major abdominal surgery. *Ann Clin Biochem* 2014;**51**:392–9.

Cummings 2019[26]

Cummings JJ, Shaw AD, Shi J, Lopez MG, O'Neal JB, Billings FT. Intraoperative prediction of cardiac surgery-associated acute kidney injury using urinary biomarkers of cell cycle arrest. *J Thorac Cardiovasc Surg* 2019;**157**:1545–53.e5.

De Loor 2017[63]

De Loor J, Herck I, Francois K, Van Wesemael A, Nuytinck L, Meyer E, Hoste EAJ. Diagnosis of cardiac surgery-associated acute kidney injury: differential roles of creatinine, chitinase 3-like protein 1 and neutrophil gelatinase-associated lipocalin: a prospective cohort study. *Ann Intensive Care* 2017;**7**:24. https://doi.org/10.1186/s13613-017-0251-z

Di Leo 2018[30]

*Di Leo L, Nalesso F, Garzotto F, Xie Y, Yang B, Virzì GM, *et al.* Predicting acute kidney injury in intensive care unit patients: the role of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein-7 biomarkers. *Blood Purif* 2018;**45**:270–7. https://doi.org/10.1159/000485591

Xie Y, Ankawi G, Yang B, Garzotto F, Passannante A, Breglia A, *et al.* Tissue inhibitor metalloproteinase-2 (TIMP-2) • IGF-binding protein-7 (IGFBP7) levels are associated with adverse outcomes in patients in the intensive care unit with acute kidney injury. *Kidney Int* 2019;**95**:1486–93.

Doi 2014[70]

*Doi K, Noiri E, Nangaku M, Yahagi N, Jayakumar C, Ramesh G. Repulsive guidance cue semaphorin 3A in urine predicts the progression of acute kidney injury in adult patients from a mixed intensive care unit. *Nephrol Dial Transplant* 2014;**29**:73–80. https://doi.org/10.1093/ndt/gft414

Doi K, Negishi K, Ishizu T, Katagiri D, Fujita T, Matsubara T, *et al.* Evaluation of new acute kidney injury biomarkers in a mixed intensive care unit. *Crit Care Med* 2011;**39**:2464–9. https://doi.org/10.1097/CCM.0b013e318225761a

Dong 2017[92]

Dong L, Ma Q, Bennett M, Devarajan P. Urinary biomarkers of cell cycle arrest are delayed predictors of acute kidney injury after pediatric cardiopulmonary bypass. *Pediatr Nephrol* 2017;**32**:2351–60. https://doi.org/10.1007/s00467-017-3748-7

Dupont 2012[52]

Dupont M, Shrestha K, Singh D, Awad A, Kovach C, Scarcipino M, *et al.* Lack of significant renal tubular injury despite acute kidney injury in acute decompensated heart failure. *Eur J Heart Fail* 2012;**14**:597–604. https://doi.org/10.1093/eurjhf/hfs039

Garcia-Alvarez 2015[46]

Garcia-Alvarez M, Glassford NJ, Betbese AJ, Ordoñez J, Baños V, Argilaga M, *et al.* Urinary neutrophil gelatinase-associated lipocalin as predictor of short- or long-term outcomes in cardiac surgery patients. *J Cardiothorac Vasc Anesth* 2015;**29**:1480–8. https://doi.org/10.1053/j.jvca.2015.05.060

Gayat 2018[32]

Gayat E, Touchard C, Hollinger A, Vieillard-Baron A, Mebazaa A, Legrand M, FROG ICU study investigators. Back-to-back comparison of penKID with NephroCheck® to predict acute kidney injury at admission in intensive care unit: a brief report. *Crit Care* 2018;**22**:24. https://doi.org/10.1186/s13054-018-1945-9

Haase 2014[60]

*Haase M, Bellomo R, Albert C, Vanpoucke G, Thomas G, Laroy W, *et al.* The identification of three novel biomarkers of major adverse kidney events. *Biomark Med* 2014;**8**:1207–17. https://doi.org/10.2217/bmm.14.90

Albert C, Albert A, Kube J, Bellomo R, Wettersten N, Kuppe H, *et al.* Urinary biomarkers may provide prognostic information for subclinical acute kidney injury after cardiac surgery. *J Thorac Cardiovasc Surg* 2018;**155**:2441–52.e13.

Hjortrup 2015[72]

Hjortrup PB, Haase N, Treschow F, Møller MH, Perner A. Predictive value of NGAL for use of renal replacement therapy in patients with severe sepsis. *Acta Anaesthesiol Scand* 2015;**59**:25–34. https://doi.org/10.1111/aas.12427

Hoste 2014[33]

Hoste EA, McCullough PA, Kashani K, Chawla LS, Joannidis M, Shaw AD, *et al.* Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. *Nephrol Dial Transplant* 2014;**29**:2054–61. https://doi.org/10.1093/ndt/gfu292

Isshiki 2018[53]

Isshiki R, Asada T, Sumida M, Hamasaki Y, Nangaku M, Noiri E, Doi K. Modest impact of serial measurements of acute kidney injury biomarkers in an adult intensive care unit. *Nephron* 2018;**139**:243–53. https://doi.org/10.1159/000488219

Itenov 2017[81]

Itenov TS, Jensen JU, Ostrowski SR, Johansson PI, Thormar KM, Lundgren JD, Bestle MH, 'Procalcitonin And Survival Study' study group. Endothelial damage signals refractory acute kidney injury in critically ill patients. *Shock* 2017;**47**:696–701. https://doi.org/10.1097/SHK.0000000000000804

Jaques 2019[62]

Jaques DA, Spahr L, Berra G, Poffet V, Lescuyer P, Gerstel E, *et al.* Biomarkers for acute kidney injury in decompensated cirrhosis: a prospective study. *Nephrology* 2019;**24**:170–80. https://doi.org/10.1111/nep.13226

Kashani 2013[34]

Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, *et al.* Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 2013;**17**:R25. https://doi.org/10.1186/cc12503

Kimmel 2016

Kimmel M, Shi J, Latus J, Wasser C, Kitterer D, Braun N, Alscher MD. Association of renal stress/damage and filtration biomarkers with subsequent AKI during hospitalization among patients presenting to the emergency department. *Clin J Am Soc Nephrol* 2016;**11**:938–46. https://doi.org/10.2215/CJN.10551015

Kimmel M, Shi J, Wasser C, Biegger D, Alscher MD, Schanz MB. Urinary [TIMP-2]·[IGFBP7] – novel biomarkers to predict acute kidney injury. *Am J Nephrol* 2016;**43**:375–82. https://doi.org/10.1159/000446451

Kokkoris 2012[54]

Kokkoris S, Parisi M, Ioannidou S, Douka E, Pipili C, Kyprianou T, *et al.* Combination of renal biomarkers predicts acute kidney injury in critically ill adults. *Ren Fail* 2012;**34**:1100–8. https://doi.org/10.3109/0886022X.2012.713279

Lagos-Arevalo 2015[93]

Lagos-Arevalo P, Palijan A, Vertullo L, Devarajan P, Bennett MR, Sabbisetti V, *et al.* Cystatin C in acute kidney injury diagnosis: early biomarker or alternative to serum creatinine? *Pediatr Nephrol* 2015;**30**:665–76.

Lee 2018[82]

*Lee DH, Lee BK, Cho YS, Jung YH, Lee SM, Park JS, Jeung KW. Plasma neutrophil gelatinase-associated lipocalin measured immediately after restoration of spontaneous circulation predicts acute kidney injury in cardiac arrest survivors who underwent therapeutic hypothermia. *Ther Hypothermia Temp Manag* 2018;**8**:99–107. https://doi.org/10.1089/ther.2017.0039

Cho YS, Lee BK, Lee DH, Jung YH, Lee SM, Park JS, Jeung KW. Association of plasma neutrophil gelatinase-associated lipocalin with acute kidney injury and clinical outcome in cardiac arrest survivors depends on the time of measurement. *Biomarkers* 2018;**23**:487–94. https://doi.org/10.1080/1354750X.2018.1452048

Liebetrau 2013[47]

Liebetrau C, Dörr O, Baumgarten H, Gaede L, Szardien S, Blumenstein J, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) for the early detection of cardiac surgery associated acute kidney injury. *Scand J Clin Lab Invest* 2013;**73**:392–9. https://doi.org/10.3109/00365513.2013.787149

Marino 2015[83]

Marino R, Struck J, Hartmann O, Maisel AS, Rehfeldt M, Magrini L, *et al.* Diagnostic and short-term prognostic utility of plasma pro-enkephalin (pro-ENK) for acute kidney injury in patients admitted with sepsis in the emergency department. *J Nephrol* 2015;**28**:717–24. https://doi.org/10.1007/s40620-014-0163-z

Mårtensson 2015[55]

Mårtensson J, Glassford NJ, Jones S, Eastwood GM, Young H, Peck L, *et al.* Urinary neutrophil gelatinase-associated lipocalin to hepcidin ratio as a biomarker of acute kidney injury in intensive care unit patients. *Minerva Anestesiol* 2015;**81**:1192–200.

Matsa 2014[73]

Matsa R, Ashley E, Sharma V, Walden AP, Keating L. Plasma and urine neutrophil gelatinase-associated lipocalin in the diagnosis of new onset acute kidney injury in critically ill patients. *Crit Care* 2014;**18**:R137. https://doi.org/10.1186/cc13958

Nickolas 2008[74]

Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, *et al.* Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med* 2008;**148**:810–19.

Nickolas 2012[56]

Nickolas TL, Schmidt-Ott KM, Canetta P, Forster C, Singer E, Sise M, *et al.* Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective cohort study. *J Am Coll Cardiol* 2012;**59**:246–55. https://doi.org/10.1016/j.jacc.2011.10.854

Nisula 2015[75]

*Nisula S, Yang R, Poukkanen M, Vaara ST, Kaukonen KM, Tallgren M, *et al.* Predictive value of urine interleukin-18 in the evolution and outcome of acute kidney injury in critically ill adult patients. *Br J Anaesth* 2015;**114**:460–8. https://doi.org/10.1093/bja/aeu382

Nisula S, Yang R, Kaukonen KM, Vaara ST, Kuitunen A, Tenhunen J, *et al.* The urine protein NGAL predicts renal replacement therapy, but not acute kidney injury or 90-day mortality in critically ill adult patients. *Anesth Analg* 2014;**119**:95–102. https://doi.org/10.1213/ANE.0000000000000243

Oezkur 2017[27]

Oezkur M, Magyar A, Thomas P, Stork T, Schneider R, Bening C, *et al.* TIMP-2*IGFBP7 (Nephrocheck®) measurements at intensive care unit admission after cardiac surgery are predictive for acute kidney injury within 48 hours. *Kidney Blood Press Res* 2017;**42**:456–67. https://doi.org/10.1159/000479298

Parikh 2011 (TRIBE-Adult)[37]

*Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, *et al.* Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. *J Am Soc Nephrol* 2011;**22**:1748–57. https://doi.org/10.1681/ASN.2010121302

Brown JR, Philbrook HT, Goodrich CA, Bohm AR, Alam SS, Coca SG, *et al.* Are urinary biomarkers better than acute kidney injury duration for predicting readmission? *Ann Thorac Surg* 2019;**107**:1699–1705.

Coca SG, Garg AX, Thiessen-Philbrook H, Koyner JL, Patel UD, Krumholz HM, *et al.* Urinary biomarkers of AKI and mortality 3 years after cardiac surgery. *J Am Soc Nephrol* 2014;**25**:1063–71.

Coca SG, Nadkarni GN, Garg AX, Koyner J, Thiessen-Philbrook H, McArthur E, *et al.* First post-operative urinary kidney injury biomarkers and association with the duration of AKI in the TRIBE-AKI cohort. *PLOS ONE* 2016;**11**:e0161098. https://doi.org/10.1371/journal.pone.0161098

Greenberg JH, Devarajan P, Thiessen-Philbrook HR, Krawczeski C, Parikh CR, Zappitelli M, TRIBE-AKI Consortium. Kidney injury biomarkers 5 years after AKI due to pediatric cardiac surgery. *Pediatr Nephrol* 2018;**33**:1069–77. https://doi.org/10.1007/s00467-018-3888-4

Koyner JL, Coca SG, Thiessen-Philbrook H, Patel UD, Shlipak MG, Garg AX, Parikh CR, Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury (TRIBE-AKI) Consortium. Urine biomarkers and perioperative acute kidney injury: the impact of preoperative estimated GFR. *Am J Kidney Dis* 2015;**66**:1006–14. https://doi.org/10.1053/j.ajkd.2015.07.027

Parikh CR, Thiessen-Philbrook H, Garg AX, Kadiyala D, Shlipak MG, Koyner JL, *et al.* Performance of kidney injury molecule-1 and liver fatty acid-binding protein and combined biomarkers of AKI after cardiac surgery. *Clin J Am Soc Nephrol* 2013;**8**:1079–88. https://doi.org/10.2215/CJN.10971012

Zhang WR, Garg AX, Coca SG, Devereaux PJ, Eikelboom J, Kavsak P, *et al.* Plasma IL-6 and IL-10 concentrations predict aki and long-term mortality in adults after cardiac surgery. *J Am Soc Nephrol* 2015;**26**:3123–32. https://doi.org/10.1681/ASN.2014080764

Parikh 2011 (TRIBE-Child)[84]

*Parikh CR, Devarajan P, Zappitelli M, Sint K, Thiessen-Philbrook H, Li S, *et al.* Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. *J Am Soc Nephrol* 2011;**22**:1737–47. https://doi.org/10.1681/ASN.2010111163

Zappitelli M, Greenberg JH, Coca SG, Krawczeski CD, Li S, Thiessen-Philbrook HR, *et al.* Association of definition of acute kidney injury by cystatin C rise with biomarkers and clinical outcomes in children undergoing cardiac surgery. *JAMA Pediatr* 2015;**169**:583–91. https://doi.org/10.1001/jamapediatrics.2015.54

Park 2017[57]

Park M, Hsu CY, Go AS, Feldman HI, Xie D, Zhang X, *et al.* Urine kidney injury biomarkers and risks of cardiovascular disease events and all-cause death: the CRIC study. *Clin J Am Soc Nephrol* 2017;**12**:761–71. https://doi.org/10.2215/CJN.08560816

Pipili 2014[58]

Pipili C, Ioannidou S, Tripodaki ES, Parisi M, Douka E, Vasileiadis I, *et al.* Prediction of the renal replacement therapy requirement in mechanically ventilated critically ill patients by combining biomarkers for glomerular filtration and tubular damage. *J Crit Care* 2014;**29**:692.e7–13. https://doi.org/10.1016/j.jcrc.2014.02.011

Schley 2015[61]

Schley G, Köberle C, Manuilova E, Rutz S, Forster C, Weyand M, *et al.* Comparison of plasma and urine biomarker performance in acute kidney injury. *PLOS ONE* 2015;**10**:e0145042. https://doi.org/10.1371/journal.pone.0145042

Seitz 2013[90]

Seitz S, Rauh M, Gloeckler M, Cesnjevar R, Dittrich S, Koch AM. Cystatin C and neutrophil gelatinase-associated lipocalin: biomarkers for acute kidney injury after congenital heart surgery. *Swiss Med Wkly* 2013;**143**:w13744. https://doi.org/10.4414/smw.2013.13744

Smith 2013[77]

Smith ER, Lee D, Cai MM, Tomlinson LA, Ford ML, McMahon LP, Holt SG. Urinary neutrophil gelatinase-associated lipocalin may aid prediction of renal decline in patients with non-proteinuric stages 3 and 4 chronic kidney disease (CKD). *Nephrol Dial Transplant* 2013;**28**:1569–79. https://doi.org/10.1093/ndt/gfs586

Tecson 2017[78]

Tecson KM, Erhardtsen E, Eriksen PM, Gaber AO, Germain M, Golestaneh L, *et al.* Optimal cut points of plasma and urine neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury among critically ill adults: retrospective determination and clinical validation of a prospective multicentre study. *BMJ Open* 2017;**7**:e016028. https://doi.org/10.1136/bmjopen-2017-016028

Thanakitcharu 2014[48]

Thanakitcharu P, Jirajan B. Determination of urinary neutrophil gelatinase-associated lipocalin (NGAL) cut-off level for early detection of acute kidney injury in Thai adult patients undergoing open cardiac surgery. *J Med Assoc Thai* 2014;**97**(Suppl. 11):48–55.

Tidbury 2019[64]

Tidbury N, Browning N, Shaw M, Morgan M, Kemp I, Matata, B. Neutrophil gelatinase-associated lipocalin as a marker of postoperative acute kidney injury following cardiac surgery in patients with pre-operative kidney impairment. *Cardiovasc Hematol Disord Drug Targets* 2019;**19**:239–48.

Treeprasertsuk 2015[59]

Treeprasertsuk S, Wongkarnjana A, Jaruvongvanich V, Sallapant S, Tiranathanagul K, Komolmit P, Tangkijvanich P. Urine neutrophil gelatinase-associated lipocalin: a diagnostic and prognostic marker for acute kidney injury (AKI) in hospitalized cirrhotic patients with AKI-prone conditions. *BMC Gastroenterol* 2015;**15**:140. https://doi.org/10.1186/s12876-015-0372-5

Verna 2012[79]

Verna EC, Brown RS, Farrand E, Pichardo EM, Forster CS, Sola-Del Valle DA, *et al.* Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. *Dig Dis Sci* 2012;**57**:2362–70. https://doi.org/10.1007/s10620-012-2180-x

Yang 2017[65]

Yang X, Chen C, Teng S, Fu X, Zha Y, Liu H, *et al.* Urinary matrix metalloproteinase-7 predicts severe AKI and poor outcomes after cardiac surgery. *J Am Soc Nephrol* 2017;**28**:3373–82. https://doi.org/10.1681/ASN.2017020142

Zelt 2018[80]

Zelt JGE, Mielniczuk LM, Liu PP, Dupuis JY, Chih S, Akbari A, Sun LY. Utility of novel cardiorenal biomarkers in the prediction and early detection of congestive kidney injury following cardiac surgery. *J Clin Med* 2018;**7**:E540.

Zwiers 2015[91]

Zwiers AJ, de Wildt SN, van Rosmalen J, de Rijke YB, Buijs EA, Tibboel D, Cransberg K. Urinary neutrophil gelatinase-associated lipocalin identifies critically ill young children with acute kidney injury following intensive care admission: a prospective cohort study. *Crit Care* 2015;**19**:181. https://doi.org/10.1186/s13054-015-0910-0

Appendix 5 Excluded studies

TABLE 26 List of excluded studies

First author	Year of publication	Reason for exclusion	Reference
Abassi	2013	< 100 participants	Abassi Z, Shalabi A, Sohotnik R, Nativ O, Awad H, Bishara B, *et al.* Urinary NGAL and KIM-1: biomarkers for assessment of acute ischemic kidney injury following nephron sparing surgery. *J Urol* 2013;**189**:1559–66. https://doi.org/10.1016/j.juro.2012.10.029
Abdelsalam	2018	Not a relevant type of population	Abdelsalam M, Elmorsy E, Abdelwahab H, Algohary O, Naguib M, El Wahab AA, *et al.* Urinary biomarkers for early detection of platinum based drugs induced nephrotoxicity. *BMC Nephrol* 2018;**19**:219
Aberg	2014	Not a relevant biomarker assay or test	Aberg F, Lempinen M, Hollmén M, Nordin A, Mäkisalo H, Isoniemi H. Neutrophil gelatinase-associated lipocalin associated with irreversibility of pre-liver transplant kidney dysfunction. *Clin Transplant* 2014;**28**:869–76. https://doi.org/10.1111/ctr.12394
Adams	2019	< 100 participants	Adams PS, Vargas D, Baust T, Saenz L, Koh W, Blasiole B, *et al.* Associations of perioperative renal oximetry via near-infrared spectroscopy, urinary biomarkers, and postoperative acute kidney injury in infants after congenital heart surgery: should creatinine continue to be the gold standard? *Pediatr Crit Care Med* 2019;**20**:27–37. https://doi.org/10.1097/PCC.0000000000001767
Adler	2018	< 100 participants	Adler C, Heller T, Schregel F, Hagmann H, Hellmich M, Adler J, Reuter H. TIMP-2/IGFBP7 predicts acute kidney injury in out-of-hospital cardiac arrest survivors. *Crit Care* 2018;**22**:126. https://doi.org/10.1186/s13054-018-2042-9
Afify	2016	< 100 participants	Afify MFM, Maher SE, Ibrahim NM, El-Hamied WMA. Serum neutrophil gelatinase-associated lipocalin in infants and children with sepsis-related conditions with or without acute renal dysfunction. *Clin Med Insights Pediatr* 2016;**10**:85–9
Afzal	2018	Not a primary study	Afzal A, Vallabhan RC, McCullough PA. Acute kidney injury in cardiogenic shock: in search of early detection and clinical certainty. *Eur J Heart Fail* 2018;**20**:582–4. https://doi.org/10.1002/ejhf.1032
Aghel	2010	< 100 participants	Aghel A, Shrestha K, Mullens W, Borowski A, Tang WH. Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. *J Card Fail* 2010;**16**:49–54. https://doi.org/10.1016/j.cardfail.2009.07.003
Ahmad	2015	No focus on DTA for AKI	Ahmad T, Wang T, O'Brien EC, Samsky MD, Pura JA, Lokhnygina Y, *et al.* Effects of left ventricular assist device support on biomarkers of cardiovascular stress, fibrosis, fluid homeostasis, inflammation, and renal injury. *JACC Heart Fail* 2015;**3**:30–9

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Ahmad	2018	Not a relevant biomarker assay or test	Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, *et al.* Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. *Circulation* 2018;**137**:2016–28
Ahmed	2012	No focus on DTA for AKI	Ahmed MS, Lim R, Selvaratnam V, James A, Kelly PO, Abraham KA, Wong CF. Survival akin to injury, hospitalized patients with acute kidney injury based on the AKIN classification. *Clin Nephrol* 2012;**78**:370–5. https://doi.org/10.5414/CN106948
Ahmed	2014	Retracted study	Ahmed QA, El Sayed FS, Emad H, Mohamed E, Ahmed B, Heba P. Urinary biomarkers of acute kidney injury in patients with liver cirrhosis. *Med Arch* 2014;**68**:132–6
Ahn	2016	Not a relevant type of population	Ahn JY, Lee MJ, Seo JS, Choi D, Park JB. Plasma neutrophil gelatinase-associated lipocalin as a predictive biomarker for the detection of acute kidney injury in adult poisoning. *Clin Toxicol* 2016;**54**:127–33. https://doi.org/10.3109/15563650.2015.1118487
Ejaz	2012	Not a relevant biomarker assay or test	Ejaz AA, Kambhampati G, Ejaz NI, Dass B, Lapsia V, Arif AA, *et al.* Post-operative serum uric acid and acute kidney injury. *J Nephrol* 2012;**25**:497–505. https://doi.org/10.5301/jn.5000173
Akcay	2012	Not a relevant type of population	Akcay AB, Ozlu MF, Sen N, Cay S, Ozturk OH, Yalcn F, *et al.* Prognostic significance of neutrophil gelatinase-associated lipocalin in ST-segment elevation myocardial infarction. *J Investig Med* 2012;**60**:508–13. https://doi.org/10.2310/JIM.0b013e31823e9d86
Akrawinthawong	2013	< 100 participants	Akrawinthawong K, Shaw MK, Kachner J, Apostolov EO, Basnakian AG, Shah S, *et al.* Urine catalytic iron and neutrophil gelatinase-associated lipocalin as companion early markers of acute kidney injury after cardiac surgery: a prospective pilot study. *Cardiorenal Med* 2013;**3**:7–16. https://doi.org/10.1159/000346815
Akrawinthawong	2015	< 100 participants	Akrawinthawong K, Ricci J, Cannon L, Dixon S, Kupfer K, Stivers D, *et al.* Subclinical and clinical contrast-induced acute kidney injury: data from a novel blood marker for determining the risk of developing contrast-induced nephropathy (ENCINO), a prospective study. *Ren Fail* 2015;**37**:187–91. https://doi.org/10.3109/0886022X.2014.991994
Al-Afify	2013	< 100 participants	Al-Afify AA. Prognostic value of neutrophil gelatinase-associated lipocalin in predicting in-hospital complications in patients with ST-segment elevation myocardial infarction. *Res J Cardiol* 2013;**6**:10–18
Albeladi	2017	< 100 participants	Albeladi FI, Algethamy HM. Urinary neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury, severe kidney injury, and the need for renal replacement therapy in the intensive care unit. *Nephron Extra* 2017;**7**:62–77. https://doi.org/10.1159/000477469

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Albert	2014	No focus on DTA for AKI	Albert C, Kube J, Haase-Fielitz A, Dittrich A, Schanze D, Zenker M, *et al.* Pilot study of association of catechol-*O*-methyl transferase rs4680 genotypes with acute kidney injury and tubular stress after open heart surgery. *Biomark Med* 2014;**8**:1227–38. https://doi.org/10.2217/bmm.14.85
Albuquerque	2019	< 100 participants	Albuquerque PLMM, da Silva Jr GB, Meneses GC, Martins AMC, Lima DB, Raubenheimer J, Fathima S, *et al.* Acute kidney injury induced by bothrops venom: insights into the pathogenic mechanisms. *Toxins (Basel)* 2019;**11**:148
Algethamy	2017	< 100 participants	Algethamy HM, Albeladi FI. Urinary neutrophil gelatinase-associated lipocalin is an excellent predictor of mortality in intensive care unit patients. *Saudi Med J* 2017;**38**:706–14. https://doi.org/10.15537/smj.2017.7.18181
Alharazy	2014	Not a relevant type of population	Alharazy SM, Kong N, Saidin R, Gafor AH, Maskon O, Mohd M, Zakaria SZ. Serum neutrophil gelatinase-associated lipocalin and cystatin C are early biomarkers of contrast-induced nephropathy after coronary angiography in patients with chronic kidney disease. *Angiology* 2014;**65**:436–42. https://doi.org/10.1177/0003319713483918
Alharazy	2014	Not a relevant type of population	Alharazy SM, Kong N, Saidin R, Gafor AHA, Maskon O, Mohd M, Zakaria SZS. Neutrophil gelatinase-associated lipocalin as an early marker of contrast-induced nephropathy after coronary angiography. *Angiol* 2014;**65**:216–23
Aljumah	2018	< 100 participants	Aljumah AA, Tamim H, Saeed M, Tamimi W, Alfawaz H, Al Qurashi S, *et al.* The role of urinary neutrophil gelatinase-associated lipocalin in predicting acute kidney dysfunction in patients with liver cirrhosis. *J Clin Med Res* 2018;**10**:419–28. https://doi.org/10.14740/jocmr3366w
Allavena	2013	< 100 participants	Allavena C, Bach-Ngohou K, Billaud E, Secher S, Dejoie T, Reliquet V, *et al.* Neutrophil gelatinase-associated lipocalin, a marker of tubular dysfunction, is not increased in long-term virologically controlled patients receiving a tenofovir/emtricitabine + nevirapine regimen. *J Antimicrob Chemother* 2013;**68**:2866–70
Almalky	2015	< 100 participants	Almalky MA, Hasan SA, Hassan TH, Shahbah DA, Arafa MA, Khalifa NA, Ibrahim RE. Detection of early renal injury in children with solid tumors undergoing chemotherapy by urinary neutrophil gelatinase-associated lipocalin. *Mol Clin Oncol* 2015;**3**:1341–6. https://doi.org/10.3892/mco.2015.631
Al-Shamma	2017	< 100 participants	Al-Shamma ZAA, Alklyali NG, Alani IY. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a predictive biomarker of kidney injury in renal transplanted patients and chronic kidney disease. *Int J Pharm Pharm Sci* 2017;**9**:59–63

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Alvelos	2011	Not a relevant biomarker assay or test	Alvelos M, Pimentel R, Pinho E, Gomes A, Lourenço P, Teles MJ, *et al.* Neutrophil gelatinase-associated lipocalin in the diagnosis of type 1 cardio-renal syndrome in the general ward. *Clin J Am Soc Nephrol* 2011;**6**:476–81. https://doi.org/10.2215/CJN.06140710
Alvelos	2013	Not a relevant biomarker assay or test	Alvelos M, Lourenço P, Dias C, Amorim M, Rema J, Leite AB, *et al.* Prognostic value of neutrophil gelatinase-associated lipocalin in acute heart failure. *Int J Cardiol* 2013;**165**:51–5. https://doi.org/10.1016/j.ijcard.2011.07.080
Anagnostopoulos	2016	Not a primary study	Anagnostopoulos PV. Prediction of severe acute kidney injury after pediatric cardiac surgery with the use of novel biomarkers: a new trend in clinical research and risk stratification. *J Thorac Cardiovasc Surg* 2016;**152**:187–8. https://doi.org/10.1016/j.jtcvs.2016.04.033
Angeletti	2016	< 100 participants	Angeletti S, Fogolari M, Morolla D, Capone F, Costantino S, Spoto S, *et al.* Role of neutrophil gelatinase-associated lipocalin in the diagnosis and early treatment of acute kidney injury in a case series of patients with acute decompensated heart failure: a case series. *Cardiol Res Pract* 2016;**2016**:3708210. https://doi.org/10.1155/2016/3708210
Anonymous	2008	Not a primary study	Anonymous. A single measurement of urinary NGAL can identify acute kidney injury. *Nat Clin Pract Nephrol* 2008;**4**:466
Anonymous	2010	Non-English-language publication	Anonymous. Early biomarker for AKI. *Jpn J Nephrol* 2010;**52**:566–571
Antonelli	2020	Systematic review – retained as background material	Antonelli A, Allinovi M, Cocci A, Russo GI, Schiavina R, Rocco B, *et al.* The predictive role of biomarkers for the detection of acute kidney injury after partial or radical nephrectomy: a systematic review of the literature. *Eur Urol Focus* 2020;**6**:344–53
Antonopoulos	2011	< 100 participants	Antonopoulos CN, Kalkanis A, Georgakopoulos G, Sergentanis TN, Rigopoulos DN. Neutrophil gelatinase-associated lipocalin in dehydrated patients: a preliminary report. *BMC Res Notes* 2011;**4**:435. https://doi.org/10.1186/1756-0500-4-435
Anusha	2015	< 100 participants	Anusha R, Silambanan S, Veerasamy M. Plasma neutrophil gelatinase associated lipocalin in the early detection of acute kidney injury in patients undergoing cardiac surgery. *Int J Pharm Biol Sci* 2015;**6**:B64–B71
Arambašić	2016	Not a relevant type of population	Arambašić J, Mandić S, Debeljak Ž, Mandić D, Horvat V, Šerić V. Differentiation of acute pyelonephritis from other febrile states in children using urinary neutrophil gelatinase-associated lipocalin (uNGAL). *Clin Chem Lab Med* 2016;**54**:55–61. https://doi.org/10.1515/cclm-2015-0377
Arampatzis	2017	Not a relevant biomarker assay or test	Arampatzis S, Chalikias G, Devetzis V, Konstantinides S, Huynh-Do U, Tziakas D. C-terminal fragment of agrin (CAF) levels predict acute kidney injury after acute myocardial infarction. *BMC Nephrol* 2017;**18**:202. https://doi.org/10.1186/s12882-017-0611-9

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Aregger	2014	< 100 participants	Aregger F, Uehlinger DE, Witowski J, Brunisholz RA, Hunziker P, Frey FJ, Jörres A. Identification of IGFBP-7 by urinary proteomics as a novel prognostic marker in early acute kidney injury. *Kidney Int* 2014;**85**:909–19. https://doi.org/10.1038/ki.2013.363
Arena	2010	< 100 participants	Arena A, Stassi G, Iannello D, Gazzara D, Calapai M, Bisignano C, *et al.* Both IL-1 beta and TNF-alpha regulate NGAL expression in polymorphonuclear granulocytes of chronic hemodialysis patients. *Mediators Inflamm* 2010;**2010**:613937
Ariza	2015	< 100 participants	Ariza X, Solà E, Elia C, Barreto R, Moreira R, Morales-Ruiz M, *et al.* Analysis of a urinary biomarker panel for clinical outcomes assessment in cirrhosis. *PLOS ONE* 2015;**10**:e0128145. https://doi.org/10.1371/journal.pone.0128145
Arora	2016	Not a primary study	Arora RC, Rigatto C, Singal RK. Neutrophil gelatinase-associated lipocalin to predict cardiac surgery-associated acute kidney injury: a holy grail or just another fancy cup? *J Thorac Cardiovasc Surg* 2016;**151**:1482–3. https://doi.org/10.1016/j.jtcvs.2016.02.042
Arora	2017	Not a primary study	Arora RC, Singal RK. Is routine use of renal injury biomarkers in cardiac surgery patients putting the cart before the horse? *J Thorac Cardiovasc Surg* 2017;**154**:938–9
Arsalan	2018	< 100 participants	Arsalan M, Ungchusri E, Farkas R, Johnson M, Kim RJ, Filardo G, *et al.* Novel renal biomarker evaluation for early detection of acute kidney injury after transcatheter aortic valve implantation. *Proc* 2018;**31**:171–6. https://doi.org/10.1080/08998280.2017.1416235
Arthur	2014	< 100 participants	Arthur JM, Hill EG, Alge JL, Lewis EC, Neely BA, Janech MG, *et al.* Evaluation of 32 urine biomarkers to predict the progression of acute kidney injury after cardiac surgery. *Kidney Int* 2014;**85**:431–8. https://doi.org/10.1038/ki.2013.333
Arun	2015	< 100 participants	Arun O, Celik G, Oc B, Unlu A, Celik JB, Oc M, Duman A. Renal effects of coronary artery bypass graft surgery in diabetic and non-diabetic patients: a study with urinary neutrophil gelatinase-associated lipocalin and serum cystatin C. *Kidney Blood Press Res* 2015;**40**:141–52. https://doi.org/10.1159/000368490
Ascher	2018	Not a relevant type of population	Ascher SB, Scherzer R, Estrella MM, Zhang WR, Muiru AN, Jotwani V, *et al.* Association of urinary biomarkers of kidney injury with estimated GFR decline in HIV-infected individuals following tenofovir disoproxil fumarate initiation. *Clin J Am Soc Nephrol* 2018;**13**:1321–9. https://doi.org/10.2215/CJN.01700218
Ashalatha	2017	No relevant outcome	Ashalatha VL, Bitla AR, Kumar VS, Rajasekhar D, Suchitra MM, Lakshmi AY, Rao PV. Biomarker response to contrast administration in diabetic and nondiabetic patients following coronary angiography. *Indian J Nephrol* 2017;**27**:20–7. https://doi.org/10.4103/0971-4065.179335

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Askenazi	2011	Not a relevant type of population	Askenazi DJ, Montesanti A, Hundley H, Koralkar R, Pawar P, Shuaib F, *et al.* Urine biomarkers predict acute kidney injury and mortality in very low birth weight infants. *J Pediatr* 2011;**159**:907–12.e1
Askenazi	2011	Not a relevant type of population	Askenazi DJ, Koralkar R, Levitan EB, Goldstein SL, Devarajan P, Khandrika S, *et al.* Baseline values of candidate urine acute kidney injury biomarkers vary by gestational age in premature infants. *Pediatr Res* 2011;**70**:302–6
Askenazi	2012	< 100 participants	Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Parwar P, Sonjara S, Ambalavanan N. Urine biomarkers predict acute kidney injury in newborns. *J Pediatr* 2012;**161**:270–5.e1
Askenazi	2016	Not a relevant type of population	Askenazi DJ, Koralkar R, Patil N, Halloran B, Ambalavanan N, Griffin R. Acute kidney injury urine biomarkers in very low-birth-weight infants. *Clin J Am Soc Nephrol* 2016;**11**:1527–35
Assadi	2019	< 100 participants	Assadi F, Sharbaf FG. Urine KIM-1 as a potential biomarker of acute renal injury after circulatory collapse in children. *Pediatr Emerg Care* 2019;**35**:104–7. https://doi.org/10.1097/PEC.0000000000000886
Ataei	2015	< 100 participants	Ataei S, Hadjibabaie M, Moslehi A, Taghizadeh-Ghehi M, Ashouri A, Amini E, *et al.* A double-blind, randomized, controlled trial on N-acetylcysteine for the prevention of acute kidney injury in patients undergoing allogeneic hematopoietic stem cell transplantation. *Hematol Oncol* 2015;**33**:67–74
Ataei	2018	< 100 participants	Ataei N, Ameli S, Yousefifard M, Oraei A, Ataei F, Bazargani B, *et al.* Urinary neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C in early detection of pediatric acute kidney injury; a diagnostic accuracy study. *Emerg* 2018;**6**:e2
Au	2016	Not a relevant biomarker assay or test	Au V, Feit J, Barasch J, Sladen RN, Wagener G. Urinary neutrophil gelatinase-associated lipocalin (NGAL) distinguishes sustained from transient acute kidney injury after general surgery. *Kidney Int Rep* 2016;**1**:3–9
Audard	2014	< 100 participants	Audard V, Moutereau S, Vandemelebrouck G, Habibi A, Khellaf M, Grimbert P, *et al.* First evidence of subclinical renal tubular injury during sickle-cell crisis. *Orphanet J Rare Dis* 2014;**9**:67
Axelrod	2016	No focus on DTA for AKI	Axelrod DM, Sutherland SM, Anglemyer A, Grimm PC, Roth SJ. A double-blinded, randomized, placebo-controlled clinical trial of aminophylline to prevent acute kidney injury in children following congenital heart surgery with cardiopulmonary bypass. *Pediatr Crit Care Med* 2016;**17**:135–43
Aydin	2014	< 100 participants	Aydin SA, Pozam S, Ozdemir F, Ozkan ML, Koksal O. The role of neutrophil gelatinase-associated lipocalin in identifying contrast induced nephropathy development in the emergency department. *J Pak Med Assoc* 2014;**64**:1109–13

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Aydoğdu	2013	Not a relevant biomarker assay or test	Aydoğdu M, Gürsel G, Sancak B, Yeni S, Sarı G, Taşyürek S, *et al.* The use of plasma and urine neutrophil gelatinase associated lipocalin (NGAL) and Cystatin C in early diagnosis of septic acute kidney injury in critically ill patients. *Dis Markers* 2013;**34**:237–46
Azzalini	2017	Not a primary study	Azzalini L, Garcia-Moll X. On contrast-induced acute kidney injury, risk prediction, and the future of predictive model development. *Can J Cardiol* 2017;**33**:711–13
Bachorzewska-Gajewska	2006	< 100 participants	Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Dobrzycki S. Neutrophil-gelatinase-associated lipocalin and renal function after percutaneous coronary interventions. *Am J Nephrol* 2006;**26**:287–92
Bachorzewska-Gajewska	2007	Not a relevant type of population	Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Pawlak K, Mysliwiec M, *et al.* Could neutrophil-gelatinase-associated lipocalin and cystatin C predict the development of contrast-induced nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine values? *Kidney Blood Press Res* 2007;**30**:408–15
Bachorzewska-Gajewska	2009	< 100 participants	Bachorzewska-Gajewska H, Poniatowski B, Dobrzycki S. NGAL (neutrophil gelatinase-associated lipocalin) and L-FABP after percutaneous coronary interventions due to unstable angina in patients with normal serum creatinine. *Adv Med Sci* 2009;**54**:221–4
Bachorzewska-Gajewska	2009	Not a relevant type of population	Bachorzewska-Gajewska H, Poniatowski B, Dobrzycki S. NGAL (neutrophil gelatinase-associated lipocalin) and L-FABP after percutaneous coronary interventions due to unstable angina in patients with normal serum creatinine. *Adv Med Sci* 2009;**54**:221–4
Bachorzewska-Gajewska	2008	Not a relevant type of population	Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Poniatowski B, Pawlak K, Dobrzycki S. NGAL (neutrophil gelatinase-associated lipocalin) and cystatin C: are they good predictors of contrast nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine? *Int J Cardiol* 2008;**127**:290–1
Bachorzewska-Gajewska	2013	Not a relevant type of population	Bachorzewska-Gajewska H, Tomaszuk-Kazberuk A, Jarocka I, Mlodawska E, Lopatowska P, Zalewska-Adamiec M, *et al.* Does neutrophil gelatinase-asociated lipocalin have prognostic value in patients with stable angina undergoing elective PCI? A 3-year follow-up study. *Kidney Blood Press Res* 2013;**37**:280–5
Baek	2019	Not a relevant type of population	Baek SD, Kang JY, Shin S, Park HS, Kim MS, Kim SM, *et al.* Predictive factors of duration of continuous renal replacement therapy in acute kidney injury survivors. *Shock* 2019;**52**:598–603

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Bagheri	2018	< 100 participants	Bagheri S, Einollahi N, Goodarzi MT, Tatari H, Moradi-Sardareh H, Sheikh N. Neutrophil gelatinase-associated lipocalin, cystatin C and matrix metalloproteinase-9 as possible biomarkers in early detection of acute kidney injury after cardiac surgery. *J Clin Diagnostic Res* 2018;**12**:BC05–9
Bagshaw	2011	Not a primary study	Bagshaw SM. Subclinical acute kidney injury: a novel biomarker-defined syndrome. *Crit Care Resusc* 2011;**13**:201–3
Bagshaw	2013	< 100 participants	Bagshaw SM, Bennett M, Devarajan P, Bellomo R. Urine biochemistry in septic and non-septic acute kidney injury: a prospective observational study. *J Crit Care* 2013;**28**:371–8
Balkanay	2015	< 100 participants	Balkanay OO, Goksedef D, Omeroglu SN, Ipek G. The dose-related effects of dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: a randomized, triple-blind, placebo-controlled study. *Interact Cardiovasc Thorac Surg* 2015;**20**:209–14
Balkanay	2018	< 100 participants	Balkanay OO, Göksedef D, Ömeroğlu SN, İpek G. The reliability of the use of serum neutrophil gelatinase-associated lipocalin levels in the assessment of renal functions after coronary artery bypass grafting. *Cardiol Res Pract* 2018;**2018**:7291254
Barbarash	2017	No focus on DTA for AKI	Barbarash OL, Bykova IS, Kashtalap VV, Zykov MV, Hryachkova ON, Kalaeva VV, *et al.* Serum neutrophil gelatinase-associated lipocalin has an advantage over serum cystatin C and glomerular filtration rate in prediction of adverse cardiovascular outcome in patients with ST-segment elevation myocardial infarction. *BMC Cardiovasc Disord* 2017;**17**:81
Baron-Stefaniak	2017	< 100 participants	Baron-Stefaniak J, Schiefer J, Miller EJ, Berlakovich GA, Baron DM, Faybik P. Comparison of macrophage migration inhibitory factor and neutrophil gelatinase-associated lipocalin-2 to predict acute kidney injury after liver transplantation: an observational pilot study. *PLOS ONE* 2017;**12**:e0183162
Bassareo	2013	Not a relevant type of population	Bassareo PP, Fanos V, Mussap M, Flore G, Noto A, Puddu M, *et al.* Urinary NGAL and hematic ADMA levels: an early sign of cardio-renal syndrome in young adults born preterm? *J Matern Fetal Neonatal Med* 2013;**26**(Suppl. 2):80–3
Basturk	2017	< 100 participants	Basturk T, Sari O, Koc Y, Eren N, Isleem M, Kara E, *et al.* Prognostic significance of NGAL in early stage chronic kidney disease. *Minerva Urol Nefrol* 2017;**69**:307–12
Basu	2014	Not a relevant biomarker assay or test	Basu RK, Wang Y, Wong HR, Chawla LS, Wheeler DS, Goldstein SL. Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. *Clin J Am Soc Nephrol* 2014;**9**:654–62
Basu	2014	Not a relevant biomarker assay or test	Basu RK, Wong HR, Krawczeski CD, Wheeler DS, Manning PB, Chawla LS, *et al.* Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. *J Am Coll Cardiol* 2014;**64**:2753–62

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Bataille	2017	No relevant outcome	Bataille A, Tiepolo A, Robert T, Boutten A, Longrois D, Dehoux M, Provenchère S. Reference change values of plasma and urine NGAL in cardiac surgery with cardiopulmonary bypass. *Clin Biochem* 2017;**50**:1098–103
Baumert	2017	< 100 participants	Baumert M, Surmiak P, Więcek A, Walencka Z. Serum NGAL and copeptin levels as predictors of acute kidney injury in asphyxiated neonates. *Clin Exp Nephrol* 2017;**21**:658–64
Bayram	2014	< 100 participants	Bayram A, Ulgey A, Baykan A, Narin N, Narin F, Esmaoglu A, Boyaci A. The effects of dexmedetomidine on early stage renal functions in pediatric patients undergoing cardiac angiography using non-ionic contrast media: a double-blind, randomized clinical trial. *Paediatr Anaesth* 2014;**24**:426–32
Bayram	2014	< 100 participants	Bayram M, Ezelsoy M, Usta E, Oral K, Saraçoğlu A, Bayramoğlu Z, Yıldırım Ö. Rapid detection of acute kidney injury by urinary neutrophil gelatinase-associated lipocalin in patients undergoing cardiopulmonary bypass. *Turk J Anaesthesiol Reanim* 2014;**42**:239–44
Bedford	2016	< 100 participants	Bedford M, Stevens P, Coulton S, Billings J, Farr M, Wheeler T, *et al.* Development of risk models for the prediction of new or worsening acute kidney injury on or during hospital admission: a cohort and nested study. *Health Serv Deliv Res* 2016;**4**(6)
Beitland	2018	Not a primary study	Beitland S, Joannidis M. Biomarkers of acute kidney injury – a mission impossible? *Acta Anaesthesiol Scand* 2018;**62**:2–5
Belcher	2014	< 100 participants	Belcher JM, Sanyal AJ, Peixoto AJ, Perazella MA, Lim J, Thiessen-Philbrook H, *et al.* Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. *Hepatology* 2014;**60**:622–32
Belcher	2015	Not a relevant type of population	Belcher JM, Garcia-Tsao G, Sanyal AJ, Thiessen-Philbrook H, Peixoto AJ, Perazella MA, *et al.* Urinary biomarkers and progression of AKI in patients with cirrhosis. *Clin J Am Soc Nephrol* 2015;**9**:1857–67
Bell	2015	< 100 participants	Bell M, Larsson A, Venge P, Bellomo R, Mårtensson J. Assessment of cell-cycle arrest biomarkers to predict early and delayed acute kidney injury. *Dis Markers* 2015;**2015**:158658
Bellos	2018	Meta-analysis – retained as background material	Bellos I, Fitrou G, Daskalakis G, Perrea DN, Pergialiotis V. Neutrophil gelatinase-associated lipocalin as predictor of acute kidney injury in neonates with perinatal asphyxia: a systematic review and meta-analysis. *Eur J Pediatr* 2018;**177**:1425–34
Benli	2017	< 100 participants	Benli E, Ayyildiz SN, Cirrik S, Noyan T, Ayyildiz A, Cirakoglu A. Early term effect of ureterorenoscopy (URS) on the Kidney: research measuring NGAL, KIM-1, FABP and CYS C levels in urine. *Int Braz J Urol* 2017;**43**:887–95

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Benoit	2019	< 100 participants	Benoit SW, Dixon BP, Goldstein SL, Bennett MR, Lane A, Lounder DT, *et al.* A novel strategy for identifying early acute kidney injury in pediatric hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2019;**54**:1453–61
Benzer	2016	< 100 participants	Benzer M, Alpay H, Baykan Ö, Erdem A, Demir IH. Serum NGAL, cystatin C and urinary NAG measurements for early diagnosis of contrast-induced nephropathy in children. *Ren Fail* 2016;**38**:27–34
Berghaus	2012	Not a primary study	Berghaus TM, Schwaiblmair M, von Scheidt W. Renal biomarkers and prognosis in acute pulmonary embolism. *Heart* 2012;**98**:1185–6
Bhavsar	2012	Not a relevant type of population	Bhavsar NA, Köttgen A, Coresh J, Astor BC. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) as predictors of incident CKD stage 3: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2012;**60**:233–40
Biernawska	2017	< 100 participants	Biernawska J, Bober J, Kotfis K, Bogacka A, Barnik E, Żukowski M. Cardiac surgery related cardio-renal syndrome assessed by conventional and novel biomarkers – under or overestimated diagnosis? *Arch Med Sci* 2017;**13**:1111–20
Biernawska	2018	< 100 participants	Biernawska J, Bober J, Kotfis K, Noceń I, Bogacka A, Barnik E, *et al.* Iron excretion in urine in patients with acute kidney injury after cardiac surgery. *Adv Clin Exp Med* 2018;**27**:1671–6
Bignami	2015	< 100 participants	Bignami E, Frati E, Meroni R, Simonini M, Di Prima AL, Manunta P, Zangrillo A. Urinary neutrophil gelatinase-associated lipocalin time course during cardiac surgery. *Ann Card Anaesth* 2015;**18**:39–44
Bojan	2016	< 100 participants	Bojan M, Basto Duarte MC, Ermak N, Lopez-Lopez V, Mogenet A, Froissart M. Structural equation modelling exploration of the key pathophysiological processes involved in cardiac surgery-related acute kidney injury in infants. *Crit Care* 2016;**20**:171
Bojan	2018	< 100 participants	Bojan M, Basto Duarte MC, Lopez V, Tourneur L, Vicca S, Froissart M. Low perfusion pressure is associated with renal tubular injury in infants undergoing cardiac surgery with cardiopulmonary bypass: a secondary analysis of an observational study. *Eur J Anaesthesiol* 2018;**35**:581–7
Bojic	2015	Not a relevant biomarker assay or test	Bojic S, Kotur-Stevuljevic J, Kalezic N, Stevanovic P, Jelic-Ivanovic Z, Bilanovic D, *et al.* Diagnostic value of matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1 in sepsis-associated acute kidney injury. *Tohoku J Exp Med* 2015;**237**:103–9
Bolignano	2008	< 100 participants	Bolignano D, Lacquaniti A, Coppolino G, Campo S, Arena A, Buemi M. Neutrophil gelatinase-associated lipocalin reflects the severity of renal impairment in subjects affected by chronic kidney disease. *Kidney Blood Press Res* 2008;**31**:255–8

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Bolignano	2009	< 100 participants	Bolignano D, Lacquaniti A, Coppolino G, Donato V, Campo S, Fazio MR, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. *Clin J Am Soc Nephrol* 2009;**4**:337–44
Bolignano	2009	Not a primary study	Bolignano D, Coppolino G, Lombardi L, Buemi M. NGAL: a new missing link between inflammation and uremic anemia? *Ren Fail* 2009;**31**:622–3
Bolignano	2009	Not a primary study	Bolignano D, Coppolino G, Lacquaniti A, Buemi M. Neutrophil gelatinase-associated lipocalin in the intensive care unit: time to look beyond a single, threshold-based measurement? *Crit Care Med* 2009;**37**:2864
Bolignano	2012	Not a primary study	Bolignano D. Serum creatinine and the search for new biomarkers of acute kidney injury (AKI): the story continues. *Clin Chem Lab Med* 2012;**50**:1495–9
Bolignano	2013	< 100 participants	Bolignano D, Lacquaniti A, Coppolino G, Donato V, Campo S, Fazio MR, G, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. *Clin J Am Soc Nephrol* 2013;**4**:337–44
Bolliger	2018	Not a primary study	Bolliger D, Siegemund M. The more, the merrier? – urinary biomarkers for prediction of acute kidney injury after cardiac surgery. *J Cardiothorac Vasc Anesth* 2018;**32**:2201–2
Bonventre	2008	No focus on DTA for AKI	Bonventre JV. Urine neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury in critically ill children. *Nat Clin Pract Nephrol* 2008;**4**:78–9
Bouchard	2015	No focus on DTA for AKI	Bouchard J, Malhotra R, Shah S, Kao YT, Vaida F, Gupta A, *et al.* Levels of protein C and soluble thrombomodulin in critically ill patients with acute kidney injury: a multicenter prospective observational study. *PLOS ONE* 2015;**10**:e0120770
Bramham	2016	No relevant outcome	Bramham K, Seed PT, Lightstone L, Nelson-Piercy C, Gill C, Webster P, *et al.* Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. *Kidney Int* 2016;**89**:874–85
Breidthardt	2012	Not a relevant biomarker assay or test	Breidthardt T, Socrates T, Drexler B, Noveanu M, Heinisch C, Arenja N, *et al.* Plasma neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury in acute heart failure. *Crit Care* 2012;**16**:R2
Breidthardt	2012	Not a relevant type of population	Breidthardt T, Christ-Crain M, Stolz D, Bingisser R, Drexler B, Klima T, *et al.* A combined cardiorenal assessment for the prediction of acute kidney injury in lower respiratory tract infections. *Am J Med* 2012;**125**:168–75
Brinkman	2015	< 100 participants	Brinkman R, HayGlass KT, Mutch WA, Funk DJ. Acute kidney injury in patients undergoing open abdominal aortic aneurysm repair: a pilot observational trial. *J Cardiothorac Vasc Anesth* 2015;**29**:1212–19

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Brulotte	2013	Not a relevant type of population	Brulotte V, Leblond FA, Elkouri S, Thérasse E, Pichette V, Beaulieu P. Bicarbonates for the prevention of postoperative renal failure in endovascular aortic aneurysm repair: a randomized pilot trial. *Anesthesiol Res Pract* 2013;**2013**:467326
Brunner	2006	< 100 participants	Brunner HI, Mueller M, Rutherford C, Passo MH, Witte D, Grom A, *et al.* Urinary neutrophil gelatinase-associated lipocalin as a biomarker of nephritis in childhood-onset systemic lupus erythematosus. *Arthritis Rheum* 2006;**54**:2577–84
Bruno	2016	< 100 participants	Bruno N, ter Maaten JM, Ovchinnikova ES, Vegter EL, Valente MA, van der Meer P, *et al.* MicroRNAs relate to early worsening of renal function in patients with acute heart failure. *Int J Cardiol* 2016;**203**:564–9
Buelow	2012	< 100 participants	Buelow MW, Dall A, Regner K, Weinberg C, Bartz PJ, Sowinski J, *et al.* Urinary interleukin-18 and urinary neutrophil gelatinase-associated lipocalin predict acute kidney injury following pulmonary valve replacement prior to serum creatinine. *Congenit Heart Dis* 2012;**7**:441–7
Buğra	2014	Not a relevant type of population	Buğra O, Baysal A, Fedakar A, Erdem K, Sunar H, Dağlar B. Does serum neutrophil gelatinase-associated lipocalin biomarker detect the early deterioration in renal functions in patients with insulin-dependent diabetes mellitus undergoing coronary artery bypass graft surgery? *Turk J Thorac Cardiovasc Surg* 2014;**22**:63–70
Bulluck	2018	Not a relevant biomarker assay or test	Bulluck H, Maiti R, Chakraborty B, Candilio L, Clayton T, Evans R, *et al.* Neutrophil gelatinase-associated lipocalin prior to cardiac surgery predicts acute kidney injury and mortality. *Heart* 2018;**104**:313–17
Bunchman	2012	Not a primary study	Bunchman TE. Biomarkers for acute kidney injury: is the serum creatinine worthless? *Pediatr Crit Care Med* 2012;**13**:119–20
Bunel	2017	< 100 participants	Bunel V, Tournay Y, Baudoux T, De Prez E, Marchand M, Mekinda Z, *et al.* Early detection of acute cisplatin nephrotoxicity: interest of urinary monitoring of proximal tubular biomarkers. *Clin Kidney J* 2017;**10**:639–47
Bunz	2015	< 100 participants	Bunz H, Weyrich P, Peter A, Baumann D, Tschritter O, Guthoff M, *et al.* Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) and proteinuria predict severity of acute kidney injury in *Puumala* virus infection. *BMC Infect Dis* 2015;**15**:464
Burke-Gaffney	2014	< 100 participants	Burke-Gaffney A, Svermova T, Mumby S, Finney SJ, Evans TW. Raised plasma Robo4 and cardiac surgery-associated acute kidney injury. *PLOS ONE* 2014;**9**:e111459
Cai	2009	< 100 participants	Cai L, Borowiec J, Xu S, Han W, Venge P. Assays of urine levels of HNL/NGAL in patients undergoing cardiac surgery and the impact of antibody configuration on their clinical performances. *Clin Chim Acta* 2009;**403**:121–5

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Camou	2013	< 100 participants	Camou F, Oger S, Paroissin C, Guilhon E, Guisset O, Mourissoux G, *et al.* [Plasma neutrophil gelatinase-associated lipocalin (NGAL) predicts acute kidney injury in septic shock at ICU admission.] *Ann Fr Anesth Reanim* 2013;**32**:157–64
Canakci	2018	< 100 participants	Canakci E, Karatas A, Noyan T, Sertacayhan B. Can acute kidney injury be diagnosed using biomarkers in intensive care patients? *Acta Medica Mediterr* 2018;**34**:2023–9
Cangemi	2013	Not a relevant type of population	Cangemi G, Storti S, Cantinotti M, Fortunato A, Emdin M, Bruschettini M, *et al.* Reference values for urinary neutrophil gelatinase-associated lipocalin (NGAL) in pediatric age measured with a fully automated chemiluminescent platform. *Clin Chem Lab Med* 2013;**51**:1101–5
Capuano	2009	< 100 participants	Capuano F, Goracci M, Luciani R, Gentile G, Roscitano A, Benedetto U, Sinatra R. Neutrophil gelatinase-associated lipocalin levels after use of mini-cardiopulmonary bypass system. *Interact Cardiovasc Thorac Surg* 2009;**9**:797–801
Carey	2018	No focus on DTA for AKI	Carey I, Byrne R, Childs K, Horner M, Bruce M, Wang B, *et al.* Serum NGAL can act as an early renal safety biomarker during long-term nucleos(t)ide analogue antiviral therapy in chronic hepatitis B. *J Viral Hepat* 2018;**25**:1139–50
Carrillo-Esper	2014	< 100 participants	Carrillo-Esper R, Perez-Calatayud AA, Pena-Perez CA, Diaz-Carrillo MA, Nava-Lopez JA, De Los Monteros-Estrada IE, Zepeda-Mendoza AD. Urinary sediment microscopic score as diagnostic marker of acute kidney lesion in sepsis. *Med Interna Mex* 2014;**30**:602–6
Carter	2014	No focus on DTA for AKI	Carter JL, Lamb EJ. Evaluating new biomarkers for acute kidney injury: putting the horse before the cart. *Am J Kidney Dis* 2014;**63**:543–6
Carter	2016	< 100 participants	Carter JL, Parker CT, Stevens PE, Eaglestone G, Knight S, Farmer CK, Lamb EJ. Biological variation of plasma and urinary markers of acute kidney injury in patients with chronic kidney disease. *Clin Chem* 2016;**62**:876–83
Cecchi	2017	< 100 participants	Cecchi E, Avveduto G, D'Alfonso MG, Terreni A, Gelera E, Caldini A, Giglioli C. Cystatin C, but not urinary or serum NGAL, may be associated with contrast induced nephropathy after percutaneous coronary invasive procedures: a single center experience on a limited number of patients. *Acta Medica Academica* 2017;**46**:34–43
Çelik	2013	< 100 participants	Çelik T, Altekin E, İşgüder R, Kenesari Y, Duman M, Arslan N. Evaluation of neutrophil gelatinase-associated lipocalin in pediatric patients with acute rotavirus gastroenteritis and dehydration. *Ital J Pediatr* 2013;**39**:52
Cemil	2014	< 100 participants	Cemil K, Elif C, Serkan YM, Fevzi Y, Deniz AE, Tamer D, Polat D. The value of serum NGAL in determination of dialysis indication. *J Pak Med Assoc* 2014;**64**:739–42

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Cervellin	2012	Not a primary study	Cervellin G, Di Somma S. Neutrophil gelatinase-associated lipocalin (NGAL): the clinician's perspective. *Clin Chem Lab Med* 2012;**50**:1489–93
Chae	2015	Not a relevant type of population	Chae H, Ryu H, Cha K, Kim M, Kim Y, Min CK. Neutrophil gelatinase-associated lipocalin as a biomarker of renal impairment in patients with multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2015;**15**:35–40
Chagan-Yasutan	2016	No focus on DTA for AKI	Chagan-Yasutan H, Chen Y, Lacuesta TL, Leano PSA, Iwasaki H, Hanan F, *et al.* Urine levels of defensin alpha1 reflect kidney injury in leptospirosis patients. *Int J Mol Sci* 2016;**17**:1637
Chang	2009	< 100 participants	Chang CK, Chuter TA, Niemann CU, Shlipak MG, Cohen MJ, Reilly LM, Hiramoto JS. Systemic inflammation, coagulopathy, and acute renal insufficiency following endovascular thoracoabdominal aortic aneurysm repair. *J Vasc Surg* 2009;**49**:1140–6
Chang	2009	< 100 participants	Chang CK, Chuter TA, Niemann CU, Shlipak MG, Cohen MJ, Reilly LM, Hiramoto JS. Systemic inflammation, coagulopathy, and acute renal insufficiency following endovascular thoracoabdominal aortic aneurysm repair. *J Vasc Surg* 2009;**49**:1140–6
Chang	2015	Not a relevant biomarker assay or test	Chang CH, Yang CH, Yang HY, Chen TH, Lin CY, Chang SW, *et al.* Urinary biomarkers improve the diagnosis of intrinsic acute kidney injury in coronary care units. *Medicine* 2015;**94**:e1703
Chang	2017	No focus on DTA for AKI	Chang C, Hu Y, Hogan SL, Mercke N, Gomez M, O'Bryant C, *et al.* Pharmacogenomic variants may influence the urinary excretion of novel kidney injury biomarkers in patients receiving cisplatin. *Int J Mol Sci* 2017;**18**:1333
Chang	2018	Not a relevant biomarker assay or test	Chang W, Zhu S, Pan C, Xie JF, Liu SQ, Qiu HB, Yang Y. Predictive utilities of neutrophil gelatinase-associated lipocalin (NGAL) in severe sepsis. *Clin Chim Acta* 2018;**481**:200–6
Channanayaka	2016	< 100 participants	Channanayaka C, Venkatkrishnan A. Clinical utility of serum neutrophil gelatinase associated lipocalin (NGAL) as an early marker of acute kidney injury in asphyxiated neonates. *J Nepal Paediatr Soc* 2016;**36**:121–5
Che	2010	< 100 participants	Che M, Xie B, Xue S, Dai H, Qian J, Ni Z, *et al.* Clinical usefulness of novel biomarkers for the detection of acute kidney injury following elective cardiac surgery. *Nephron Clin Pract* 2010;**115**:c66–72
Chen	2014	< 100 participants	Chen T, Lu YH, Wang WJ, Bian CY, Cheng XY, Su Y, Zhou PM. Elevated urinary levels of cystatin C and neutrophil gelatinase-associated lipocalin in Henoch–Schonlein purpura patients with renal involvement. *PLOS ONE* 2014;**9**:e101026
Chen	2019	Not a relevant type of population	Chen X, Chen Z, Wei T, Li P, Zhang L, Fu P. The effect of serum neutrophil gelatinase-associated lipocalin on the discontinuation of continuous renal replacement therapy in critically ill patients with acute kidney injury. *Blood Purif* 2019;**48**:10–17

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Chen	2012	Not a relevant biomarker assay or test	Chen TH, Chang CH, Lin CY, Jenq CC, Chang MY, Tian YC, *et al.* Acute kidney injury biomarkers for patients in a coronary care unit: a prospective cohort study. *PLOS ONE* 2012;**7**:e32328
Chen	2016	Not a relevant type of population	Chen C, Yang X, Lei Y, Zha Y, Liu H, Ma C, *et al.* Urinary biomarkers at the time of AKI diagnosis as predictors of progression of AKI among patients with acute cardiorenal syndrome. *Clin J Am Soc Nephrol* 2016;**11**:1536–44
Chen	2016	Not a primary study	Chen CF, Lin CC. Neutrophil gelatinase-associated lipocalin: still a good predictive marker of acute kidney injury in severe septic patients? *J Chin Med Assoc* 2016;**79**:411–12
Cheng	2012	< 100 participants	Cheng CW, Chen YC, Chang CH, Yu HP, Lin CC, Yang MW, *et al.* The ratio of plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury in patients undergoing liver transplantation. *Transplant Proc* 2012;**44**:776–9
Vermi	2014	< 100 participants	Vermi AC, Costopoulos C, Latib A, Piraino D, Maisano F, Naim C, *et al.* Urinary neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury after transcatheter aortic valve implantation. *Hellenic J Cardiol* 2014;**55**:77–9
Chindarkar	2015	No relevant outcome	Chindarkar NS, Chawla LS, Straseski JA, Jortani SA, Uettwiller-Geiger D, Orr RR, *et al.* Demographic data for urinary Acute Kidney Injury (AKI) marker [IGFBP7]·[TIMP2] reference range determinations. *Data Brief* 2015;**5**:888–92
Chindarkar	2016	Not a relevant type of population	Chindarkar NS, Chawla LS, Straseski JA, Jortani SA, Uettwiller-Geiger D, Orr RR, *et al.* Reference intervals of urinary acute kidney injury (AKI) markers [IGFBP7]·[TIMP2] in apparently healthy subjects and chronic comorbid subjects without AKI. *Clin Chim Acta* 2016;**452**:32–7
Cho	2014	< 100 participants	Cho E, Lee JH, Lim HJ, Oh SW, Jo SK, Cho WY, *et al.* Soluble CD25 is increased in patients with sepsis-induced acute kidney injury. *Nephrology* 2014;**19**:318–24
Cho	2018	Not a primary study	Cho SY, Hur M. Neutrophil gelatinase-associated lipocalin as a promising novel biomarker for early detection of kidney injury. *Ann Lab Med* 2018;**38**:393–4
Choi	2013	Not a relevant type of population	Choi HM, Park KT, Lee JW, Cho E, Jo SK, Cho WY, Kim HK. Urine neutrophil gelatinase-associated lipocalin predicts graft outcome up to 1 year after kidney transplantation. *Transplant Proc* 2013;**45**:122–8
Choi	2015	Not a relevant type of population	Choi JW, Fujii T, Fujii N. Corrected neutrophil gelatinase-associated lipocalin (NGAL) level adjusted by the scoring system of an inflammation index for screening renal dysfunction in patients with systemic inflammation. *Ann Clin Lab Sci* 2015;**45**:248–55

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Choi	2017	Not a relevant type of population	Choi JW, Fujii T, Fujii N. Diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin (NGAL) as an inflammatory biomarker for low-grade inflammation. *Biomed Res India* 2017;**28**:6406–11
Chou	2013	Not a relevant type of population	Chou KM, Lee CC, Chen CH, Sun CY. Clinical value of NGAL, L-FABP and albuminuria in predicting GFR decline in type 2 diabetes mellitus patients. *PLOS ONE* 2013;**8**:e54863
Choudhry	2018	Not a relevant type of population	Choudhry N, Ihsan A, Mahmood S, Haq FU, Gondal AJ. Neutrophil gelatinase associated lipocalin, an early biomarker for diagnosis of acute kidney injury after percutaneous coronary intervention. *Turk J Biochem* 2018;**43**:15–21
Chun	2018	< 100 participants	Chun W, Kim Y, Yoon J, Lee S, Yim H, Cho YS, *et al.* Assessment of plasma neutrophil gelatinase-associated lipocalin for early detection of acute kidney injury and prediction of mortality in severely burned patients. *J Burn Care Res* 2018;**39**:387–93
Civiletti	2019	< 100 participants	Civiletti F, Assenzio B, Mazzeo AT, Medica D, Giaretta F, Deambrosis I, *et al.* Acute tubular injury is associated with severe traumatic brain injury: in vitro study on human tubular epithelial cells. *Sci Rep* 2019;**9**:6090
Coca	2013	Retained as background material	Coca SG, Garg AX, Swaminathan M, Garwood S, Hong K, Thiessen-Philbrook H, *et al.* Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. *Nephrol Dial Transplant* 2013;**28**:2787–99
Coca	2008	Systematic review – retained as background material	Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int* 2008;**73**:1008–16
Codorniu	2018	Meta-analysis – retained as background material	Codorniu A, Lemasle L, Legrand M, Blet A, Mebazaa A, Gayat E. Methods used to assess the performance of biomarkers for the diagnosis of acute kidney injury: a systematic review and meta-analysis. *Biomarkers* 2018;**23**:766–72
Codsi	2017	Not a relevant type of population	Codsi E, Garovic VD, Gonzalez-Suarez ML, Milic N, Borowski KS, Rose CH, *et al.* Longitudinal characterization of renal proximal tubular markers in normotensive and preeclamptic pregnancies. *Am J Physiol Regul Integr Comp Physiol* 2017;**312**:R773–R778
Connolly	2018	Not a relevant type of population	Connolly M, Kinnin M, McEneaney D, Menown I, Kurth M, Lamont J, *et al.* Prediction of contrast induced acute kidney injury using novel biomarkers following contrast coronary angiography. *QJM* 2018;**111**:103–10
Constantin	2010	< 100 participants	Constantin JM, Futier E, Perbet S, Roszyk L, Lautrette A, Gillart T, *et al.* Plasma neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in adult critically ill patients: a prospective study. *J Crit Care* 2010;**25**:176

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Corbacıoglu	2017	< 100 participants	Corbacıoglu SK, Cevik Y, Akinci E, Uzunosmanoglu H, Dagar S, Safak T, *et al.* Value of plasma neutrophil gelatinase-associated lipocalin (NGAL) in distinguishing between acute kidney injury (AKI) and chronic kidney disease (CKD). *Turk J Emerg Med* 2017;**17**:85–8
Córdova-Sánchez	2019	< 100 participants	Córdova-Sánchez BM, Ruiz-García EB, López-Yañez A, Barragan-Dessavre M, Bautista-Ocampo AR, Meneses-García A, *et al.* Plasma neutrophil gelatinase-associated lipocalin and factors related to acute kidney injury and mortality in critically ill cancer patients. *ecancermedicalscience* 2019;**13**:903
Coupes	2015	< 100 participants	Coupes B, de Freitas DG, Roberts SA, Read I, Riad H, Brenchley PE, Picton ML. rhErythropoietin-b as a tissue protective agent in kidney transplantation: a pilot randomized controlled trial. *BMC Res Notes* 2015;**8**:21
Cruz	2009	Not a primary study	Cruz DN, Soni S, Ronco C. NGAL and cardiac surgery-associated acute kidney injury. *Am J Kidney Dis* 2009;**53**:565–6
Cruz	2012	Systematic review – retained as background material	Cruz DN, Gaiao S, Maisel A, Ronco C, Devarajan P. Neutrophil gelatinase-associated lipocalin as a biomarker of cardiovascular disease: a systematic review. *Clin Chem Lab Med* 2012;**50**:1533–45
Cruz	2010	Not a relevant biomarker assay or test	Cruz DN, de Cal M, Garzotto F, Perazella MA, Lentini P, Corradi V, *et al.* Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. *Intensive Care Med* 2010;**36**:444–51
Cruz	2016	< 100 participants	Cruz DN, Virzì GM, Brocca A, Ronco C, Giavarina D. A comparison of three commercial platforms for urinary NGAL in critically ill adults. *Clin Chem Lab Med* 2016;**54**:353–62
Cuartero	2017	< 100 participants	Cuartero M, Ballús J, Sabater J, Pérez X, Nin N, Ordonez-Llanos J, Betbesé AJ. Cell-cycle arrest biomarkers in urine to predict acute kidney injury in septic and non-septic critically ill patients. *Ann Intensive Care* 2017;**7**:92
Cullaro	2017	Not a relevant biomarker assay or test	Cullaro G, Kim G, Pereira MR, Brown RS, Verna EC. Ascites neutrophil gelatinase-associated lipocalin identifies spontaneous bacterial peritonitis and predicts mortality in hospitalized patients with cirrhosis. *Dig Dis Sci* 2017;**62**:3487–94
Cullaro	2018	< 100 participants	Cullaro G, Pisa JF, Brown RS, Wagener G, Verna EC. Early postoperative neutrophil gelatinase-associated lipocalin predicts the development of chronic kidney disease after liver transplantation. *Transplantation* 2018;**102**:809–15
da Rocha	2018	< 100 participants	da Rocha EP, Yokota LG, Sampaio BM, Cardoso Eid KZ, Dias DB, de Freitas FM, *et al.* Urinary neutrophil gelatinase-associated lipocalin is excellent predictor of acute kidney injury in septic elderly patients. *Aging Dis* 2018;**9**:182–91

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Daggülli	2016	< 100 participants	Daggülli M, Utangaç MM, Dede O, Bodakci MN, Hatipoglu NK, Penbegül N, *et al.* Potential biomarkers for the early detection of acute kidney injury after percutaneous nephrolithotripsy. *Ren Fail* 2016;**38**:151–6
Dahlén	2001	< 100 participants	Dahlén I, Janson C, Björnsson E, Stålenheim G, Peterson CG, Venge P. Changes in inflammatory markers following treatment of acute exacerbations of obstructive pulmonary disease. *Respir Med* 2001;**95**:891–7
Dai	2015	Not a relevant biomarker assay or test	Dai X, Zeng Z, Fu C, Zhang S, Cai Y, Chen Z. Diagnostic value of neutrophil gelatinase-associated lipocalin, cystatin C, and soluble triggering receptor expressed on myeloid cells-1 in critically ill patients with sepsis-associated acute kidney injury. *Crit Care* 2015;**19**:223
Dai	2016	< 100 participants	Dai X, Li T, Zeng Z, Fu C, Wang S, Cai Y, Chen Z. The effect of continuous venovenous hemofiltration on neutrophil gelatinase-associated lipocalin plasma levels in patients with septic acute kidney injury. *BMC Nephrol* 2016;**17**:154
Damman	2017	Not a relevant biomarker assay or test	Damman K, Valente MAE, van Veldhuisen DJ, Cleland JGF, O'Connor CM, Metra M, *et al.* Plasma neutrophil gelatinase-associated lipocalin and predicting clinically relevant worsening renal function in acute heart failure. *Int J Mol Sci* 2017;**18**:1470
Daniels	2012	Not a relevant type of population	Daniels LB, Barrett-Connor E, Clopton P, Laughlin GA, Ix JH, Maisel AS. Plasma neutrophil gelatinase-associated lipocalin is independently associated with cardiovascular disease and mortality in community-dwelling older adults: the Rancho Bernardo study. *J Am Coll Cardiol* 2012;**59**:1101–9
Daniels	2012	Not a primary study	Daniels RC, Bunchman TE. Is it the neutrophil gelatinase-associated lipocalin or the pediatricRIFLE? *Pediatr Crit Care Med* 2012;**13**:698
Dankova	2016	< 100 participants	Dankova M, Pazmanova T, Hricak V, Gergel J, Svobodova V, Zitny B, *et al.* Urinary NGAL as a predictor of acute kidney injury in patients with acute heart failure. *Cardiol Lett* 2016;**25**:9–15
Dardashti	2014	< 100 participants	Dardashti A, Ederoth P, Algotsson L, Bronden B, Grins E, Larsson M, *et al.* Erythropoietin and protection of renal function in cardiac surgery (the EPRICS trial). *Anesthesiology* 2014;**121**:582–90
Darmon	2011	Not a primary study	Darmon M, Gonzalez F, Vincent F. Limits of neutrophil gelatinase-associated lipocalin at intensive care unit admission for prediction of acute kidney injury. *Am J Respir Crit Care Med* 2011;**184**:142–3
Darmon	2017	Not a primary study	Darmon M, Ostermann M, Joannidis M. Predictions are difficult … especially about AKI. *Intensive Care Med* 2017;**43**:932–4
Datzmann	2018	< 100 participants	Datzmann T, Hoenicka M, Reinelt H, Liebold A, Gorki H. Influence of 6% hydroxyethyl starch 130/0.4 versus crystalloid solution on structural renal damage markers after coronary artery bypass grafting: a post hoc subgroup analysis of a prospective trial. *J Cardiothorac Vasc Anesth* 2018;**32**:205–11

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Daubin	2017	No focus on DTA for AKI	Daubin D, Cristol JP, Dupuy AM, Kuster N, Besnard N, Platon L, *et al.* Urinary Biomarkers IGFBP7 and TIMP-2 for the diagnostic assessment of transient and persistent acute kidney injury in critically ill patients. *PLOS ONE* 2017;**12**:e0169674
De Berardinis	2015	Not a relevant biomarker assay or test	De Berardinis B, Gaggin HK, Magrini L, Belcher A, Zancla B, Femia A, *et al.* Comparison between admission natriuretic peptides, NGAL and sST2 testing for the prediction of worsening renal function in patients with acutely decompensated heart failure. *Clin Chem Lab Med* 2015;**53**:613–21
de Geus	2010	Not a primary study	de Geus HR, Betjes MG, Bakker J. Neutrophil gelatinase-associated lipocalin clearance during veno-venous continuous renal replacement therapy in critically ill patients. *Intensive Care Med* 2010;**36**:2156–7
de Geus	2011	Not a relevant biomarker assay or test	de Geus HR, Bakker J, Lesaffre EM, le Noble JL. Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. *Am J Respir Crit Care Med* 2011;**183**:907–14
de Geus	2011	Not a relevant biomarker assay or test	de Geus HR, Woo JG, Wang Y, Devarajan P, Betjes MG, le Noble JL, Bakker J. Urinary neutrophil gelatinase-associated lipocalin measured on admission to the intensive care unit accurately discriminates between sustained and transient acute kidney injury in adult critically ill patients. *Nephron Extra* 2011;**1**:9–2
de Geus	2013	Not a relevant biomarker assay or test	de Geus HR, Fortrie G, Betjes MG, van Schaik RH, Groeneveld AB. Time of injury affects urinary biomarker predictive values for acute kidney injury in critically ill, non-septic patients. *BMC Nephrol* 2013;**14**:273
de Geus	2013	Not a relevant biomarker assay or test	de Geus HR, Betjes MG, Schaick Rv, Groeneveld JA. Plasma NGAL similarly predicts acute kidney injury in sepsis and nonsepsis. *Biomark Med* 2013;**7**:415–21
de Geus	2017	Not a primary study	de Geus HR, Haase M, Jacob L. The cardiac surgery-associated neutrophil gelatinase-associated lipocalin score for postoperative acute kidney injury: does subclinical acute kidney injury matter? *J Thorac Cardiovasc Surg* 2017;**154**:939–40
de Grooth	2018	Not a primary study	de Grooth HJ, Parienti JJ, Schetz M. AKI biomarkers are poor discriminants for subsequent need for renal replacement therapy, but do not disqualify them yet. *Intensive Care Med* 2018;**44**:1156–8
De Loor	2016	Pilot study or preliminary analysis only	De Loor J, Decruyenaere J, Demeyere K, Nuytinck L, Hoste EA, Meyer E. Urinary chitinase 3-like protein 1 for early diagnosis of acute kidney injury: a prospective cohort study in adult critically ill patients. *Crit Care* 2016;**20**:38
Dede	2015	< 100 participants	Dede O, Dağguli M, Utanğaç M, Yuksel H, Bodakcı MN, Hatipoğlu NK, *et al.* Urinary expression of acute kidney injury biomarkers in patients after RIRS: it is a prospective, controlled study. *Int J Clin Exp Med* 2015;**8**:8147–52

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Dedeoglu	2013	< 100 participants	Dedeoglu B, de Geus HR, Fortrie G, Betjes MG. Novel biomarkers for the prediction of acute kidney injury in patients undergoing liver transplantation. *Biomark Med* 2013;**7**:947–57
Deger	2020	< 100 participants	Deger SM, Erten Y, Suyani E, Aki SZ, Ulusal Okyay G, Pasaoglu OT, *et al.* Early diagnostic markers for detection of acute kidney injury in allogeneic hematopoietic stem cell transplant recipients. *Exp Clin Transplant* 2020;**18**:98–105
Deininger	2016	No relevant outcome	Deininger S, Hoenicka M, Müller-Eising K, Rupp P, Liebold A, Koenig W, Gorki H. Renal function and urinary biomarkers in cardiac bypass surgery: a prospective randomized trial comparing three surgical techniques. *Thorac Cardiovasc Surg* 2016;**64**:561–8
Dekker	2019	No focus on DTA for AKI	Dekker SEI, Ruhaak LR, Romijn FPHTM, Meijer E, Cobbaert CM, de Fijter JW, Soonawala D. Urinary tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 do not correlate with disease severity in ADPKD patients. *Kidney Int Rep* 2019;**4**:833–41
Delcroix	2013	< 100 participants	Delcroix G, Gillain N, Moonen M, Radermacher L, Damas F, Minon JM, Fraipont V. NGAL Usefulness in the intensive care unit three hours after cardiac surgery. *ISRN Nephrol* 2013;**2013**:865164
Delfino Duarte	2015	< 100 participants	Delfino Duarte PA, Fumagalli AC, Wandeur V, Becker D. Urinary neutrophil gelatinase-associated lipocalin in critically ill surgical cancer patients. *Indian J Crit Care Med* 2015;**19**:251–6
Demirtas	2013	< 100 participants	Demirtas S, Caliskan A, Karahan O, Yavuz C, Guclu O, Cayir MC, *et al.* Neutrophil gelatinase-associated lipocalin as a biomarker for acute kidney injury in patients undergoing coronary artery bypass grafting. *Exp Clin Cardiol* 2013;**18**:107–9
Dent	2007	Not a relevant biomarker assay or test	Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, Devarajan P. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. *Crit Care* 2007;**11**:R127
Dépret	2018	< 100 participants	Dépret F, Boutin L, Jarkovský J, Chaussard M, Soussi S, Bataille A, *et al.* Prediction of major adverse kidney events in critically ill burn patients. *Burns* 2018;**44**:1887–94
Derhaschnig	2014	< 100 participants	Derhaschnig U, Testori C, Riedmueller E, Hobl EL, Mayr FB, Jilma B. Decreased renal function in hypertensive emergencies. *J Hum Hypertens* 2014;**28**:427–31
Devarajan	2008	Meta-analysis – retained as background material	Devarajan P. Emerging urinary biomarkers in the diagnosis of acute kidney injury. *Expert Opin Med Diagn* 2008;**2**:387–98
Devarajan	2008	Not a primary study	Devarajan P. Neutrophil gelatinase-associated lipocalin – an emerging troponin for kidney injury. *Nephrol Dial Transplant* 2008;**23**:3737–43

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Devarajan	2009	Not a primary study	Devarajan P. (2009) Neutrophil Gelatinase-associated Lipocalin: An Emerging Biomarker for Angina Renalis. In Vincent JL, editor. *Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer; 2009. pp. 620–6
Devarajan	2014	Not a primary study	Devarajan P. NGAL for the detection of acute kidney injury in the emergency room. *Biomark Med* 2014;**8**:217–19
Dewey	2013	Not a primary study	Dewey M, Schonenberger E. Increase in creatinine for the prediction of contrast-induced nephropathy. *Radiology* 2013;**269**:623–4
Dewitte	2015	< 100 participants	Dewitte A, Joannes-Boyau O, Sidobre C, Fleureau C, Bats ML, Derache P, *et al.* Kinetic eGFR and novel AKI biomarkers to predict renal recovery. *Clin J Am Soc Nephrol* 2015;**10**:1900–10
Di Nardo	2013	< 100 participants	Di Nardo M, Ficarella A, Ricci Z, Luciano R, Stoppa F, Picardo S, *et al.* Impact of severe sepsis on serum and urinary biomarkers of acute kidney injury in critically ill children: an observational study. *Blood Purif* 2013;**35**:172–6
Díaz de León-Martínez	2019	< 100 participants	Díaz de León-Martínez L, Díaz-Barriga F, Barbier O, Ortíz DLG, Ortega-Romero M, Pérez-Vázquez F, Flores-Ramírez R. Evaluation of emerging biomarkers of renal damage and exposure to aflatoxin-B1 in Mexican indigenous women: a pilot study. *Environ Sci Pollut Res Int* 2019;**26**:12205–216
Doi	2013	Not a relevant biomarker assay or test	Doi K, Urata M, Katagiri D, Inamori M, Murata S, Hisagi M, *et al.* Plasma neutrophil gelatinase-associated lipocalin in acute kidney injury superimposed on chronic kidney disease after cardiac surgery: a multicenter prospective study. *Crit Care* 2013;**17**:R270
Donadio	2014	Not a relevant biomarker assay or test	Donadio C. Effect of glomerular filtration rate impairment on diagnostic performance of neutrophil gelatinase-associated lipocalin and B-type natriuretic peptide as markers of acute cardiac and renal failure in chronic kidney disease patients. *Crit Care* 2014;**18**:R39
Downes	2017	< 100 participants	Downes KJ, Dong M, Fukuda T, Clancy JP, Haffner C, Bennett MR, *et al.* Urinary kidney injury biomarkers and tobramycin clearance among children and young adults with cystic fibrosis: a population pharmacokinetic analysis. *J Antimicrob Chemother* 2017;**72**:254–60
Du	2011	Not a relevant biomarker assay or test	Du Y, Zappitelli M, Mian A, Bennett M, Ma Q, Devarajan P, *et al.* Urinary biomarkers to detect acute kidney injury in the pediatric emergency center. *Pediatr Nephrol* 2011;**26**:267–74
Du	2014	< 100 participants	Du Y, Hou L, Guo J, Sun T, Wang X, Wu Y. Renal neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 expression in children with acute kidney injury and Henoch–Schönlein purpura nephritis. *Exp Ther Med* 2014;**7**:1130–4
Du	2017	< 100 participants	Du W, Shen T, Li H, Liu Y, He L, Tan L, Hu M. Urinary NGAL for the diagnosis of the renal injury from multiple myeloma. *Cancer Biomark* 2017;**18**:41–6

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Dubin	2018	Not a relevant type of population	Dubin RF, Judd S, Scherzer R, Shlipak M, Warnock DG, Cushman M, *et al.* Urinary tubular injury biomarkers are associated with ESRD and death in the REGARDS study. *Kidney Int Rep* 2018;**3**:1183–92
Dusse	2016	< 100 participants	Dusse F, Edayadiyil-Dudásova M, Thielmann M, Wendt D, Kahlert P, Demircioglu E, *et al.* Early prediction of acute kidney injury after transapical and transaortic aortic valve implantation with urinary G1 cell cycle arrest biomarkers. *BMC Anesthesiol* 2016;**16**:76
Dwipa	2012	< 100 participants	Dwipa L, Soelaeman R, Roesli RM, Martanto E, Adhiarta IG. Cardiometabolic risk factors and acute kidney injury based on urinary neutrophil gelatinase associated lipocalin (NGALu) in acute coronary syndrome patients. *Acta Med Indones* 2012;**44**:3–9
Egal	2016	Not a relevant biomarker assay or test	Egal M, de Geus HR, Groeneveld AB. Neutrophil gelatinase-associated lipocalin as a diagnostic marker for acute kidney injury in oliguric critically ill patients: a post-hoc analysis. *Nephron* 2016;**134**:81–8
Eilenberg	2016	< 100 participants	Eilenberg W, Stojkovic S, Piechota-Polanczyk A, Kaun C, Rauscher S, Gröger M, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) is associated with symptomatic carotid atherosclerosis and drives pro-inflammatory state in vitro. *Eur J Vasc Endovasc Surg* 2016;**51**:623–31
Eirin	2012	< 100 participants	Eirin A, Gloviczki ML, Tang H, Rule AD, Woollard JR, Lerman A, *et al.* Chronic renovascular hypertension is associated with elevated levels of neutrophil gelatinase-associated lipocalin. *Nephrol Dial Transplant* 2012;**27**:4153–61
Eisenhart	2010	Not a relevant type of population	Eisenhart E, Benson S, Lacombe P, Himmelfarb J, Zimmerman R, Schimelman B, Parker MG. Safety of low volume iodinated contrast administration for arteriovenous fistula intervention in chronic kidney disease stage 4 or 5 utilizing a bicarbonate prophylaxis strategy. *Semin Dial* 2010;**23**:638–42
Ejaz	2015	< 100 participants	Ejaz AA, Alquadan KF, Dass B, Shimada M, Kanbay M, Johnson RJ. Effects of serum uric acid on estimated GFR in cardiac surgery patients: a pilot study. *Am J Nephrol* 2015;**42**:402–9
Raggal	2013	< 100 participants	Raggal NE, Khafagy SM, Mahmoud NH, Beltagy SE. Serum neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury in asphyxiated neonates. *Indian Pediatr* 2013;**50**:459–62
El Shahawy	2018	< 100 participants	El Shahawy MS, Hemida MH, Abdel-Hafez HA, El-Baz TZ, Lotfy AWM, Emran TM. Urinary neutrophil gelatinase-associated lipocalin as a marker for disease activity in lupus nephritis. *Scand J Clin Lab Invest* 2018;**78**:264–8
El-Akabawy	2017	< 100 participants	El-Akabawy H, Shafee M, Roshdy AM, Abd Al Salam A. Urinary neutrophil gelatinase associated lipocalin as an early marker of acute kidney injury in the recipient after liver transplantation. *Egypt J Crit Care Med* 2017;**5**:49–55

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
El-Farghali	2012	< 100 participants	El-Farghali OG, El-Raggal NM, Mahmoud NH, Zaina GA. Serum neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury in critically-ill neonates. *Pak J Biol Sci* 2012;**15**:231–7
Elia	2015	< 100 participants	Elia C, Graupera I, Barreto R, Solà E, Moreira R, Huelin P, *et al.* Severe acute kidney injury associated with non-steroidal anti-inflammatory drugs in cirrhosis: a case-control study. *J Hepatol* 2015;**63**:593–600
Elmas	2017	< 100 participants	Elmas AT, Karadag A, Tabel Y, Ozdemir R, Otlu G. Analysis of urine biomarkers for early determination of acute kidney injury in non-septic and non-asphyxiated critically ill preterm neonates. *J Matern Fetal Neonatal Med* 2017;**30**:302–8
Elmedany	2017	< 100 participants	Elmedany SM, Naga SS, Elsharkawy R, Mahrous RS, Elnaggar AI. Novel urinary biomarkers and the early detection of acute kidney injury after open cardiac surgeries. *J Crit Care* 2017;**40**:171–7
Elmer	2016	< 100 participants	Elmer J, Jeong K, Abebe KZ, Guyette FX, Murugan R, Callaway CW, Rittenberger JC, Pittsburgh post-cardiac arrest service. serum neutrophil gelatinase-associated lipocalin predicts survival after resuscitation from cardiac arrest. *Crit Care Med* 2016;**44**:111–19
Elsharawy	2016	< 100 participants	Elsharawy S, Raslan L, Morsy S, Hassan B, Khalifa N. Plasma neutrophil gelatinase-associated lipocalin as a marker for the prediction of worsening renal function in children hospitalized for acute heart failure. *Saudi J Kidney Dis Transpl* 2016;**27**:49–54
Emlet	2017	Not a relevant type of population	Emlet DR, Pastor-Soler N, Marciszyn A, Wen X, Gomez H, Humphries WH, *et al.* Insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases-2: differential expression and secretion in human kidney tubule cells. *Am J Physiol Renal Physiol* 2017;**312**:F284–F296
Endre	2011	Not a relevant biomarker assay or test	Endre ZH, Pickering JW, Walker RJ, Devarajan P, Edelstein CL, Bonventre JV, *et al.* Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. *Kidney Int* 2011;**79**:1119–30
Endre	2014	No focus on DTA for AKI	Endre ZH. Novel biomarkers of acute kidney injury: time for implementation? *Biomark Med* 2014;**8**:1185–8
Endre	2014	Not a primary study	Endre ZH, and Pickering JW. Acute kidney injury: late-onset acute kidney injury-subacute or more of the same? *Nat Rev Nephrol* 2014;**10**:133–4
Endre	2014	Not a primary study	Endre ZH, Pickering JW. Acute kidney injury: cell cycle arrest biomarkers win race for AKI diagnosis. *Nat Rev Nephrol* 2014;**10**:683–5
Erturk	2015	< 100 participants	Erturk A, Cure E, Parlak E, Cure MC, Sahin SB, Yuce S. Clinical significance of neutrophil gelatinase-associated lipocalin in Crimean-Congo hemorrhagic fever. *Biomed Res Int* 2015;**2015**:374010

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Espinosa-Sevilla	2013	Not a primary study	Espinosa-Sevilla A, Amezcua-Macias AI, Ruiz-Palacios PC, Rodriguez-Weber F, Diaz-Greene E. New markers of acute kidney injury in critically ill patients. *Med Interna Mex* 2013;**29**:513–17
Essajee	2015	Not a relevant biomarker assay or test	Essajee F, Were F, Admani B. Urine neutrophil gelatinase-associated lipocalin in asphyxiated neonates: a prospective cohort study. *Pediatr Nephrol* 2015;**30**:1189–96
Essajee	2015	Not a relevant type of population	Essajee F, Were F, Admani B. Urine neutrophil gelatinase-associated lipocalin in asphyxiated neonates: a prospective cohort study. *Pediatr Nephrol* 2015;**30**:1189–96
Cho	2013	Duplicate of a study that had already been assessed	Cho E, Yang HN, Jo SK, Cho WY, Kim HK. The role of urinary liver-type fatty acid-binding protein in critically ill patients. *J Korean Med Sci* 2013;**28**:100–5
Ezenwaka	2016	Not a relevant biomarker assay or test	Ezenwaka CE, Idris S, Davis G, Roberts L. Measurement of neutrophil gelatinase-associated lipocalin (NGAL) in patients with non-communicable diseases: any additional benefit? *Arch Physiol Biochem* 2016;**122**:70–4
Fadel	2012	< 100 participants	Fadel FI, Abdel Rahman AM, Mohamed MF, Habib SA, Ibrahim MH, Sleem ZS, *et al.* Plasma neutrophil gelatinase-associated lipocalin as an early biomarker for prediction of acute kidney injury after cardio-pulmonary bypass in pediatric cardiac surgery. *Arch Med Sci* 2012;**8**:250–5
Fagundes	2012	No focus on DTA for AKI	C. Fagundes, M. N. Pepin, M. Guevara, R. Barreto, G. Casals, E. Sola, G. Pereira, E. Rodriguez, E. Garcia, V. Prado, E. Poch, W. Jimenez, J. Fernandez, V. Arroyo and P. Gines. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012;**57**:267–73
Fan	2018	Not a relevant biomarker assay or test	Fan H, Zhao Y, Sun M, Zhu JH. Urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, N-acetyl-beta-D-glucosaminidase levels and mortality risk in septic patients with acute kidney injury. *Arch Med Sci* 2018;**14**:1381–6
Fan	2014	Not a relevant biomarker assay or test	Fan H, Zhao Y, Zhu JH, Song FC. Urine neutrophil gelatinase-associated lipocalin in septic patients with and without acute kidney injury. *Renal Fail* 2014;**36**:1399–1403
Fanning	2016	< 100 participants	Fanning N, Galvin S, Parke R, Gilroy J, Bellomo R, McGuinness S. A prospective study of the timing and accuracy of neutrophil gelatinase-associated lipocalin levels in predicting acute kidney injury in high-risk cardiac surgery patients. *J Cardiothorac Vasc Anesth* 2016;**30**:76–81
Fathimah	2012	< 100 participants	Fathimah M, Alicezah MK, Thevarajah M. Neutrophil gelatinase-associated lipocalin (NGAL): an early marker for diabetic nephropathy. *Int J Diabetes Dev Ctries* 2012;**32**:19–24

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Feldkamp	2011	Not a primary study	Feldkamp T, Bienholz A, Kribben A. Urinary neutrophil gelatinase-associated lipocalin (NGAL) for the detection of acute kidney injury after orthotopic liver transplantation. *Nephrol Dial Transplant* 2011;**26**:1456–8
Feng	2016	No relevant outcome	Feng YG, Liang B, Liu J, Jiang MD, Liu HJ, Huang YQ, Xiao L. Correlation study of podocyte injury and kidney function in patients with acute kidney injury. *J Acute Dis* 2016;**5**:493–6
Ferguson	2010	< 100 participants	Ferguson MA, Vaidya VS, Waikar SS, Collings FB, Sunderland KE, Gioules CJ, Bonventre JV. Urinary liver-type fatty acid-binding protein predicts adverse outcomes in acute kidney injury. *Kidney Int* 2010;**77**:708–14
Fernandes	2014	< 100 participants	Fernandes A, Ettinger J, Amaral F, Ramalho MJ, Alves R, Modolo NS. General anesthesia type does not influence serum levels of neutrophil gelatinase-associated lipocalin during the perioperative period in video laparoscopic bariatric surgery. *Clinics* 2014;**69**:655–9
Filho	2017	Systematic review – retained as background material	Filho LT, Grande AJ, Colonetti T, Della ÉSP, da Rosa MI. Accuracy of neutrophil gelatinase-associated lipocalin for acute kidney injury diagnosis in children: systematic review and meta-analysis. *Pediatr Nephrol* 2017;**32**:1979–88
Filiopoulos	2013	Not a relevant type of population	Filiopoulos V, Biblaki D, Lazarou D, Chrisis D, Fatourou M, Lafoyianni S, Vlassopoulos D. Plasma neutrophil gelatinase-associated lipocalin (NGAL) as an early predictive marker of contrast-induced nephropathy in hospitalized patients undergoing computed tomography. *Clin Kidney J* 2013;**6**:578–83
Filiopoulos	2014	No focus on DTA for AKI	Filiopoulos V, Biblaki D, Vlassopoulos D. Neutrophil gelatinase-associated lipocalin (NGAL): a promising biomarker of contrast-induced nephropathy after computed tomography. *Ren Fail* 2014;**36**:979–86
Finge	2017	< 100 participants	Finge T, Bertran S, Roger C, Candela D, Pereira B, Scott C, *et al.* Interest of urinary [TIMP-2] × [IGFBP-7] for predicting the occurrence of acute kidney injury after cardiac surgery: a gray zone approach. *Anesth Analg* 2017;**125**:762–9
Fiorentino	2019	< 100 participants	Fiorentino M, Tohme FA, Murugan R, Kellum JA. Plasma biomarkers in predicting renal recovery from acute kidney injury in critically ill patients. *Blood Purif* 2019;**48**:253–61
Flechet	2017	Not a relevant biomarker assay or test	Flechet M, Güiza F, Schetz M, Wouters P, Vanhorebeek I, Derese I, *et al.* AKI predictor, an online prognostic calculator for acute kidney injury in adult critically ill patients: development, validation and comparison to serum neutrophil gelatinase-associated lipocalin. *Intensive Care Med* 2017;**43**:764–73
Foroughi	2014	No focus on DTA for AKI	Foroughi M, Argani H, Hassntash SA, Hekmat M, Majidi M, Beheshti M, *et al.* Lack of renal protection of ultrafiltration during cardiac surgery: a randomized clinical trial. *J Cardiovasc Surg* 2014;**55**:407–13

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Forster	2019	< 100 participants	Forster CS, Goldstein S, Pohl H, Jackson E. Association between urodynamic parameters and urine neutrophil gelatinase-associated lipocalin concentrations in children with neuropathic bladders. *J Pediatr Urol* 2019;**15**:155
Fortova	2011	< 100 participants	Fortova M, Lejsek J, Pechova M, Prusa R. Examination of urine neutrophil gelatinase-associated lipocalin following cardiac surgery in adults. *Aktual v Nefrol* 2011;**17**:136–141
Fouad	2019	< 100 participants	Fouad TR, Abdelsameea E, Elsabaawy M, Ashraf Eljaky M, Zaki El-shenawy S, Omar N. Urinary neutrophil gelatinase-associated lipocalin for diagnosis of spontaneous bacterial peritonitis. *Trop Doct* 2019;**49**:189–92
Fouda	2013	< 100 participants	Fouda M, Sherif HM, Shehata M, Ibrahim A. Early expression of urinary neutrophil gelatinase-associated lipocalin biomarker predicts acute kidney injury complicating circulatory shock. *Egypt J Crit Care Med* 2013;**1**:79–86
Fox	2018	Not a relevant type of population	Fox E, Levin K, Zhu Y, Segers B, Balamuth N, Womer R, *et al.* Pantoprazole, an inhibitor of the organic cation transporter 2, does not ameliorate cisplatin-related ototoxicity or nephrotoxicity in children and adolescents with newly diagnosed osteosarcoma treated with methotrexate, doxorubicin, and cisplatin. *Oncologist* 2018;**23**:762–e79
Francoz	2014	Not a primary study	Francoz C, Durand F. Type-1 hepatorenal syndrome in patients with cirrhosis and infection vs. sepsis-induced acute kidney injury: what matters? *J Hepatol* 2014;**60**:907–9
Friedrich	2017	< 100 participants	Friedrich MG, Bougioukas I, Kolle J, Bireta C, Jebran FA, Placzek M, Tirilomis T. NGAL expression during cardiopulmonary bypass does not predict severity of postoperative acute kidney injury. *BMC Nephrol* 2017;**18**:1–7
Fuernau	2015	Not a relevant biomarker assay or test	Fuernau G, Poenisch C, Eitel I, Denks D, de Waha S, Pöss J, *et al.* Prognostic impact of established and novel renal function biomarkers in myocardial infarction with cardiogenic shock: a biomarker substudy of the IABP-SHOCK II-trial. *Int J Cardiol* 2015;**191**:159–66
Gaipov	2015	< 100 participants	Gaipov A, Solak Y, Turkmen K, Toker A, Baysal AN, Cicekler H, *et al.* Serum uric acid may predict development of progressive acute kidney injury after open heart surgery. *Ren Fail* 2015;**37**:96–102
Gallagher	2015	< 100 participants	Gallagher SM, Jones DA, Kapur A, Wragg A, Harwood SM, Mathur R, *et al.* Remote ischemic preconditioning has a neutral effect on the incidence of kidney injury after coronary artery bypass graft surgery. *Kidney Int* 2015;**87**:473–81
Gan	2018	Not a primary study	Gan J, Zhou X. Comparison of urine neutrophil gelatinase-associated lipocalin and interleukin-18 in prediction of acute kidney injury in adults. *Medicine* 2018;**97**:e12570

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Garg	2017	Not a primary study	Garg N, Gupta R. Can serum neutrophil gelatinase-associated lipocalin be precisely used as a diagnostic marker of sepsis in pediatric cases? *Pediatr Crit Care Med* 2017;**18**:1191–2
Gaspari	2010	Not a relevant type of population	Gaspari F, Cravedi P, Mandalà M, Perico N, de Leon FR, Stucchi N, *et al.* Predicting cisplatin-induced acute kidney injury by urinary neutrophil gelatinase-associated lipocalin excretion: a pilot prospective case-control study. *Nephron Clin Pract* 2010;**115**:c154–60
Gerbes	2011	Not a primary study	Gerbes AL, Benesic A, Vogeser M, Krag A, Bendtsen F, Møller S. Serum neutrophil gelatinase-associated lipocalin – a sensitive novel marker of renal impairment in liver cirrhosis? *Digestion* 2011;**84**:82–3
Ghonemy	2014	< 100 participants	Ghonemy TA, Amro GM. Plasma neutrophil gelatinase-associated lipocalin (NGAL) and plasma cystatin C (CysC) as biomarker of acute kidney injury after cardiac surgery. *Saudi J Kidney Dis Transpl* 2014;**25**:582–8
Gil	2009	Not a relevant type of population	Gil HW, Yang JO, Lee EY, Hong SY. Clinical implication of urinary neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 in patients with acute paraquat intoxication. *Clin Toxicol* 2009;**47**:870–5
Gilquin	2017	Not a relevant type of population	Gilquin B, Louwagie M, Jaquinod M, Cez A, Picard G, El Kholy L, *et al.* Multiplex and accurate quantification of acute kidney injury biomarker candidates in urine using Protein Standard Absolute Quantification (PSAQ) and targeted proteomics. *Talanta* 2017;**164**:77–84
Gist	2017	< 100 participants	Gist KM, Goldstein SL, Wrona J, Alten JA, Basu RK, Cooper DS, *et al.* Kinetics of the cell cycle arrest biomarkers (TIMP-2*IGFBP-7) for prediction of acute kidney injury in infants after cardiac surgery. *Pediatr Nephrol* 2017;**32**:1611–19
Glassford	2013	Not a relevant type of population	Glassford NJ, Schneider AG, Xu S, Eastwood GM, Young H, Peck L, *et al.* The nature and discriminatory value of urinary neutrophil gelatinase-associated lipocalin in critically ill patients at risk of acute kidney injury. *Intensive Care Med* 2013;**39**:1714–24
Gocze	2015	Not a relevant type of population	Gocze I, Koch M, Renner P, Zeman F, Graf BM, Dahlke MH, *et al.* Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. *PLOS ONE* 2015;**10**:e0120863
Göcze	2017	No focus on DTA for AKI	Göcze I, Jauch D, Götz M, Kennedy P, Jung B, Zeman F, *et al.* Biomarker-guided intervention to prevent acute kidney injury after major surgery. *Ann Surg* 2017;**267**:1013–20
Goknar	2015	No focus on DTA for AKI	Goknar N, Oktem F, Ozgen IT, Torun E, Kuçukkoc M, Demir AD, Cesur Y. Determination of early urinary renal injury markers in obese children. *Pediatr Nephrol* 2015;**30**:139–44

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Goksuluk	2019	Not a relevant type of population	Goksuluk H, Esenboga K, Kerimli N, Atmaca Y. The effect of renin–angiotensin system blocking agents on the risk of contrast-induced nephropathy and early detection with neutrophil gelatinase-associated lipocalin in diabetic patients undergoing coronary procedures. *Acta Medica Mediterr* 2019;**35**:187–92
Goldstein	2018	< 100 participants	Goldstein BH, Goldstein SL, Devarajan P, Zafar F, Kwiatkowski DM, Marino BS, *et al.* First-stage palliation strategy for univentricular heart disease may impact risk for acute kidney injury. *Cardiol Young* 2018;**28**:93–100
Gomaa	2019	< 100 participants	Gomaa SH, Shamseya MM, Madkour MA. Clinical utility of urinary neutrophil gelatinase-associated lipocalin and serum cystatin C in a cohort of liver cirrhosis patients with renal dysfunction: a challenge in the diagnosis of hepatorenal syndrome. *Eur J Gastroenterol Hepatol* 2019;**31**:692–702
Gombert	2018	< 100 participants	Gombert A, Prior I, Martin L, Grommes J, Barbati ME, Foldenauer AC, *et al.* Urine neutrophil gelatinase-associated lipocalin predicts outcome and renal failure in open and endovascular thoracic abdominal aortic aneurysm surgery. *Sci Rep* 2018;**8**:12676
Gombert	2019	< 100 participants	Gombert A, Martin L, Foldenauer AC, Krajewski C, Greiner A, Kotelis D, *et al.* Comparison of urine and serum neutrophil gelatinase-associated lipocalin after open and endovascular thoraco-abdominal aortic surgery and their meaning as indicators of acute kidney injury. *Vasa* 2019;**48**:79–87
Gong	2015	Non-English-language publication	Gong M, Yang Y, Zhang S. [Value of acute renal injury associated biomarkers for patients in intensive care unit.] *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2015;**40**:1083–8
Gordillo	2016	< 100 participants	Gordillo R, Ahluwalia T, Woroniecki R. Hyperglycemia and acute kidney injury in critically ill children. *Int J Nephrol Renov Dis* 2016;**9**:201–4
Greenberg	2018	No relevant outcome	Greenberg JH, Zappitelli M, Jia Y, Thiessen-Philbrook HR, De Fontnouvelle CA, Wilson FP, *et al.* Biomarkers of AKI progression after pediatric cardiac surgery. *J Am Soc Nephrol* 2018;**29**:1549–56
Grosman-Rimon	2019	< 100 participants	Grosman-Rimon L, Hui SG, Freedman D, Elbaz-Greener G, Cherney D, Rao V. Biomarkers of inflammation, fibrosis, and acute kidney injury in patients with heart failure with and without left ventricular assist device implantation. *Cardiorenal Med* 2019;**9**:108–16
Gubhaju	2014	Not a relevant type of population	Gubhaju L, Sutherland MR, Horne RS, Medhurst A, Kent AL, Ramsden A, *et al.* Assessment of renal functional maturation and injury in preterm neonates during the first month of life. *Am J Physiol Renal Physiol* 2014;**307**:F149–58

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Guerci	2018	< 100 participants	Guerci P, Claudot JL, Novy E, Settembre N, Lalot JM, Losser MR. Immediate postoperative plasma neutrophil gelatinase-associated lipocalin to predict acute kidney injury after major open abdominal aortic surgery: a prospective observational study. *Anaesth Crit Care Pain Med* 2018;**37**:327–34
Guerrero-Orriach	2016	< 100 participants	Guerrero-Orriach JL, Ariza-Villanueva D, Florez-Vela A, Garrido-Sánchez L, Moreno-Cortés MI, Galán-Ortega M, *et al.* Cardiac, renal, and neurological benefits of preoperative levosimendan administration in patients with right ventricular dysfunction and pulmonary hypertension undergoing cardiac surgery: evaluation with two biomarkers neutrophil gelatinase-associated lipocalin and neuronal enolase. *Ther Clin Risk Manag* 2016;**12**:623–30
Güneş	2016	< 100 participants	Güneş A, Ece A, Akça H, Aktar F, Mete Ş, Samanci S, *et al.* Urinary kidney injury molecules in children with febrile seizures. *Ren Fail* 2016;**38**:1377–82
Gungor	2014	< 100 participants	Gungor G, Ataseven H, Demir A, Solak Y, Gaipov A, Biyik M, *et al.* Neutrophil gelatinase-associated lipocalin in prediction of mortality in patients with hepatorenal syndrome: a prospective observational study. *Liver Int* 2014;**34**:49–57
Gunnerson	2016	No relevant outcome. Subgroup analysis of already included study	Gunnerson KJ, Shaw AD, Chawla LS, Bihorac A, Al-Khafaji A, Kashani K, *et al.* TIMP2•IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients. *J Trauma Acute Care Surg* 2016;**80**:243–9
Haase	2009	Meta-analysis – retained as background material	Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, NGAL Meta-analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009;**54**:1012–24
Haase	2011	Not a primary study	Haase M, Bellomo R, Haase-Fielitz A. Neutrophil gelatinase-associated lipocalin: a superior biomarker for detection of subclinical acute kidney injury and poor prognosis. *Biomark Med* 2011;**5**:415–17
Haase	2009	Not a relevant biomarker assay or test	Haase M, Bellomo R, Devarajan P, Ma Q, Bennett MR, Möckel M, *et al.* Novel biomarkers early predict the severity of acute kidney injury after cardiac surgery in adults. *Ann Thorac Surg* 2009;**88**:124–30
Haase-Fielitz	2009	Not a relevant biomarker assay or test	Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Dragun D, Haase M. Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery – a prospective cohort study. *Crit Care Med* 2009;**37**:553–60
Haase-Fielitz	2009	Not a relevant biomarker assay or test	Haase-Fielitz A, Bellomo R, Devarajan P, Bennett M, Story D, Matalanis G, *et al.* The predictive performance of plasma neutrophil gelatinase-associated lipocalin (NGAL) increases with grade of acute kidney injury. *Nephrol Dial Transplant* 2009;**24**:3349–54

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Haase-Fielitz	2014	Systematic review – retained as background material	Haase-Fielitz A, Haase M, Devarajan P. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: a critical evaluation of current status. *Ann Clin Biochem* 2014;**51**:335–51
Hahn	2017	Not a primary study	Hahn RG, Zdolsek J. Nephrocheck results should be corrected for dilution. *Acta Anaesthesiol Scand* 2017;**61**:261–2
Hall	2012	Not a relevant type of population	Hall IE, Doshi MD, Reese PP, Marcus RJ, Thiessen-Philbrook H, Parikh CR. Association between peritransplant kidney injury biomarkers and 1-year allograft outcomes. *Clin J Am Soc Nephrol* 2012;**7**:1224–33
Hall	2018	Systematic review – retained as background material	Hall PS, Mitchell ED, Smith AF, Cairns DA, Messenger M, Hutchinson M, *et al.* The future for diagnostic tests of acute kidney injury in critical care: evidence synthesis, care pathway analysis and research prioritisation. *Health Technol Assess* 2018;**22**(32)
Hamdy	2018	< 100 participants	Hamdy HS, El-Ray A, Salaheldin M, Lasheen M, Aboul-Ezz M, Abdel-Moaty AS, Abdel-Rahim A. Urinary neutrophil gelatinase-associated lipocalin in cirrhotic patients with acute kidney injury. *Ann Hepatol* 2018;**17**:624–30
Hamishehkar	2017	Not a relevant type of population	Hamishehkar H, Sanaie S, Fattahi V, Mesgari M, Mahmoodpoor A. The effect of furosemide on the level of neutrophil gelatinase-associated lipocalin in critically hospitalized patients with acute kidney injury. *Indian J Crit Care Med* 2017;**21**:442–7
Han	2009	< 100 participants	Han WK, Wagener G, Zhu Y, Wang S, Lee HT. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery. *Clin J Am Soc Nephrol* 2009;**4**:873–82
Hang	2017	Not a relevant biomarker assay or test	Hang CC, Yang J, Wang S, Li CS, Tang ZR. Evaluation of serum neutrophil gelatinase-associated lipocalin in predicting acute kidney injury in critically ill patients. *J Int Med Res* 2017;**45**:1231–44
Hanna	2016	< 100 participants	Hanna M, Brophy PD, Giannone PJ, Joshi MS, Bauer JA, RamachandraRao S. Early urinary biomarkers of acute kidney injury in preterm infants. *Pediatr Res* 2016;**80**:218–23
Hassan	2017	< 100 participants	Hassan RH, Kandil SM, Zeid MS, Zaki ME, Fouda AE. Kidney injury in infants and children with iron-deficiency anemia before and after iron treatment. *Hematology* 2017;**22**:565–70
Hayashi	2017	< 100 participants	Hayashi H, Sato W, Kosugi T, Nishimura K, Sugiyama D, Asano N, *et al.* Efficacy of urinary midkine as a biomarker in patients with acute kidney injury. *Clin Exp Nephrol* 2017;**21**:597–607
Hazle	2013	< 100 participants	Hazle MA, Gajarski RJ, Aiyagari R, Yu S, Abraham A, Donohue J, Blatt NB. Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age. *J Thorac Cardiovasc Surg* 2013;**146**:861–7.e1

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Heise	2011	< 100 participants	Heise D, Rentsch K, Braeuer A, Friedrich M, Quintel M. Comparison of urinary neutrophil glucosaminidase-associated lipocalin, cystatin C, and alpha1-microglobulin for early detection of acute renal injury after cardiac surgery. *Eur J Cardiothorac Surg* 2011;**39**:38–43
Helanova	2015	Not a relevant type of population	Helanova K, Littnerova S, Kubena P, Ganovska E, Pavlusova M, Kubkova L, *et al.* Prognostic impact of neutrophil gelatinase-associated lipocalin and B-type natriuretic in patients with ST-elevation myocardial infarction treated by primary PCI: a prospective observational cohort study. *BMJ Open* 2015;**5**:e006872
Herbert	2015	No focus on DTA for AKI	Herbert C, Patel M, Nugent A, Dimas VV, Guleserian KJ, Quigley R, Modem V. Serum cystatin C as an early marker of neutrophil gelatinase-associated lipocalin-positive acute kidney injury resulting from cardiopulmonary bypass in infants with congenital heart disease. *Congenit Heart Dis* 2015;**10**:E180–8
Heung	2016	No relevant outcome. Subgroup analysis of already included study	Heung M, Ortega LM, Chawla LS, Wunderink RG, Self WH, Koyner JL, *et al.* Common chronic conditions do not affect performance of cell cycle arrest biomarkers for risk stratification of acute kidney injury. *Nephrol Dial Transplant* 2016;**31**:1633–40
Heydari	2017	< 100 participants	Heydari B, Khalili H, Beigmohammadi MT, Abdollahi A, Karimzadeh I. Effects of atorvastatin on biomarkers of acute kidney injury in amikacin recipients: a pilot, randomized, placebo-controlled, clinical trial. *J Res Med Sci* 2017;**22**:39
Hinck	2018	< 100 participants	Hinck BD, Miyaoka R, Lingeman JE, Assimos DG, Matlaga BR, Pramanik R, *et al.* Urine kidney injury markers do not increase following gastric bypass: a multi-center cross-sectional study. *Can J Urol* 2018;**25**:9199–204
Hirsch	2007	Not a relevant type of population	Hirsch R, Dent C, Pfriem H, Allen J, Beekman RH, Ma Q, *et al.* NGAL is an early predictive biomarker of contrast-induced nephropathy in children. *Pediatr Nephrol* 2007;**22**:2089–95
Hjortrup	2013	Systematic review – retained as background material	Hjortrup PB, Haase N, Wetterslev M, Perner A. Clinical review: predictive value of neutrophil gelatinase-associated lipocalin for acute kidney injury in intensive care patients. *Crit Care* 2013;**17**:211
Ho	2009	< 100 participants	Ho J, Lucy M, Krokhin O, Hayglass K, Pascoe E, Darroch G, *et al.* Mass spectrometry-based proteomic analysis of urine in acute kidney injury following cardiopulmonary bypass: a nested case-control study. *Am J Kidney Dis* 2009;**53**:584–95
Ho	2015	Meta-analysis – retained as background material	Ho J, Tangri N, Komenda P, Kaushal A, Sood M, Brar R, *et al.* Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: a meta-analysis. *Am J Kidney Dis* 2015;**66**:993–1005

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Hodgson	2019	< 100 participants	Hodgson LE, Venn RM, Short S, Roderick PJ, Hargreaves D, Selby N, Forni LG. Improving clinical prediction rules in acute kidney injury with the use of biomarkers of cell cycle arrest: a pilot study. *Biomarkers* 2019;**24**:23–8
Hoffman	2013	< 100 participants	Hoffman SB, Massaro AN, Soler-García AA, Perazzo S, Ray PE. A novel urinary biomarker profile to identify acute kidney injury (AKI) in critically ill neonates: a pilot study. *Pediatr Nephrol* 2013;**28**:2179–88
Holderied	2018	Not a relevant type of population	Holderied A. IGFBP7/TIMP-2 based prevention of acute kidney injury: does 'time is nephron' apply in AKI? *Nephrologe* 2018;**13**:192–4
Hollmen	2011	Not a primary study	Hollmen M. Diagnostic test for early detection of acute kidney injury. *Expert Rev Mol Diagn* 2011;**11**:553–5
Holzscheiter	2014	Not a relevant type of population	Holzscheiter L, Beck C, Rutz S, Manuilova E, Domke I, Guder WG, Hofmann W. NGAL, L-FABP, and KIM-1 in comparison to established markers of renal dysfunction. *Clin Chem Lab Med* 2014;**52**:537–46
Hong	2013	< 100 participants	Hong DY, Lee JH, Park SO, Baek KJ, Lee KR. Plasma neutrophil gelatinase-associated lipocalin as early biomarker for acute kidney injury in burn patients. *J Burn Care Res* 2013;**34**:e326–32
Honore	2016	No relevant outcome. Subgroup analysis of already included study	Honore PM, Nguyen HB, Gong M, Chawla LS, Bagshaw SM, Artigas A, *et al.* Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 for risk stratification of acute kidney injury in patients with sepsis. *Crit Care Med* 2016;**44**:1851–60
Honore	2016	Not a primary study	Honore PM, Spapen HD. Neutrophil gelatinase-associated lipocalin elimination by renal replacement therapy: minding the membrane! *Crit Care* 2016;**20**:87
Hoskova	2013	< 100 participants	Hoskova L, Franekova J, Malek I, Secnik P Jr, Pirk J, Kautzner J, *et al.* Relationship of cardiorenal biomarkers for prediction of renal dysfunction in patients after heart transplantation. *Cor Vasa* 2013;**55**:E364–9
Hoskova	2016	No relevant outcome	Hoskova L, Franekova J, Malek I, Kautzner J, Szarszoi O, Jabor A, *et al.* Comparison of cystatin C and NGAL in early diagnosis of acute kidney injury after heart transplantation. *Ann Transplant* 2016;**21**:239–45
Hosohata	2016	< 100 participants	Hosohata K, Washino S, Kubo T, Natsui S, Fujisaki A, Kurokawa S, *et al.* Early prediction of cisplatin-induced nephrotoxicity by urinary vanin-1 in patients with urothelial carcinoma. *Toxicology* 2016;**359-360**:71–5
Hoste	2018	Not a primary study	Hoste EA, Vandenberghe W. Plasma neutrophil gelatinase-associated lipocalin (NGAL) for timing of initiation of renal replacement therapy for acute kidney injury? *J Thorac Dis* 2018;**10**(Suppl. 33): S3989–93

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Howell	2015	< 100 participants	Howell E, Sen S, Palmieri T, Godwin Z, Bockhold J, Greenhalgh D, Tran NK. Point-of-care B-type natriuretic peptide and neutrophil gelatinase-associated lipocalin measurements for acute resuscitation: a pilot study. *J Burn Care Res* 2015;**36**:e26–33
Hryniewiecka	2014	No focus on DTA for AKI	Hryniewiecka E, Gala K, Krawczyk M, Pączek L. Is neutrophil gelatinase-associated lipocalin an optimal marker of renal function and injury in liver transplant recipients? *Transplant Proc* 2014;**46**:2782–5
Hsiao	2012	< 100 participants	Hsiao PG, Hsieh CA, Yeh CF, Wu HH, Shiu TF, Chen YC, Chu PG. Early prediction of acute kidney injury in patients with acute myocardial injury. *J Crit Care* 2012;**27**:525
Hsu	2012	Not a primary study	Hsu RK, Hsu CY. We can diagnose AKI 'early'. *Clin J Am Soc Nephrol* 2012;**7**:1741–2
Huang	2016	< 100 participants	Huang CY, Shih CC, Chung K, Kao KC, Wu HP. Predictive value of plasma neutrophil gelatinase-associated lipocalin for acute renal failure in patients with severe sepsis. *J Chin Med Assoc* 2016;**79**:428–34
Huelin	2019	Not a relevant type of population	Huelin P, Solà E, Elia C, Solé C, Risso A, Moreira R, *et al.* Neutrophil gelatinase-associated lipocalin for assessment of acute kidney injury in cirrhosis: a prospective study. *Hepatology* 2019;**70**:319–33
Hui-Miao	2017	Meta-analysis – retained as background material	Hui-Miao J, Li-Feng H, Zheng Y, Wen-Xiong L, Jia HM, Huang LF, *et al.* Diagnostic value of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 for acute kidney injury: a meta-analysis. *Crit Care* 2017;**21**:1–11
Hunsicker	2017	< 100 participants	Hunsicker O, Feldheiser A, Weimann A, Liehre D, Sehouli J, Wernecke KD, Spies C. Diagnostic value of plasma NGAL and intraoperative diuresis for AKI after major gynecological surgery in patients treated within an intraoperative goal-directed hemodynamic algorithm. *Medicine* 2017;**96**:e7357
Hur	2014	Not a relevant biomarker assay or test	Hur M, Kim H, Lee S, Cristofano F, Magrini L, Marino R, *et al.* Diagnostic and prognostic utilities of multimarkers approach using procalcitonin, B-type natriuretic peptide, and neutrophil gelatinase-associated lipocalin in critically ill patients with suspected sepsis. *BMC Infect Dis* 2014;**14**:224
Hurry	2017	< 100 participants	Hurry PK, Poulsen JH, Bendtsen F, Møller S. Neutrophil gelatinase-associated lipocalin and cystatin C in cirrhosis and portal hypertension: Relations to organ extraction and dysfunction. *J Gastroenterol Hepatol* 2017;**32**:473–81
Hwang	2014	< 100 participants	Hwang YJ, Hyun MC, Choi BS, Chun SY, Cho MH. Acute kidney injury after using contrast during cardiac catheterization in children with heart disease. *J Korean Med Sci* 2014;**29**:1102–7

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Ibrahim	2019	< 100 participants	Ibrahim ME, Chang C, Hu Y, Hogan SL, Mercke N, Gomez M, *et al.* Pharmacokinetic determinants of cisplatin-induced subclinical kidney injury in oncology patients. *Eur J Clin Pharmacol* 2019;**75**:51–7
Iguchi	2012	< 100 participants	Iguchi N, Uchiyama A, Hosotsubo K, Fujino Y. Plasma neutrophil gelatinase-associated lipocalin clearance during venovenous hemodiafiltration. *Clin Exp Nephrol* 2012;**16**:356–7
Iguchi	2015	< 100 participants	Iguchi N, Uchiyama A, Ueta K, Sawa Y, Fujino Y. Neutrophil gelatinase-associated lipocalin and liver-type fatty acid-binding protein as biomarkers for acute kidney injury after organ transplantation. *J Anesth* 2015;**29**:249–55
In	2014	Not a relevant type of population	In JW, Kim JE, Jeong JS, Song SH, Kim HK. Diagnostic and prognostic significance of neutrophil gelatinase-associated lipocalin in disseminated intravascular coagulation. *Clin Chim Acta* 2014;**430**:145–9
Innami	2014	< 100 participants	Innami Y, Katori N, Mori K, Kosugi S, Suzuki T, Sakurai N, *et al.* Increased prothrombotic property as a risk factor of acute kidney injury after surgical repair of abdominal aortic aneurysm: a prospective observational study. *J Intensive Care* 2014;**2**:46
Introcaso	2018	< 100 participants	Introcaso G, Nafi M, Bonomi A, L'Acqua C, Salvi L, Ceriani R, *et al.* Improvement of neutrophil gelatinase-associated lipocalin sensitivity and specificity by two plasma measurements in predicting acute kidney injury after cardiac surgery. *Biochemia Medica* 2018;**28**:030701
Işıkkent	2018	< 100 participants	Işıkkent A, Yılmaz S, Özturan IU, Doğan NO, Yaka E, Gültekin H, *et al.* Utility of neutrophil celatinase-associated lipocalin in the management of acute kidney injury: a prospective, observational study. *Hong Kong J Emerg Med* 2018;**27**:8–14
Isler	2018	< 100 participants	Isler Y, Ozdinc S, Kaya H. Can NGAL be used as an early marker of contrast-induced nephropathy in emergency department? *Acta Medica Mediterr* 2018;**34**:1889–94
Ismail	2012	< 100 participants	Ismail G, Bobeica R, Ioanitescu S, Jurubita R. Association of serum and urinary neutrophil gelatinase-associated lipocalin (NGAL) levels with disease severity in patients with early-stage autosomal dominant polycystic kidney disease. *Rev Roman Med Lab* 2012;**20**:109–16
Isshiki	2016	No relevant outcome	Isshiki R, Asada T, Sato D, Sumida M, Hamasaki Y, Inokuchi R, *et al.* Association of urinary neutrophil gelatinase-associated lipocalin with long-term renal outcomes in ICU survivors: a retrospective observational cohort study. *Shock* 2016;**46**:44–51
Itenov	2014	No focus on DTA for AKI	Itenov TS, Bangert K, Christensen PH, Jensen JU, Bestle MH, Jakobsen ML, *et al.* Serum and plasma neutrophil gelatinase associated lipocalin (NGAL) levels are not equivalent in patients admitted to intensive care. *J Clin Lab Anal* 2014;**28**:163–7

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Izadi	2016	Systematic review – retained as background material	Izadi A, Yousefifard M, Nakhjavan-Shahraki B, Baikpour M, Razaz JM, Ataei N, Hosseini M. Value of plasma/serum neutrophil gelatinase-associated lipocalin in detection of pediatric acute kidney injury; a systematic review and meta-analysis. *Int J Pediatr* 2016;**4**:3815–36
Jafari	2018	< 100 participants	Jafari M, Ala S, Haddadi K, Alipour A, Mojtahedzadeh M, Ehteshami S, *et al.* Cotreatment with furosemide and hypertonic saline decreases serum neutrophil gelatinase-associated lipocalin (NGAL) and serum creatinine concentrations in traumatic brain injury: a randomized, single-blind clinical trial. *Iran J Pharm Res* 2018;**17**:1130–40
Jahnukainen	2018	< 100 participants	Jahnukainen T, Keski-Nisula J, Tainio J, Valkonen H, Patila T, Jalanko H, Suominen P. Efficacy of corticosteroids in prevention of acute kidney injury in neonates undergoing cardiac surgery – a randomized controlled trial. *Acta Anaesthesiol Scand* 2018;**62**:1072–9
Jain	2016	< 100 participants	Jain V, Mehta Y, Gupta A, Sharma R, Raizada A, Trehan N. The role of neutrophil gelatinase-associated lipocalin in predicting acute kidney injury in patients undergoing off-pump coronary artery bypass graft: a pilot study. *Ann Card Anaesth* 2016;**19**:225–30
Jayaraman	2014	Not a relevant biomarker assay or test	Jayaraman R, Sunder S, Sathi S, Gupta VK, Sharma N, Kanchi P, *et al.* Post cardiac surgery acute kidney injury: a woebegone status rejuvenated by the novel biomarkers. *Nephrourol Mon* 2014;**6**:e19598
Jelinek	2018	Not a relevant type of population	Jelinek MJ, Lee SM, Wyche Okpareke A, Wing C, Koyner JL, Murray PT, *et al.* Predicting acute renal injury in cancer patients receiving cisplatin using urinary neutrophil gelatinase-associated lipocalin and cystatin C. *Clin Transl Sci* 2018;**11**:420–7
Jeong	2012	< 100 participants	Jeong TD, Kim S, Lee W, Song GW, Kim YK, Chun S, *et al.* Neutrophil gelatinase-associated lipocalin as an early biomarker of acute kidney injury in liver transplantation. *Clin Transplant* 2012;**26**:775–81
Je-Yeob	2013	Not a relevant biomarker assay or test	Je-Yeob LEE, Jin-Young KIM, Sang OP, Kyeong-Ryong LEE, Kwang-Je B, Dae-Young H. Plasma neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury. *J Korean Soc Emerg Med* 2013;**2**:157–163
Jia	2017	Meta-analysis – retained as background material	Jia HM, Huang LF, Zheng Y, Li WX. Diagnostic value of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 for acute kidney injury: a meta-analysis. *Crit Care* 2017;**21**:77
Jia	2017	Meta-analysis – retained as background material	Jia HM, Huang LF, Zheng Y, Li WX. Prognostic value of cell cycle arrest biomarkers in patients at high risk for acute kidney injury: a systematic review and meta-analysis. *Nephrology* 2017;**22**:831–7
Jiang	2015	Not a relevant type of population	Jiang L, Cui H. Could blood neutrophil gelatinase-associated lipocalin (NGAL) be a diagnostic marker for acute kidney injury in neonates? A systemic review and meta-analysis. *Clin Lab* 2015;**61**:1815–20

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Jiang	2018	No relevant outcome	Jiang QQ, Han MF, Ma K, Chen G, Wan XY, Kilonzo SB, *et al.* Acute kidney injury in acute-on-chronic liver failure is different from in decompensated cirrhosis. *World J Gastroenterol* 2018;**24**:2300–10
Joannes-Boyau	2012	Not a primary study	Joannes-Boyau O, Fichet J. NGAL and sepsis. *Ann Fr Anesth Reanim* 2012;**31:**8–9
Jobs	2014	< 100 participants	Jobs K, Straż-Żebrowska E, Placzyńska M, Zdanowski R, Kalicki B, Lewicki S, Jung A. Interleukin-18 and NGAL in assessment of ESWL treatment safety in children with urolithiasis. *Cent Eur J Immunol* 2014;**39**:384–91
Jochmans	2017	< 100 participants	Jochmans I, Meurisse N, Neyrinck A, Verhaegen M, Monbaliu D, Pirenne J. Hepatic ischemia/reperfusion injury associates with acute kidney injury in liver transplantation: prospective cohort study. *Liver Transpl* 2017;**23**:634–44
Journois	2013	Not a primary study	Journois D, Jacob L. [NGAL more or less than a biomarker?] *Ann Fr Anesth Reanim* 2013;**3**:134–5
Jungbauer	2011	No focus on DTA for AKI	Jungbauer CG, Birner C, Jung B, Buchner S, Lubnow M, Von Bary C, *et al.* Kidney injury molecule-1 and *N*-acetyl-β-D-glucosaminidase in chronic heart failure: possible biomarkers of cardiorenal syndrome. *Eur J Heart Fail* 2011;**13**:1104–10
Kaddourah	2016	< 100 participants	Kaddourah A, Goldstein SL, Basu R, Nehus EJ, Terrell TC, Brunner L, *et al.* Novel urinary tubular injury markers reveal an evidence of underlying kidney injury in children with reduced left ventricular systolic function: a pilot study. *Pediatr Nephrol* 2016;**31**:1637–45
Kafkas	2012	Not a relevant type of population	Kafkas N, Demponeras C, Zouboulloglou F, Spanou L, Babalis D, Makris K. Serum levels of gelatinase associated lipocalin as indicator of the inflammatory status in coronary artery disease. *Int J Inflam* 2012;**2012**:189797
Kafkas	2016	Not a relevant type of population	Kafkas N, Liakos C, Zouboulloglou F, Dagadaki O, Dragasis S, Makris K. Neutrophil gelatinase-associated lipocalin as an early marker of contrast-induced nephropathy after elective invasive cardiac procedures. *Clin Cardiol* 2016;**39**:464–70
Kahli	2014	< 100 participants	Kahli A, Guenancia C, Zeller M, Grosjean S, Stamboul K, Rochette L, *et al.* Growth differentiation factor-15 (GDF-15) levels are associated with cardiac and renal injury in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. *PLOS ONE* 2014;**9**:e105759
Kališnik	2017	< 100 participants	Kališnik JM, Hrovat E, Hrastovec A, Žibert J, Jerin A, Skitek M, *et al.* Creatinine, neutrophil gelatinase-associated lipocalin, and cystatin C in determining acute kidney injury after heart operations using cardiopulmonary bypass. *Artif Organs* 2017;**41**:481–9
Kalisnik	2017	Not a primary study	Kalisnik JM, Fischlein T, Santarpino G. Cardiac surgery-associated neutrophil gelatinase-associated lipocalin score for postoperative acute kidney injury: what is the clinical implication? *J Thorac Cardiovasc Surg* 2017;**154**:938

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Kambhampat	2013	Not a relevant biomarker assay or test	Kambhampati G, Ejaz NI, Asmar A, Aiyer RK, Aiyer R, Arif AA, *et al.* Fluid balance and conventional and novel biomarkers of acute kidney injury in cardiovascular surgery. *J Cardiovasc Surg* 2013;**54**:639–46
Kamis	2016	Not a relevant biomarker assay or test	Kamis F, Yegenaga I, Musul M, Baydemir C, Bek S, Kalender B, Baykara N. Neutrophil gelatinase-associated lipocalin levels during the first 48 hours of intensive care may indicate upcoming acute kidney injury. *J Crit Care* 2016;**34**:89–94
Kanchi	2017	< 100 participants	Kanchi M, Manjunath R, Massen J, Vincent L, Belani K. Neutrophil gelatinase-associated lipocalin as a biomarker for predicting acute kidney injury during off-pump coronary artery bypass grafting. *Ann Card Anaesth* 2017;**20**:297–302
Kandil	2017	< 100 participants	Kandil MA, Abouelenain KM, Alsebaey A, Rashed HS, Afifi MH, Mahmoud MA, Yassen KA. Impact of terlipressin infusion during and after live donor liver transplantation on incidence of acute kidney injury and neutrophil gelatinase-associated lipocalin serum levels: a randomized controlled trial. *Clin Transplant* 2017;**31**:e13019
Kandur	2016	< 100 participants	Kandur Y, Gonen S, Fidan K, Soylemezoglu O. Evaluation of urinary KIM-1, NGAL, and IL-18 levels in determining early renal injury in pediatric cases with hypercalciuria and/or renal calculi. *Clin Nephrol* 2016;**86**:62–9
Karademir	2016	< 100 participants	Karademir LD, Dogruel F, Kocyigit I, Yazici C, Unal A, Sipahioglu MH, *et al.* The efficacy of theophylline in preventing cisplatin-related nephrotoxicity in patients with cancer. *Ren Fail* 2016;**38**:806–14
Savran Karadeniz	2019	< 100 participants	Savran Karadeniz M, Alp Enişte I, Şentürk Çiftçi H, Usta S, Tefik T, Şanlı Ö, *et al.* Neutrophil gelatinase-associated lipocalin significantly correlates with ischemic damage in patients undergoing laparoscopic partial nephrectomy *Balkan Med J* 2019;**36**:121–8
Karaolanis	2015	< 100 participants	Karaolanis G, Katsaros A, Palla VV, Lionaki S, Moris D, Karanikola E, *et al.* Urine NGAL as a biomarker of kidney damage after on- and off-pump coronary artery bypass graft surgery: a prospective pilot study. *Hellenic J Cardiol* 2015;**56**:160–8
Kardakos	2014	< 100 participants	Kardakos IS, Volanis DI, Kalikaki A, Tzortzis VP, Serafetinides EN, Melekos MD, Delakas DS. Evaluation of neutrophil gelatinase-associated lipocalin, interleukin-18, and cystatin C as molecular markers before and after unilateral shock wave lithotripsy. *Urology* 2014;**84**:783–8
Kari	2018	< 100 participants	Kari JA, Shalaby MA, Sofyani K, Sanad AS, Ossra AF, Halabi RS, *et al.* Urinary neutrophil gelatinase-associated lipocalin (NGAL) and serum cystatin C measurements for early diagnosis of acute kidney injury in children admitted to PICU. *World J Pediatr* 2018;**14**:134–42

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Karimzadeh	2017	< 100 participants	Karimzadeh I, Heydari M, Ramzi M, Sagheb MM, Zomorodian K. Urinary Neutrophil gelatinase-associated lipocalin as a biomarker of kidney injury in hematologic-oncologic patients receiving amphotericin B. *Iran J Kidney Dis* 2017;**11**:201–8
Katagiri	2012	< 100 participants	Katagiri D, Doi K, Honda K, Negishi K, Fujita T, Hisagi M, *et al.* Combination of two urinary biomarkers predicts acute kidney injury after adult cardiac surgery. *Ann Thorac Surg* 2012;**93**:577–83
Katagiri	2013	Not a relevant biomarker assay or test	Katagiri D, Doi K, Matsubara T, Negishi K, Hamasaki Y, Nakamura K, *et al.* New biomarker panel of plasma neutrophil gelatinase-associated lipocalin and endotoxin activity assay for detecting sepsis in acute kidney injury. *J Crit Care* 2013;**28**:564–70
Katagiri	2016	No relevant outcome	Katagiri M, Takahashi M, Doi K, Myojo M, Kiyosue A, Ando J, *et al.* Serum neutrophil gelatinase-associated lipocalin concentration reflects severity of coronary artery disease in patients without heart failure and chronic kidney disease. *Heart Vessels* 2016;**31**:1595–602
Kesik	2015	< 100 participants	Kesik V, Demirkaya E, Buyukpamukçu M. Urinary neutrophil gelatinase associated lipocalin as a biomarker in ifosfamide induced chronic renal failure. *Eur Rev Med Pharmacol Sci* 2015;**19**:4851–7
Khan	2014	No relevant outcome	Khan UA, Coca SG, Hong K, Koyner JL, Garg AX, Passik CS, *et al.* Blood transfusions are associated with urinary biomarkers of kidney injury in cardiac surgery. *J Thorac Cardiovasc Surg* 2014;**148**:726–32
Khan	2014	< 100 participants	Khan M, Choudhry N, Haq MFU, Shahjahan, Mahmood S, Sarmad S, Yasmin R. Evaluation of neutrophil gelatinase associated lipocalin, as a biomarker of renal injury in type 2 diabetic patients. *Pakistan J Medical Health Sci* 2014;**8**:612–15
Khatami	2015	Not a relevant type of population	Khatami MR, Sabbagh MR, Nikravan N, Khazaeipour Z, Boroumand MA, Sadeghian S, Davoudi B. The role of neutrophil-gelatinase-associated lipocalin in early diagnosis of contrast nephropathy. *Indian J Nephrol* 2015;**25**:292–6
Khawaja	2019	< 100 participants	Khawaja S, Jafri L, Siddiqui I, Hashmi M, Ghani F. The utility of neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury (AKI) in critically ill patients. *Biomark Res* 2019;**7**:4
Khosravi	2013	< 100 participants	Khosravi MB, Milani S, Kakaei F. Serum Neutrophil gelatinase-associated lipocalin versus serum creatinine for the prediction of acute kidney injury after liver transplantation. *Int J Organ Transplant Med* 2013;**4**:102–9
Kidher	2014	< 100 participants	Kidher E, Harling L, Ashrafian H, Naase H, Chukwuemeka A, Anderson J, *et al.* Pulse wave velocity and neutrophil gelatinase-associated lipocalin as predictors of acute kidney injury following aortic valve replacement. *J Cardiothorac Surg* 2014;**9**:89

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Kift	2013	< 100 participants	Kift RL, Messenger MP, Wind TC, Hepburn S, Wilson M, Thompson D, *et al.* A comparison of the analytical performance of five commercially available assays for neutrophil gelatinase-associated lipocalin using urine. *Ann Clin Biochem* 2013;**50**:236–44
Kil	2018	< 100 participants	Kil HK, Kim JY, Choi YD, Lee HS, Kim TK, Kim JE. Effect of combined treatment of ketorolac and remote ischemic preconditioning on renal ischemia-reperfusion injury in patients undergoing partial nephrectomy: pilot study. *J Clin Med* 2018;**7**:470
Kim	2011	< 100 participants	Kim T, Arnaoutakis GJ, Bihorac A, Martin TD, Hess PJ, Klodell CT, *et al.* Early blood biomarkers predict organ injury and resource utilization following complex cardiac surgery. *J Surg Res* 2011;**168**:168–72
Kim	2013	Not a relevant biomarker assay or test	Kim H, Hur M, Cruz DN, Moon HW, Yun YM. Plasma neutrophil gelatinase-associated lipocalin as a biomarker for acute kidney injury in critically ill patients with suspected sepsis. *Clin Biochem* 2013;**46**:1414–18
Kim	2013	Not a relevant type of population	Kim SM, Park JS, Norwitz ER, Jung HJ, Kim BJ, Park CW, Jun JK. Circulating levels of neutrophil gelatinase-associated lipocalin (NGAL) correlate with the presence and severity of preeclampsia. *Reprod Sci* 2013;**20**:1083–9
Kim	2014	No focus on DTA for AKI	Kim BH, Yu N, Kim HR, Yun KW, Lim IS, Kim TH, Lee MK. Evaluation of the optimal neutrophil gelatinase-associated lipocalin value as a screening biomarker for urinary tract infections in children. *Ann Lab Med* 2014;**34**:354–9
Kim	2014	< 100 participants	Kim JD, Chee HK, Shin JK, Kim JS, Lee SA, Kim YH, *et al.* Novel early predictor of acute kidney injury after open heart surgery under cardiopulmonary bypass using plasma neutrophil gelatinase-associated lipocalin. *Korean J Thorac Cardiovasc Surg* 2014;**47**:240–8
Kim	2016	Meta-analysis – retained as background material	Kim S, Kim HJ, Ahn HS, Song JY, Um TH, Cho CR, *et al.* Is plasma neutrophil gelatinase-associated lipocalin a predictive biomarker for acute kidney injury in sepsis patients? A systematic review and meta-analysis. *J Crit Care* 2016;**33**:213–23
Kim	2016	Not a primary study	Kim JE, Song SW, Kim JY, Lee HJ, Chung KH, Shim YH. Effect of a single bolus of erythropoietin on renoprotection in patients undergoing thoracic aortic surgery with moderate hypothermic circulatory arrest. *Ann Thorac Surg* 2016;**101**:690–6
Kim	2017	Not a relevant biomarker assay or test	Kim H, Hur M, Lee S, Marino R, Magrini L, Cardelli P, *et al.* Proenkephalin, neutrophil gelatinase-associated lipocalin, and estimated glomerular filtration rates in patients with sepsis. *Ann Lab Med* 2017;**37**:388–97
Kim	2018	< 100 participants	Kim Y, Cho YS, Kym D, Yoon J, Yim H, Hur J, Chun W. Diagnostic performance of plasma and urine neutrophil gelatinase-associated lipocalin, cystatin C, and creatinine for acute kidney injury in burn patients: a prospective cohort study. *PLOS ONE* 2018;**13**:e0199600

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Kim	2019	Not a primary study	Kim HY, Kim CS, Bae EH, Kim SW, Ma SK. Clinical significance of the interval change of plasma neutrophil gelatinase-associated lipocalin in acute kidney injury and acute kidney injury superimposed on chronic kidney disease. *Chonnam Med J* 2019;**55**:68–9
Kipnis	2016	Not a primary study	Kipnis E. Predicting acute kidney injury after hip-fracture surgery: join the (renal) resistance! *Anaesth Crit Care Pain Med* 2016;**35**:369–70
Kirbiš	2015	< 100 participants	Kirbiš S, Gorenjak M, Sinkovič A. The role of urine neutrophil gelatinase – associated lipocalin (NGAL) in acute heart failure in patients with ST – elevation myocardial infarction. *BMC Cardiovasc Disord* 2015;**15**:49
Kiseli	2017	< 100 participants	Kiseli M, Caglar GS, Yilmaz H, Gursoy AY, Candar T, Pabuccu EG, *et al.* Neutrophil gelatinase-associated lipocalin levels during pneumoperitoneum. *JSLS* 2017;**21**:e2016.00091
Kisoon	2015	< 100 participants	Kisoon RYU, Jae-Yun AHN, Mi-Jin LEE, Woo-Young NHO, Seong-Hun KIM. Early detection and staging of acute kidney injury in non-traumatic rhabdomyolysis in emergency department. *J Korean Soc Emerg Med* 2015;**5**:370–8
Kit	2015	< 100 participants	Kit OI, Frantsiyants EM, Dimitriadi SN, Kaplieva IV, Trepitaki LK, Cheryarina ND, Pogorelova YA. Role of markers for acute kidney injury in surgical management of patients with renal cancer. *Onkourologiya* 2015;**11**:34–9
Kit	2017	< 100 participants	Kit OI, Frantsiyants EM, Rozenko DA, Ushakova ND, Dimitriadi SN, Pogorelova YA, *et al.* Dynamics of markers of markers of acute kidney injury when using epidural block during resection under warm ischemia. *Onkourologiya* 2017;**13**:25–33
Kitao	2015	< 100 participants	Kitao T, Kimata T, Yamanouchi S, Kato S, Tsuji S, Kaneko K. Urinary biomarkers for screening for renal scarring in children with febrile urinary tract infection: pilot study. *J Urol* 2015;**194**:766–71
Klein	2018	Meta-analysis – retained as background material	Klein SJ, Brandtner AK, Lehner GF, Ulmer H, Bagshaw SM, Wiedermann CJ, Joannidis M. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med* 2018;**44**:323–36
Knafl	2017	< 100 participants	Knafl D, Muller M, Pajenda S, Genc Z, Hecking M, Wagner L. The urine biomarker panel [IGFBP7] × [TIMP-2] (NephroCheck® parameter) does not correlate with IGFBP7 and TIMP-2 gene expression in urinary sediment. *PLOS ONE* 2017;**12**:e0188316
Ko	2018	Not a relevant biomarker assay or test	Ko SW, Chi NH, Wu CH, Huang TM, Chueh SJ, Wang CH, *et al.* Hemojuvelin predicts acute kidney injury and poor outcomes following cardiac surgery. *Sci Rep* 2018;**8**:1938

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Koch	2011	Not a relevant biomarker assay or test	Koch AM, Dittrich S, Cesnjevar R, Rüffer A, Breuer C, Glöckler M. Plasma neutrophil gelatinase-associated lipocalin measured in consecutive patients after congenital heart surgery using point-of-care technology. *Interact Cardiovasc Thorac Surg* 2011;**13**:133–6
Kohagura	2012	Not a primary study	Kohagura K, Ohya Y. Early detection and prediction by biomarkers of acute kidney injury after cardiac surgery. *Circ J* 2012;**76**:53–4
Kokot	2012	< 100 participants	Kokot M, Biolik G, Ziaja D, Fojt T, Cisak K, Antoniak K, *et al.* Acute kidney injury after abdominal aortic aneurysm surgery: detailed assessment of early effects using novel markers. *Pol Arch Med Wewn* 2012;**122**:353–60
Konvalinka	2014	Not a primary study	Konvalinka A. Urine proteomics for acute kidney injury prognosis: another player and the long road ahead. *Kidney Int* 2014;**85**:735–8
Koo	2015	No focus on DTA for AKI	Koo KC, Hong JH, Lee HS, Jeh SU, Choi YD, Rha KH, Ham WS. Accuracy of urinary neutrophil gelatinase-associated lipocalin in quantifying acute kidney injury after partial nephrectomy in patients with normal contralateral kidney. *PLOS ONE* 2015;**10**:e0133675
Kooiman	2015	Not a relevant type of population	Kooiman J, van de Peppel WR, Sijpkens YW, Brulez HF, de Vries PM, Nicolaie MA, *et al.* No increase in kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin excretion following intravenous contrast enhanced-CT. *Eur Radiol* 2015;**25**:1926–34
Kos	2013	< 100 participants	Kos FT, Sendur MAN, Aksoy S, Celik HT, Sezer S, Civelek B, *et al.* Evaluation of renal function using the level of neutrophil gelatinase-associated lipocalin is not predictive of nephrotoxicity associated with cisplatin-based chemotherapy. *Asian Pac J Cancer Prev* 2013;**14**:1111–4
Kostic	2019	< 100 participants	Kostic D, Dos Santos Beozzo GPN, do Couto SB, Kato AHT, Lima L, Palmeira P, *et al.* First-year profile of biomarkers for early detection of renal injury in infants with congenital urinary tract obstruction. *Pediatr Nephrol* 2019;**34**:1117–28
Kostrubiec	2012	Not a relevant type of population	Kostrubiec M, Łabyk A, Pedowska-Włoszek J, Dzikowska-Diduch O, Wojciechowski A, Garlińska M, *et al.* Neutrophil gelatinase-associated lipocalin, cystatin C and eGFR indicate acute kidney injury and predict prognosis of patients with acute pulmonary embolism. *Heart* 2012;**98**:1221–8
Koukoulaki	2013	< 100 participants	Koukoulaki M, Spyropoulos C, Hondrogiannis P, Papachristou E, Mitsi E, Kalfarentzos F, Goumenos DS. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury in patients with morbid obesity who underwent bariatric surgery. *Nephron Extra* 2013;**3**:101–5
Koyner	2010	Not a relevant biomarker assay or test	Koyner JL, Vaidya VS, Bennett MR, Ma Q, Worcester E, Akhter SA, *et al.* Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. *Clin J Am Soc Nephrol* 2010;**5**:2154–65

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Koyner	2008	< 100 participants	Koyner JL, Bennett MR, Worcester EM, Ma Q, Raman J, Jeevanandam V, *et al.* Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. *Kidney Int* 2008;**74**:1059–69
Koyner	2014	< 100 participants	Koyner JL, Garg AX, Thiessen-Philbrook H, Coca SG, Cantley LG, Peixoto A, *et al.* Adjudication of etiology of acute kidney injury: experience from the TRIBE-AKI multi-center study. *BMC Nephrol* 2014;**15**:105
Krawczeski	2011	Not a relevant biomarker assay or test	Krawczeski CD, Goldstein SL, Woo JG, Wang Y, Piyaphanee N, Ma Q, *et al.* Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. *J Am Coll Cardiol* 2011;**58**:2301–9
Krawczeski	2011	Not a relevant biomarker assay or test	Krawczeski CD, Woo JG, Wang Y, Bennett MR, Ma Q, Devarajan P. Neutrophil gelatinase-associated lipocalin concentrations predict development of acute kidney injury in neonates and children after cardiopulmonary bypass. *J Pediatr* 2011;**158**:1009–15.e1
Kumar	2011	Not a primary study	Kumar AB, Suneja M. Cardiopulmonary bypass-associated acute kidney injury. *Anesthesiology* 2011;**114**:964–70
Kunutsor	2018	Not a relevant type of population	Kunutsor SK, Flores-Guerrero JL, Kieneker LM, Nilsen T, Hidden C, Sundrehagen E, *et al.* Plasma neutrophil gelatinase-associated lipocalin and risk of cardiovascular disease: findings from the PREVEND prospective cohort study. *Clin Chim Acta* 2018;**486**:66–75
Kuribayashi	2016	Not a relevant type of population	Kuribayashi R, Suzumura H, Sairenchi T, Watabe Y, Tsuboi Y, Imataka G, *et al.* Urinary neutrophil gelatinase-associated lipocalin is an early predictor of acute kidney injury in premature infants. *Exp Ther Med* 2016;**12**:3706–10
Lábr	2018	Not a relevant biomarker assay or test	Lábr K, Špinar J, Pařenica J, Špinarová L, Málek F, Špinarová M, *et al.* Renal functions and prognosis stratification in chronic heart failure patients and the importance of neutrophil gelatinase-associated lipocalin. *Kidney Blood Press Res* 2018;**43**:1865–77
Lacquaniti	2013	Not a relevant type of population	Lacquaniti A, Buemi F, Lupica R, Giardina C, Murè G, Arena A, *et al.* Can neutrophil gelatinase-associated lipocalin help depict early contrast material-induced nephropathy? *Radiology* 2013;**267**:86–93
Lacquaniti	2013	< 100 participants	Lacquaniti A, Giardina M, Lucisano S, Messina R, Buemi A, Risitano CD, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) and endothelial progenitor cells (EPCs) evaluation in aortic aneurysm repair. *Curr Vasc Pharmacol* 2013;**11**:1001–10
Lahoud	2015	< 100 participants	Lahoud Y, Hussein O, Shalabi A, Nativ O, Awad H, Khamaisi M, *et al.* Effects of phosphodiesterase-5 inhibitor on ischemic kidney injury during nephron sparing surgery: quantitative assessment by NGAL and KIM-1. *World J Urol* 2015;**33**:2053–62
Lane	2020	< 100 participants	Lane BR, Babitz SK, Vlasakova K, Wong A, Noyes SL, Boshoven W, P *et al.* Evaluation of urinary renal biomarkers for early prediction of acute kidney injury following partial nephrectomy: a feasibility study. *Eur Urol Focus* 2020;**6**:1240–7

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Lavery	2008	< 100 participants	Lavery AP, Meinzen-Derr JK, Anderson E, Ma Q, Bennett MR, Devarajan P, Schibler KR. Urinary NGAL in premature infants. *Pediatr Res* 2008;**64**:423–8
Lee	2015	< 100 participants	Lee HE, Kim DK, Kang HK, Park K. The diagnosis of febrile urinary tract infection in children may be facilitated by urinary biomarkers. *Pediatr Nephrol* 2015;**30**:123–30
Lee	2016	< 100 participants	Lee SK, Lanaspa MA, Sánchez-Lozada LG, Johnson RJ. Hyponatremia with persistent elevated urinary fractional uric acid excretion: evidence for proximal tubular injury? *Kidney Blood Press Res* 2016;**41**:535–44
Lee	2018	Not a relevant biomarker assay or test	Lee CC, Chang CH, Chen SW, Fan PC, Chang SW, Chen YT, *et al.* Preoperative risk assessment improves biomarker detection for predicting acute kidney injury after cardiac surgery. *PLOS ONE* 2018;**13**:e0203447
Lee	2018	< 100 participants	Lee CW, Kou HW, Chou HS, Chou HH, Huang SF, Chang CH, *et al.* A combination of SOFA score and biomarkers gives a better prediction of septic AKI and in-hospital mortality in critically ill surgical patients: a pilot study. *World J Emerg Surg* 2018;**13**:41
Lee	2019	< 100 participants	Lee NM, Deriy L, Petersen TR, Shah VO, Hutchens MP, Gerstein NS. Impact of isolyte versus 0.9% saline on postoperative event of acute kidney injury assayed by urinary [TIMP-2] × [IGFBP7] in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2019;**33**:348–56
Legrand	2014	< 100 participants	Legrand M, De Berardinis B, Gaggin HK, Magrini L, Belcher A, Zancla B, *et al.* Evidence of uncoupling between renal dysfunction and injury in cardiorenal syndrome: insights from the BIONICS study. *PLOS ONE* 2014;**9**:e112313
Legrand	2013	< 100 participants	Legrand M, Collet C, Gayat E, Henao J, Giraudeaux V, Mateo J, *et al.* Accuracy of urine NGAL commercial assays in critically ill patients. *Intensive Care Med* 2013;**39**:541–2
Legrand	2013	Not a primary study	Legrand M, Darmon M, Joannidis M. NGAL and AKI: the end of a myth? *Intensive Care Med* 2013;**39**:1861–3
Legrand	2015	Not a relevant type of population	Legrand M, Jacquemod A, Gayat E, Collet C, Giraudeaux V, Launay JM, Payen D. Failure of renal biomarkers to predict worsening renal function in high-risk patients presenting with oliguria. *Intensive Care Med* 2015;**41**:68–76
Lei	2018	Not a relevant biomarker assay or test	Lei L, Li LP, Zeng Z, Mu JX, Yang X, Zhou C, *et al.* Value of urinary KIM-1 and NGAL combined with serum Cys C for predicting acute kidney injury secondary to decompensated cirrhosis. *Sci Rep* 2018;**8**:7962
Lentini	2012	< 100 participants	Lentini P, de Cal M, Clementi A, D'Angelo A, Ronco C. Sepsis and AKI in ICU patients: the role of plasma biomarkers. *Crit Care Res Pract* 2012;**2012**:856401

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Leoncini	2011	Not a relevant type of population	Leoncini G, Mussap M, Viazzi F, Fravega M, Degrandi R, Bezante GP, *et al.* Combined use of urinary neutrophil gelatinase-associated lipocalin (uNGAL) and albumin as markers of early cardiac damage in primary hypertension. *Clin Chim Acta* 2011;**412**:1951–6
Leung	2009	< 100 participants	Leung JC, Lam MF, Tang SC, Chan LY, Tam KY, Yip TP, Lai KN. Roles of neutrophil gelatinase-associated lipocalin in continuous ambulatory peritoneal dialysis-related peritonitis. *J Clin Immunol* 2009;**29**:365–78
Levante	2017	Pilot study or preliminary analysis only	Levante C, Ferrari F, Manenti C, Husain-Syed F, Scarpa M, Hinna Danesi T, *et al.* Routine adoption of TIMP2 and IGFBP7 biomarkers in cardiac surgery for early identification of acute kidney injury. *Int J Artif Organs* 2017;**40**:714–18
Levitsky	2014	< 100 participants	Levitsky J, Baker TB, Jie C, Ahya S, Levin M, Friedewald J, *et al.* Plasma protein biomarkers enhance the clinical prediction of kidney injury recovery in patients undergoing liver transplantation. *Hepatology* 2014;**60**:2017–26
Lewandowska	2014	< 100 participants	Lewandowska L, Matuszkiewicz-Rowińska J, Jayakumar C, Oldakowska-Jedynak U, Looney S, Galas M, *et al.* Netrin-1 and semaphorin 3A predict the development of acute kidney injury in liver transplant patients. *PLOS ONE* 2014;**9**:e107898
Li	2012	< 100 participants	Li Y, Zhu M, Xia Q, Wang S, Qian J, Lu R, *et al.* Urinary neutrophil gelatinase-associated lipocalin and L-type fatty acid binding protein as diagnostic markers of early acute kidney injury after liver transplantation. *Biomarkers* 2012;**17**:336–42
Li	2014	Non-English-language publication	Li J, Zhang H, Shang Y, Cao S. [The study of early diagnosis and prognostic effect using detection of NGAL in community acquired pneumonia with acute kidney injury.] *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2014;**26**:269–71
Li	2018	Not a relevant type of population	Li H, Yu Z, Gan L, Peng L, Zhou Q. Serum NGAL and FGF23 may have certain value in early diagnosis of CIN. *Ren Fail* 2018;**40**:547–53
Liangos	2009	Not a relevant biomarker assay or test	Liangos O, Tighiouart H, Perianayagam MC, Kolyada A, Han WK, Wald R, *et al.* Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. *Biomarkers* 2009;**14**:423–31
Liangos	2009	Pilot study or preliminary analysis only	Liangos O, Tighiouart H, Perianayagam MC, Kolyada A, Han WK, Wald R, *et al.* Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. *Biomarkers* 2009;**14**:423–31
Liao	2019	Not a relevant type of population	Liao B, Nian W, Xi A, Zheng M. Evaluation of a diagnostic test of serum neutrophil gelatinase-associated lipocalin (NGAL) and urine KIM-1 in contrast-induced nephropathy (CIN). *Med Sci Monit* 2019;**25**:565–70

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Libório	2015	< 100 participants	Libório AB, Braz MB, Seguro AC, Meneses GC, Neves FM, Pedrosa DC, *et al.* Endothelial glycocalyx damage is associated with leptospirosis acute kidney injury. *Am J Trop Med Hyg* 2015;**92**:611–16
Lichosik	2015	< 100 participants	Lichosik M, Jung A, Jobs K, Mierzejewska A, Zdanowski R, Kalicki B. Interleukin 18 and neutrophil-gelatinase associated lipocalin in assessment of the risk of contrast-induced nephropathy in children. *Cent Eur J Immunol* 2015;**40**:447–53
Lim	2017	Not a relevant biomarker assay or test	Lim YM, Moon JY, Min D, Kim SH, Yang WI, Kim WJ, *et al.* Serial measurements of neutrophil gelatinase-associated lipocalin: prognostic value in patients with ST-segment elevation myocardial infarction treated with a primary percutaneous coronary intervention. *Coron Artery Dis* 2017;**28**:690–6
Lin	2013	Not a relevant type of population	Lin HYH, Lee SC, Lin SF, Hsiao HH, Liu YC, Yang WC, *et al.* Urinary neutrophil gelatinase-associated lipocalin levels predict cisplatin-induced acute kidney injury better than albuminuria or urinary cystatin C levels. *Kaohsiung J Medical Sci* 2013;**29**:304–11
Lin	2018	Not a primary study	Lin Q, Mao JH. Early prediction of acute kidney injury in children: known biomarkers but novel combination. *World J Pediatr* 2018;**14**:617–20
Lindberg	2016	Not a relevant type of population	Lindberg S, Jensen JS, Hoffmann S, Iversen AZ, Pedersen SH, Biering-Sørensen T, *et al.* Plasma neutrophil gelatinase-associated lipocalin reflects both inflammation and kidney function in patients with myocardial infarction. *Cardiorenal Med* 2016;**6**:180–90
Lindberg	2012	Not a relevant type of population	Lindberg S, Pedersen SH, Mogelvang R, Jensen JS, Flyvbjerg A, Galatius S, Magnusson NE. Prognostic utility of neutrophil gelatinase-associated lipocalin in predicting mortality and cardiovascular events in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol* 2012;**60**:339–45
Lindsey-Yoojin	2017	Not a relevant biomarker assay or test	Lindsey-Yoojin C, Won-Sik C, Eui-Kyung C, Jeonghee S, Hyung-Eun YIM, Byung-Min C. Clinical utility of rapid plasma neutrophil gelatinase-associated lipocalin assays for diagnosing acute kidney injury in critically ill newborn infants. *Neonatal Med* 2017;**4**:164–70
Ling	2008	Not a relevant type of population	Ling W, Zhaohui N, Ben H, Leyi G, Jianping L, Huili D, Jiaqi Q. Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. *Nephron Clin Pract* 2008;**108**:c176–81
Ling	2008	Not a relevant type of population	Ling W, Zhaohui N, Ben H, Leyi G, Jianping L, Huili D, Jiaqi Q. Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. *Nephron Clin Pract* 2008;**108**:c176–81 [3990]

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Linko	2013	Not a relevant biomarker assay or test	Linko R, Pettilä V, Kuitunen A, Korhonen AM, Nisula S, Alila S, *et al.* Plasma neutrophil gelatinase-associated lipocalin and adverse outcome in critically ill patients with ventilatory support. *Acta Anaesthesiol Scand* 2013;**57**:855–62
Lipcsey	2014	No focus on DTA for AKI	Lipcsey M, Hayward P, Haase M, Haase-Fielitz A, Eastwood G, Peck L, Matalanis G, Bellomo R. Neutrophil gelatinase-associated lipocalin after off pump versus on pump coronary artery surgery. *Biomarkers* 2014;**19**:22–8
Lipinski	2015	Not a relevant type of population	Lipinski M, Rydzewska-Rosolowska A, Rydzewski A, Rydzewska G. Urinary neutrophil gelatinase-associated lipocalin as an early predictor of disease severity and mortality in acute pancreatitis. *Pancreas* 2015;**44**:448–52
Lippi	2012	Not a primary study	Lippi G, Cervellin G. Neutrophil gelatinase-associated lipocalin: a more specific assay is needed for diagnosing renal injury. *Clin Chim Acta* 2012;**413**:1160–1
Liu	2013	Not a relevant biomarker assay or test	Liu S, Che M, Xue S, Xie B, Zhu M, Lu R, *et al.* Urinary L-FABP and its combination with urinary NGAL in early diagnosis of acute kidney injury after cardiac surgery in adult patients. *Biomarkers* 2013;**18**:95–101
Liu	2016	Compares clinical adjudication between NephroCheck and KDIGO – retained as background material	Liu KD, Vijayan A, Rosner MH, Shi J, Chawla LS, Kellum JA. Clinical adjudication in acute kidney injury studies: findings from the pivotal TIMP-2*IGFBP7 biomarker study. *Nephrol Dial Transplant* 2016;**31**:1641–6
Liu	2017	Systematic review – retained as background material	Liu C, Lu X, Mao Z, Kang H, Liu H, Pan L, *et al.* The diagnostic accuracy of urinary [TIMP-2]·[IGFBP7] for acute kidney injury in adults. *Medicine* 2017;**96**:e7484
Lu	2019	< 100 participants	Lu J, Lin L, Ye C, Tao Q, Cui M, Zheng S, *et al.* Serum NGAL Is superior to cystatin C in predicting the prognosis of acute-on-chronic liver failure. *Ann Hepatol* 2019;**18**:155–64
Lubell	2017	No focus on DTA for AKI	Lubell TR, Barasch JM, Xu K, Ieni M, Cabrera KI, Dayan PS. Urinary neutrophil gelatinase-associated lipocalin for the diagnosis of urinary tract infections. *Pediatrics* 2017;**140**:e20171090
Luka	2013	< 100 participants	Luk CC, Chow KM, Kwok JS, Kwan BC, Chan MH, Lai KB, *et al.* Urinary biomarkers for the prediction of reversibility in acute-on-chronic renal failure. *Dis Markers* 2013;**34**:179–85
Lukasz	2014	< 100 participants	Lukasz A, Beneke J, Menne J, Vetter F, Schmidt BM, Schiffer M, *et al.* Serum neutrophil gelatinase-associated lipocalin (NGAL) in patients with Shiga toxin mediated haemolytic uraemic syndrome (STEC-HUS). *Thromb Haemost* 2014;**111**:365–72
Luo	2013	Not a relevant type of population	Luo Q, Zhou F, Dong H, Wu L, Chai L, Lan K, Wu M. Implication of combined urinary biomarkers in early diagnosis of acute kidney injury following percutaneous coronary intervention. *Clin Nephrol* 2013;**79**:85–92
Luthra	2019	Not a primary study	Luthra A, Tyagi A. [TIMP-2]*[IGFBP7] for predicting early AKI. *Anaesth Crit Care Pain Med* 2019;**38**:677

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
MacDonald	2012	< 100 participants	Macdonald S, Arendts G, Nagree Y, Xu XF. Neutrophil Gelatinase-Associated Lipocalin (NGAL) predicts renal injury in acute decompensated cardiac failure: a prospective observational study. *BMC Cardiovasc Disord* 2012;**12**:8
Macedo	2013	Not a primary study	Macedo E, Mehta RL. Biomarkers for acute kidney injury: combining the new silver with the old gold. *Nephrol Dial Transplant* 2013;**28**:1064–7
Madsen	2012	< 100 participants	Madsen MG, Norregaard R, Palmfeldt J, Olsen LH, Frokiaer J, Jorgensen TM. Urinary NGAL, cystatin C, beta 2-microglobulin, and osteopontin significance in hydronephrotic children. *Pediatr Nephrol* 2012;**27**:2099–106
Maeda	2017	< 100 participants	Maeda A, Ando H, Ura T, Muro K, Aoki M, Saito K, *et al.* Differences in Urinary Renal Failure Biomarkers in Cancer Patients Initially Treated with Cisplatin. *Anticancer Res* 2017;**37**:5235–9
Mahmoodpoor	2018	< 100 participants	Mahmoodpoor A, Hamishehkar H, Fattahi V, Sanaie S, Arora P, Nader ND. Urinary versus plasma neutrophil gelatinase-associated lipocalin (NGAL) as a predictor of mortality for acute kidney injury in intensive care unit patients. *J Clin Anesth* 2018;**44**:12–17
Maisel	2011	Not a relevant biomarker assay or test	Maisel AS, Mueller C, Fitzgerald R, Brikhan R, Hiestand BC, Iqbal N, *et al.* Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: the NGAL evaLuation Along with B-type NaTriuretic peptide in acutely decompensated heart failure (GALLANT) trial. *Eur J Heart Fail* 2011;**13**:846–51
Maisel	2016	Not a relevant biomarker assay or test	Maisel AS, Wettersten N, van Veldhuisen DJ, Mueller C, Filippatos G, Nowak R, *et al.* Neutrophil gelatinase-associated lipocalin for acute kidney injury during acute heart failure hospitalizations: the AKINESIS study. *J Am Coll Cardiol* 2016;**68**:1420–31
Maizel	2019	Not a relevant type of population	Maizel J, Daubin D, Vong LV, Titeca-Beauport D, Wetzstein M, Kontar L, *et al.* Urinary TIMP2 and IGFBP7 identifies high risk patients of short-term progression from mild and moderate to severe acute kidney injury during septic shock: a prospective cohort study. *Dis Markers* 2019;**2019**:3471215
Makris	2009	< 100 participants	Makris K, Markou N, Evodia E, Dimopoulou E, Drakopoulos I, Ntetsika K, *et al.* Urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early marker of acute kidney injury in critically ill multiple trauma patients. *Clin Chem Lab Med* 2009;**47**:79–82
Malyszko	2009	Not a relevant type of population	Malyszko J, Bachorzewska-Gajewska H, Poniatowski B, Malyszko JS, Dobrzycki S. Urinary and serum biomarkers after cardiac catheterization in diabetic patients with stable angina and without severe chronic kidney disease. *Ren Fail* 2009;**31**:910–19
Malyszko	2015	Not a relevant type of population	Malyszko J, Bachorzewska-Gajewska H, Koc-Zorawska E, Malyszko JS, Kobus G, Dobrzycki S. Midkine: a novel and early biomarker of contrast-induced acute kidney injury in patients undergoing percutaneous coronary interventions. *Biomed Res Int* 2015;**2015**:879509

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Malyszko	2019	Not a relevant type of population	Malyszko J, Bachorzewska-Gajewska H, Malyszko JS, Koc-Zorawska E, Matuszkiewicz-Rowinska J, Dobrzycki S. Hepcidin – potential biomarker of contrast-induced acute kidney injury in patients undergoing percutaneous coronary interventions. *Adv Med Sci* 2019;**64**:211–15
Mamikonian	2014	< 100 participants	Mamikonian LS, Mamo LB, Smith PB, Koo J, Lodge AJ, Turi JL. Cardiopulmonary bypass is associated with hemolysis and acute kidney injury in neonates, infants, and children. *Pediatr Crit Care Med* 2014;**15**:e111–9
Mandei	2015	< 100 participants	Mandei J, Iskandar E, Umboh A, Lestari H. Relationship between serum cystatin-C and urinary neutrophil gelatinase-associated lipocalin in septic children. *Paediatr Indones* 2015;**55**:83–6
Marcelino	2014	< 100 participants	Marcelino P, Tavares I, Carvalho D, Marques C, Silvestre MJ, Perdigoto R, Barroso E. Is urinary gamma-glutamyl transpeptidase superior to urinary neutrophil gelatinase-associated lipocalin for early prediction of acute kidney injury after liver transplantation? *Transplant Proc* 2014;**46**:1812–18
Mårtensson	2013	Not relevant biomarker assay or test	Mårtensson J, Bell M, Xu S, Bottai M, Ravn B, Venge P, Martling CR. Association of plasma neutrophil gelatinase-associated lipocalin (NGAL) with sepsis and acute kidney dysfunction. *Biomarkers* 2013;**18**:349–56
Mårtensson	2016	< 100 participants	Mårtensson J, Jonsson N, Glassford NJ, Bell M, Martling CR, Bellomo R, Larsson A. Plasma endostatin may improve acute kidney injury risk prediction in critically ill patients. *Ann Intensive Care* 2016;**6**:6
Mårtensson	2010	< 100 participants	Mårtensson J, Bell M, Oldner A, Xu S, Venge P, Martling CR. Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. *Intensive Care Med* 2010;**36**:1333–40
Martin-Moreno	2015	Not a relevant type of population	Martin-Moreno PL, Varo N, Martínez-Ansó E, Martin-Calvo N, Sayón-Orea C, Bilbao JI, Garcia-Fernandez N. Comparison of intravenous and oral hydration in the prevention of contrast-induced acute kidney injury in low-risk patients: a randomized trial. *Nephron* 2015;**131**:51–8
Martino	2012	Pilot study or preliminary analysis only	Martino FK, Filippi I, Giavarina D, Kaushik M, Rodighiero MP, Crepaldi C, *et al.* Neutrophil gelatinase-associated lipocalin in the early diagnosis of peritonitis: the case of neutrophil gelatinase-associated lipocalin. *Contrib Nephrol* 2012;**178**:258–63
Mathew	2008	Not a relevant biomarker assay or test	Mathew A, Garg AX. A single measure of urinary neutrophil gelatinase-associated lipocalin was accurate for diagnosing acute kidney injury. *ACP J Club* 2008;**149**:13
Matsuura	2018	< 100 participants	Matsuura R, Komaru Y, Miyamoto Y, Yoshida T, Yoshimoto K, Isshiki R, *et al.* Response to different furosemide doses predicts AKI progression in ICU patients with elevated plasma NGAL levels. *Ann Intensive Care* 2018;**8**:8

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Matys	2013	Not a relevant type of population	Matys U, Bachorzewska-Gajewska H, Malyszko J, Dobrzycki S. Assessment of kidney function in diabetic patients. Is there a role for new biomarkers NGAL, cystatin C and KIM-1? *Adv Med Sci* 2013;**58**:353–61
Mawad	2016	< 100 participants	Mawad H, Laurin LP, Naud JF, Leblond FA, Henley N, Vallée M, *et al.* Changes in urinary and serum levels of novel biomarkers after administration of gadolinium-based contrast agents. *Biomark Insights* 2016;**11**:91–4
Mayer	2017	Pilot study or preliminary analysis only	Mayer T, Bolliger D, Scholz M, Reuthebuch O, Gregor M, Meier P, *et al.* Urine biomarkers of tubular renal cell damage for the prediction of acute kidney injury after cardiac surgery–a pilot study. *J Cardiothorac Vasc Anesth* 2017;**31**:2072–9
Mazar	2014	No focus on DTA for AKI	Mazar M, Ivancan V, Segotic I, Colak Z, Gabelica R, Rajsman G, *et al.* A diagnosis of a renal injury by early biomarkers in patients exposed to cardiopulmonary bypass during cardiac surgery. *Signa Vitae* 2014;**9**(Suppl. 1):45–8
Mazzeffi	2016	< 100 participants	Mazzeffi MA, Stafford P, Wallace K, Bernstein W, Deshpande S, Odonkor P, *et al.* Intra-abdominal hypertension and postoperative kidney dysfunction in cardiac surgery patients. *J Cardiothorac Vasc Anesth* 2016;**30**:1571–7
McCaffrey	2015	< 100 participants	McCaffrey J, Coupes B, Chaloner C, Webb NJ, Barber R, Lennon R. Towards a biomarker panel for the assessment of AKI in children receiving intensive care. *Pediatr Nephrol* 2015;**30**:1861–71
McCullough	2011	Not a primary study	McCullough PA, El-Ghoroury M, Yamasaki H. Early detection of acute kidney injury with neutrophil gelatinase-associated lipocalin. *J Am Coll Cardiol* 2011;**57**:1762–4
McCullough	2012	Not a relevant type of population	McCullough PA, Williams FJ, Stivers DN, Cannon L, Dixon S, Alexander P, *et al.* Neutrophil gelatinase-associated lipocalin: a novel marker of contrast nephropathy risk. *Am J Nephrol* 2012;**35**:509–14
McIlroy	2010	Not a relevant biomarker assay or test	McIlroy DR, Wagener G, Lee HT. Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery: the effect of baseline renal function on diagnostic performance. *Clin J Am Soc Nephrol* 2010;**5**:211–19
McIlroy	2010	Not a primary study	McIlroy DR, Wagener G, Lee HT. Biomarkers of acute kidney injury: an evolving domain. *Anesthesiology* 2010;**112**:998–1004
McIlroy	2015	Not a relevant biomarker assay or test	McIlroy DR, Farkas D, Matto M, Lee HT. Neutrophil gelatinase-associated lipocalin combined with delta serum creatinine provides early risk stratification for adverse outcomes after cardiac surgery: a prospective observational study. *Crit Care Med* 2015;**43**:1043–52

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
McWilliam	2012	< 100 participants	McWilliam SJ, Antoine DJ, Sabbisetti V, Turner MA, Farragher T, Bonventre JV, *et al.* Mechanism-based urinary biomarkers to identify the potential for aminoglycoside-induced nephrotoxicity in premature neonates: a proof-of-concept study. *PLOS ONE* 2012;**7**:e43809
McWilliam	2018	Not a relevant type of population	McWilliam SJ, Antoine DJ, Jorgensen AL, Smyth RL, Pirmohamed M. Urinary Biomarkers of aminoglycoside-induced nephrotoxicity in cystic fibrosis: kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin. *Sci Rep* 2018;**8**:5094
Md Ralib	2017	Not a relevant type of population	Md Ralib A, Mat Nor MB, Pickering JW. Plasma Neutrophil gelatinase-associated lipocalin diagnosed acute kidney injury in patients with systemic inflammatory disease and sepsis. *Nephrology* 2017;**22**:412–19
Meersch	2018	Not a primary study	Meersch M, Zarbock A, Küllmar M. Renal biomarkers for the initiation of renal replacement therapy – is this the future? *J Thorac Dis* 2018;**10**:S3229–S3232
Meersh	2014	< 100 participants	Meersch M, Schmidt C, Van Aken H, Martens S, Rossaint J, Singbartl K, *et al.* Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. *PLOS ONE* 2014;**9**:e93460
Meersh	2017	No focus on DTA for AKI	Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, Zarbock A. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med* 2017;**43**:1551–61
Meersh	2014	< 100 participants	Meersch M, Schmidt C, Van Aken H, Rossaint J, Görlich D, Stege D, *et al.* Validation of cell-cycle arrest biomarkers for acute kidney injury after pediatric cardiac surgery. *PLOS ONE* 2014;**9**:e110865
Meisner	2018	Not a relevant biomarker assay or test	Meisner A, Kerr KF, Thiessen-Philbrook H, Wilson FP, Garg AX, Shlipak MG, *et al.* Development of biomarker combinations for postoperative acute kidney injury via Bayesian model selection in a multicenter cohort study. *Biomark Res* 2018;**6**:3
Mellor	2012	< 100 participants	Mellor AJ, Woods D. Serum neutrophil gelatinase-associated lipocalin in ballistic injuries: a comparison between blast injuries and gunshot wounds. *J Crit Care* 2012;**27**:419.e1–5
Meneses	2018	< 100 participants	Meneses GC, De Francesco Daher E, da Silva Junior GB, Bezerra GF, da Rocha TP, de Azevedo IEP, *et al.* Visceral leishmaniasis-associated nephropathy in hospitalised Brazilian patients: new insights based on kidney injury biomarkers. *Trop Med Int Health* 2018;**23**:1046–57
Menon	2016	Not a relevant biomarker assay or test	Menon S, Goldstein SL, Mottes T, Fei L, Kaddourah A, Terrell T, *et al.* Urinary biomarker incorporation into the renal angina index early in intensive care unit admission optimizes acute kidney injury prediction in critically ill children: a prospective cohort study. *Nephrol Dial Transplant* 2016;**31**:586–94

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Merrikhi	2014	< 100 participants	Merrikhi A, Gheissari A, Mousazadeh H. Urine and serum neutrophil gelatinase-associated lipocalin cut-off point for the prediction of acute kidney injury. *Adv Biomed Res* 2014;**3**:66
Mertoglu	2018	< 100 participants	Mertoglu C, Gunay M, Gurel A, Gungor M. Myo-inositol oxygenase as a novel marker in the diagnosis of acute kidney injury. *J Med Biochem* 2018;**37**:1–6
Metzger	2010	< 100 participants	Metzger J, Kirsch T, Schiffer E, Ulger P, Mentes E, Brand K, *et al.* Urinary excretion of twenty peptides forms an early and accurate diagnostic pattern of acute kidney injury. *Kidney Int* 2010;**78**:1252–62
Metzger	2016	Not a relevant biomarker assay or test	Metzger J, Mullen W, Husi H, Stalmach A, Herget-Rosenthal S, Groesdonk HV, *et al.* Acute kidney injury prediction in cardiac surgery patients by a urinary peptide pattern: a case-control validation study. *Crit Care* 2016;**20**:157
Miah	2018	No focus on DTA for AKI	Miah OF, Dowel FA, Latif A, Hai AN, Mahmud MA, Razzak MA, Ahammod T. NGAL (neutrophil gelatinase-associated lipocalin) is an early predictor of acute kidney injury after cardiac surgery and variation of ngal values in homogenous study subject. *Mymensingh Med J* 2018;**27**:212–15
Miah	2018	< 100 participants	Miah OF, Roy DK, Chowdhury AA, Alam KS, Alam MB, Anwar MR, *et al.* Plasma Neutrophil gelatinase associated lipocalin (pNGAL) level to identify aki early in patients undergoing cardiac valve surgery. *Mymensingh Med J* 2018;**27**:263–9
Mironova	2019	Non-English-language publication	Mironova SA, Yudina YS, Ionov MV, Avdonina NG, Emelyanov IV, Vasilyeva EY, *et al.* Novel biomarkers of kidney injury and fibrosis in patients with different severity of hypertension: relation to vascular reactivity and stiffness. *Russ J Cardiol* 2019;**24**:44–51
Mishra	2013	< 100 participants	Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2013;**365**:1231–8
Mishra	2017	< 100 participants	Mishra OP, Rai AK, Srivastava P, Pandey K, Abhinay A, Prasad R, *et al.* Predictive ability of urinary biomarkers for outcome in children with acute kidney injury. *Pediatr Nephrol* 2017;**32**:521–7
Mitsnefes	2007	< 100 participants	Mitsnefes MM, Kathman TS, Mishra J, Kartal J, Khoury PR, Nickolas TL, *et al.* Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in children with chronic kidney disease. *Pediatr Nephrol* 2007;**22**:101–8
MohamadiSichani	2017	< 100 participants	MohamadiSichani M, Tolou Ghamari Z. Investigation of urinary neutrophil gelatinase associated lipocalin (NGAL) for early diagnosis of acute kidney injury after percutaneous nephrolithotomy. *Afr J Urol* 2017;**23**:214–18

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Mohamed	2015	< 100 participants	Mohamed F, Buckley NA, Jayamanne S, Pickering JW, Peake P, Palangasinghe C, *et al.* Kidney damage biomarkers detect acute kidney injury but only functional markers predict mortality after paraquat ingestion. *Toxicol Lett* 2015;**237**:140–50
Mohamed	2016	< 100 participants	Mohamed F, Endre ZH, Pickering JW, Jayamanne S, Palangasinghe C, Shahmy S, *et al.* Mechanism-specific injury biomarkers predict nephrotoxicity early following glyphosate surfactant herbicide (GPSH) poisoning. *Toxicol Lett* 2016;**258**:1–10
Mohtat	2011	< 100 participants	Mohtat D, Thomas R, Du Z, Boakye Y, Moulton T, Driscoll C, Woroniecki R. Urinary transforming growth factor beta-1 as a marker of renal dysfunction in sickle cell disease. *Pediatr Nephrol* 2011;**26**:275–80
Mohtat	2011	Not a relevant type of population	Mohtat D, Thomas R, Du Z, Boakye Y, Moulton T, Driscoll C, Woroniecki R. Urinary transforming growth factor beta-1 as a marker of renal dysfunction in sickle cell disease. *Pediatr Nephrol* 2011;**26**:275–80
Moledina	2015	Not a relevant biomarker assay or test	Moledina DG, Parikh CR, Garg AX, Thiessen-Philbrook H, Koyner JL, Patel UD, *et al.* Association of perioperative plasma neutrophil gelatinase-associated lipocalin levels with 3-year mortality after cardiac surgery: a prospective observational cohort study. *PLOS ONE* 2015;**10**:e0129619
Moledina	2017	No focus on DTA for AKI	Moledina DG, Hall IE, Thiessen-Philbrook H, Reese PP, Weng FL, Schröppel B, *et al.* Performance of serum creatinine and kidney injury biomarkers for diagnosing histologic acute tubular injury. *Am J Kidney Dis* 2017;**70**:807–16
Moon	2019	Not a relevant type of population	Moon JM, Chun BJ, Shin MH, Cho YS. Predictive value of plasma neutrophil gelatinase-associated lipocalin in acute charcoal-burning carbon monoxide poisoning. *Hum Exp Toxicol* 2019;**38**:877–87
Morales-Buenrostro	2014	< 100 participants	Morales-Buenrostro LE, Salas-Nolasco OI, Barrera-Chimal J, Casas-Aparicio G, Irizar-Santana S, Pérez-Villalva R, Bobadilla NA. Hsp72 is a novel biomarker to predict acute kidney injury in critically ill patients. *PLOS ONE* 2014;**9**:e109407
Moriyama	2016	< 100 participants	Moriyama T, Hagihara S, Shiramomo T, Nagaoka M, Iwakawa S, Kanmura Y. Comparison of three early biomarkers for acute kidney injury after cardiac surgery under cardiopulmonary bypass. *J Intensive Care* 2016;**4**:41
Moriyama	2017	< 100 participants	Moriyama T, Hagihara S, Shiramomo T, Nagaoka M, Iwakawa S, Kanmura Y. The protective effect of human atrial natriuretic peptide on renal damage during cardiac surgery. *J Anesth* 2017;**31**:163–9
Mortara	2013	< 100 participants	Mortara A, Bonadies M, Mazzetti S, Fracchioni I, Delfino P, Chioffi M, *et al.* Neutrophil gelatinase-associated lipocalin predicts worsening of renal function in acute heart failure: methodological and clinical issues. *J Cardiovasc Med* 2013;**14**:629–34

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Mosa	2018	Not a relevant biomarker assay or test	Mosa OF. Prognostic significance of serum NGAL and troponin I against acute kidney injury in Egyptian ICU patients after open heart surgery: a pilot study. *Kidney Dis* 2018;**4**:246–54
Moyake	2016	Not a relevant type of population	Moyake N, Buchmann E, Crowther NJ. Neutrophil gelatinase-associated lipocalin as a diagnostic marker of acute kidney injury in pre-eclampsia. *J Obstet Gynaecol Res* 2016;**42**:1483–8
Muhammad Usman	2013	< 100 participants	Muhammad Usman M, Dilshad Ahmed K, Farooq Ahmad K, Syed Muhammad Shahab N. Comparison of urine with plasma neutrophil gelatinase-associated lipocalin in detecting acute kidney injury after cardiopulmonary bypass surgery. *Pak Armed Forces Med J* 2013;**63**:179–83
Munir	2013	< 100 participants	Munir MU, Khan DA, Khan FA, Shahab Naqvi SM. Rapid detection of acute kidney injury by urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass surgery. *J Coll Physicians Surg Pak* 2013;**23**:103–6
Munshi	2014	Not a primary study	Munshi R, Zimmerman JJ. Neutrophil gelatinase-associated lipocalin-can it predict the future? *Pediatr Crit Care Med* 2014;**15**:173–4
Muratoglu	2016	Not a relevant type of population	Muratoglu M, Kavalci C, Kilicli E, Findik M, Kayipmaz AE, Durukan P. Serum neutrophil gelatinase-associated lipocalin levels in early detection of contrast-induced nephropathy. *Clin Invest Med* 2016;**39**:E88–94
Murphy	2014	< 100 participants	Murphy N, Vijayan A, Frohlich S, O'Farrell F, Barry M, Sheehan S, *et al.* Remote ischemic preconditioning does not affect the incidence of acute kidney injury after elective abdominal aortic aneurysm repair. *J Cardiothorac Vasc Anesth* 2104;**28**:1285–92
Musiol	2016	< 100 participants	Musiol K, Sobol-Milejska G, Nowotka Ł, Torba K, Kniażewska M, Wos H. Renal function in children treated for central nervous system malignancies. *Childs Nerv Syst* 2016;**32**:1431–40
Nadkarni	2017	No focus on DTA for AKI	Nadkarni GN, Coca SG, Meisner A, Patel S, Kerr KF, Patel UD, *et al.* Urinalysis findings and urinary kidney injury biomarker concentrations. *BMC Nephrol* 2017;**18**:218
Nam	2015	Meta-analysis – retained as background material	Nam MJ, Lim CH, Kim HJ, Kim YH, Choi H, Son HS, *et al.* A meta-analysis of renal function after adult cardiac surgery with pulsatile perfusion. *Artif Organs* 2015;**39**:788–94
Nasonova	2019	Non-English-language publication	Nasonova SN, Zhirov IV, Ledyakhova MV, Sharf TV, Bosykh EG, Masenko VP, Tereshchenko SN. Early diagnosis of acute renal injury in patients with acute decompensation of chronic heart failure. *Ter Arkh* 2019;**91**:67–73

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Nayak	2016	Not a relevant biomarker assay or test	Nayak NM, Madhumitha S, Annigeri RA, Venkataraman R, Balasubramaian S, Seshadri R, *et al.* Clinical utility of urine neutrophil gelatinase-associated lipocalin measured at admission to predict outcomes in heterogeneous population of critically ill patients. *Indian J Nephrol* 2016;**26**:119–24
Negrin	2018	< 100 participants	Negrin LL, Hahn R, Heinz T, Hajdu S. Diagnostic utility of serum neutrophil gelatinase-associated lipocalin in polytraumatized patients suffering acute kidney injury: a prospective study. *Biomed Res Int* 2018;**2018**:2687584
Nehus	2017	No focus on DTA for AKI	Nehus E, Kaddourah A, Bennett M, Pyles O, Devarajan P. Subclinical kidney injury in children receiving nonsteroidal anti-inflammatory drugs after cardiac surgery. *J Pediatr* 2017;**189**:175–80
Nejat	2012	No relevant outcome	Nejat M, Pickering JW, Devarajan P, Bonventre JV, Edelstein CL, Walker RJ, Endre ZH. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. *Kidney Int* 2012;**81**:1254–62
Nguyen	2019	Not a relevant type of population	Nguyen LS, Spagnoli V, Kerneis M, Hauguel-Moreau M, Barthélémy O, Collet JP, *et al.* Evaluation of neutrophil gelatinase-associated lipocalin and cystatin C as biomarkers of acute kidney injury after ST-segment elevation myocardial infarction treated by percutaneous coronary intervention. *Arch Cardiovasc Dis* 2019;**112**:180–6
Nickavar	2016	< 100 participants	Nickavar A, Safaeian B, Valavi E, Moradpour F. Validity of neutrophil gelatinase associated lipocaline as a biomarker for diagnosis of children with acute pyelonephritis. *Urol J* 2016;**13**:2860–3
Niemann	2009	< 100 participants	Niemann CU, Walia A, Waldman J, Davio M, Roberts JP, Hirose R, Feiner J. Acute kidney injury during liver transplantation as determined by neutrophil gelatinase-associated lipocalin. *Liver Transpl* 2009;**15**:1852–60
Ning	2018	Not a relevant type of population	Ning L, Li Z, Wei D, Chen H, Yang C, Wu D, *et al.* Urinary semaphorin 3A as an early biomarker to predict contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention. *Braz J Med Biol Res* 2018;**51**:e6487
Nishida	2010	< 100 participants	Nishida M, Kawakatsu H, Okumura Y, Hamaoka K. Serum and urinary neutrophil gelatinase-associated lipocalin levels in children with chronic renal diseases. *Pediatr Int* 2010;**52**:563–8
Noto	2019	< 100 participants	Noto A, Cortegiani A, David A. Nephrocheck: should we consider urine osmolality? *Crit Care* 2019;**23**:23
Noyan	2015	< 100 participants	Noyan A, Parmaksiz G, Dursun H, Ezer SS, Anarat R, Cengiz N. Urinary NGAL, KIM-1 and L-FABP concentrations in antenatal hydronephrosis. *J Pediatr Urol* 2015;**11**:249.e1–249.e6
Nusca	2018	Not a relevant type of population	Nusca A, Miglionico M, Proscia C, Ragni L, Carassiti M, Pepe FL, Sciascio GD. Early prediction of contrast-induced acute kidney injury by a 'bedside' assessment of neutrophil gelatinase-associated lipocalin during elective percutaneous coronary interventions. *PLOS ONE* 2018;**13**:e0197833

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Nymo	2012	Not a relevant biomarker assay or test	Nymo SH, Ueland T, Askevold ET, Flo TH, Kjekshus J, Hulthe J, *et al.* The association between neutrophil gelatinase-associated lipocalin and clinical outcome in chronic heart failure: results from CORONA. *J Intern Med* 2012;**271**:436–43
Odum	2014	< 100 participants	Odum L, Andersen AS, Hviid TVF. Urinary neutrophil gelatinase-associated lipocalin (NGAL) excretion increases in normal pregnancy but not in preeclampsia. *Clin Chem Lab Med* 2014;**52**:221–5
Oh	2012	< 100 participants	Oh SW, Chin HJ, Chae DW, Na KY. Erythropoietin improves long-term outcomes in patients with acute kidney injury after coronary artery bypass grafting. *J Korean Med Sci* 2012;**27**:506–11
Olvera-Posada	2017	< 100 participants	Olvera-Posada D, Dayarathna T, Dion M, Alenezi H, Sener A, Denstedt JD, *et al.* KIM-1 Is a potential urinary biomarker of obstruction: results from a prospective cohort study. *J Endourol* 2017;**31**:111–18
Omerika	2014	No focus on DTA for AKI	Omerika L, Rasić S, Serdarević N. Importance of determination of urine neutrophile gelatinase associated lipocalin in early detection of acute kidney injury. *Coll Antropol* 2014;**38**:161–6
Oncel	2016	< 100 participants	Oncel MY, Canpolat FE, Arayici S, Alyamac Dizdar E, Uras N, Oguz SS. Urinary markers of acute kidney injury in newborns with perinatal asphyxia. *Ren Fail* 2016;**38**:882–8
Onk	2016	Not a relevant biomarker assay or test	Onk OA, Onk D, Ozcelik F, Gunay M, Turkmen K. Risk factors for acute kidney injury after coronary artery bypass surgery and its detection using neutrophil gelatinase-associated lipocalin. *Cardiorenal Med* 2016;**6**:216–29
Opotowsky	2017	No focus on DTA for AKI	Opotowsky AR, Baraona FR, Mc Causland FR, Loukas B, Landzberg E, Landzberg MJ, *et al.* Estimated glomerular filtration rate and urine biomarkers in patients with single-ventricle Fontan circulation. *Heart* 2017;**103**:434–42
Ordooei Javan	2017	< 100 participants	Ordooei Javan A, Salamzadeh J, Shokouhi S, Sahraei Z. Evaluation of renal toxicity of colistin therapy with neutrophil gelatinase-associated lipocalin: a biomarker of renal tubular damage. *Iran J Kidney Dis* 2017;**11**:447–55
Orsolya	2015	No focus on DTA for AKI	Orsolya M, Attila-Zoltan M, Gherman V, Zaharie F, Bolboaca S, Chira C, *et al.* The effect of anaesthetic management on neutrophil gelatinase associated lipocalin (NGAL) levels after robotic surgical oncology. *J BUON* 2015;**20**:317–24
Ostermann	2015	Not a primary study	Ostermann M, Joannidis M. Biomarkers for AKI improve clinical practice: no. *Intensive Care Med* 2015;**41**:618–22
Ostermann	2018	Substudy measuring associations in NephroCheck levels and exposure to renal insult – retained as background material	Ostermann M, McCullough PA, Forni LG, Bagshaw SM, Joannidis M, Shi J, *et al.* Kinetics of urinary cell cycle arrest markers for acute kidney injury following exposure to potential renal insults. *Crit Care Med* 2018;**46**:375–83

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Owens	2011	< 100 participants	Owens GE, King K, Gurney JG, Charpie JR. Low renal oximetry correlates with acute kidney injury after infant cardiac surgery. *Pediatr Cardiol* 2011;**32**:183–8
Oz	2016	Not a relevant biomarker assay or test	Oz K, Gode S, Basgoze S, Koser M, Oz A, Goksel OS, *et al.* Cystatin C and NGAL as biomarkers for early detection of acute kidney injury in geriatrics. *Int Surg* 2016;**101**:390–8
Ozdemir	2014	Not a relevant type of population	Ozdemir O, Oguz AD, Eren A, Sanli C, Sylemezoglu HO, Cayci AB. Cystatin C as biomarker of contrast-induced nephropathy in pediatric cardiac angiography. *Turk J Med Sci* 2014;**44**:178–85
Ozkan	2014	< 100 participants	Ozkan S, Durukan P, Kavalci C, Duman A, Sayhan MB, Salt O, Ipekci A. Importance of neutrophil gelatinase-associated lipocalin in differential diagnosis of acute and chronic renal failure. *Iran Red Crescent Med J* 2014;**16**:e14133
Paapstel	2016	< 100 participants	Paapstel K, Zilmer M, Eha J, Tootsi K, Piir A, Kals J. Early biomarkers of renal damage in relation to arterial stiffness and inflammation in male coronary artery disease patients. *Kidney Blood Press Res* 2016;**41**:488–97
Paarmann	2013	Not a relevant biomarker assay or test	Paarmann H, Charitos EI, Beilharz A, Heinze H, Schon J, Berggreen A, Heringlake M. Duration of cardiopulmonary bypass is an important confounder when using biomarkers for early diagnosis of acute kidney injury in cardiac surgical patients. *Appl Cardiopulm Pathophysiol* 2013;**17**:284–97
Padhy	2014	Not a relevant type of population	Padhy M, Kaushik S, Girish MP, Mohapatra S, Shah S, Koner BC. Serum neutrophil gelatinase associated lipocalin (NGAL) and cystatin C as early predictors of contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention. *Clin Chim Acta* 2014;**435**:48–52
Pajenda	2015	< 100 participants	Pajenda S, Ilhan-Mutlu A, Preusser M, Roka S, Druml W, Wagner L. NephroCheck data compared to serum creatinine in various clinical settings. *BMC Nephrol* 2015;**16**:0203–5
Palazzuoli	2014	Not a relevant biomarker assay or test	Palazzuoli A, Ruocco G, Beltrami M, Franci B, Pellegrini M, Lucani B, *et al.* Admission plasma neutrophil gelatinase associated lipocalin (NGAL) predicts worsening renal function during hospitalization and post discharge outcome in patients with acute heart failure. *Acute Card Care* 2014;**16**:93–101
Palazzuoli	2014	Not a relevant biomarker assay or test	Palazzuoli A, Ruocco G, Pellegrini M, Martini S, Del Castillo G, Beltrami M, *et al.* Patients with cardiorenal syndrome revealed increased neurohormonal activity, tubular and myocardial damage compared to heart failure patients with preserved renal function. *Cardiorenal Med* 2014;**4**:257–68
Palazzuoli	2015	Not a relevant biomarker assay or test	Palazzuoli A, Ruocco G, Pellegrini M, De Gori C, Del Castillo G, Franci B, *et al.* Comparison of neutrophil gelatinase-associated lipocalin versus B-type natriuretic peptide and cystatin C to predict early acute kidney injury and outcome in patients with acute heart failure. *Am J Cardiol* 2015;**116**:104–11

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Palermo	2017	< 100 participants	Palermo J, Dart AB, De Mello A, Devarajan P, Gottesman R, Garcia Guerra G, *et al.* Biomarkers for early acute kidney injury diagnosis and severity prediction: a pilot multicenter Canadian study of children admitted to the ICU. *Pediatr Crit Care Med* 2017;**18**:e235–e244
Pan	2018	< 100 participants	Pan JJ, Sun ZY, Zhou XY, Hu YH, Cheng R, Chen XQ, Yang Y. Is neutrophil gelatinase-associated lipocalin a good diagnostic marker for renal injury in asphyxiated preterm infants? *J Res Med Sci* 2018;**23**:90
Pang	2016	Not a relevant type of population	Pang Y, Tan Y, Li Y, Zhang J, Guo Y, Guo Z, *et al.* Pentraxin 3 is closely associated with tubulointerstitial injury in lupus nephritis: a large multicenter cross-sectional study. *Medicine* 2016;**95**:e2520
Pang	2017	< 100 participants	Pang HM, Qin XL, Liu TT, Wei WX, Cheng DH, Lu H, *et al.* Urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin as early biomarkers for predicting vancomycin-associated acute kidney injury: a prospective study. *Eur Rev Med Pharmacol Sci* 2017;**21**:4203–13
Papadopoulou-Marketou	2015	< 100 participants	Papadopoulou-Marketou N, Skevaki C, Kosteria I, Peppa M, Chrousos GP, Papassotiriou I, Kanaka-Gantenbein C. NGAL and cystatin C: two possible early markers of diabetic nephropathy in young patients with type 1 diabetes mellitus: one year follow up. *Hormones* 2015;**14**:232–40
Papassotiriou	2016	< 100 participants	Papassotiriou GP, Kastritis E, Gkotzamanidou M, Christoulas D, Eleutherakis-Papaiakovou E, Migkou M, *et al.* Neutrophil gelatinase-associated lipocalin and cystatin C are sensitive markers of renal injury in patients with multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2016;**16**:29–35
Parekh	2013	< 100 participants	Parekh DJ, Weinberg JM, Ercole B, Torkko KC, Hilton W, Bennett M, *et al.* Tolerance of the human kidney to isolated controlled ischemia. *J Am Soc Nephrol* 2013;**24**:506–17
Parikh	2012	Not a primary study	Parikh A, Shaw A. The economics of renal failure and kidney disease in critically ill patients. *Crit Care Clin* 2012;**28**:99–111
Parikh	2013	< 100 participants	Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, *et al.* Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2013;**70**:199–203
Parikh	2013	Not a primary study	Parikh CR, Han G. Variation in performance of kidney injury biomarkers due to cause of acute kidney injury. *Am J Kidney Dis* 2013;**62**:1023–6
Parikh	2016	Uses simulated data from the TRIBE AKI study – retained as background material	Parikh CR, Moledina DG, Coca SG, Thiessen-Philbrook HR, Garg AX. Application of new acute kidney injury biomarkers in human randomized controlled trials. *Kidney Int* 2016;**89**:1372–9

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Parikh	2017	No relevant outcome	Parikh CR, Puthumana J, Shlipak MG, Koyner JL, Thiessen-Philbrook H, McArthur E, *et al.* Relationship of kidney injury biomarkers with long-term cardiovascular outcomes after cardiac surgery. *J Am Soc Nephrol* 2017;**28**:3699–707
Parikh	2017	Not a primary study	Parikh A, Rizzo JA, Canetta P, Forster C, Sise M, Maarouf O, *et al.* Correction: does NGAL reduce costs? A cost analysis of urine NGAL (uNGAL) & serum creatinine (sCr) for acute kidney injury (AKI) diagnosis. *PLOS ONE* 2017;**12**:e0185772
Parikh	2017	Not a primary study	Parikh A, Rizzo JA, Canetta P, Forster C, Sise M, Maarouf O, *et al.* Does NGAL reduce costs? A cost analysis of urine NGAL (uNGAL) & serum creatinine (sCr) for acute kidney injury (AKI) diagnosis. *PLOS ONE* 2017;**12**:e0178091
Park	2012	< 100 participants	Park HD, Seo JY, Lee SY. The relationship between serum neutrophil gelatinase-associated lipocalin and renal function in patients with vancomycin treatment. *Ann Clin Lab Sci* 2012;**42**:7–13
Park	2015	< 100 participants	Park GY, Yu CH, Kim JS, Kang YJ, Kwon O, Choi JY, *et al.* Plasma neutrophil gelatinase-associated lipocalin as a potential predictor of adverse renal outcomes in immunoglobulin A nephropathy. *Korean J Intern Med* 2015;**30**:345–53
Park	2016	< 100 participants	Park SO, Ahn JY, Lee YH, Kim YJ, Min YH, Ahn HC, *et al.* Plasma neutrophil gelatinase-associated lipocalin as an early predicting biomarker of acute kidney injury and clinical outcomes after recovery of spontaneous circulation in out-of-hospital cardiac arrest patients. *Resuscitation* 2016;**101**:84–90
Park	2018	< 100 participants	Park YR, Oh JS, Jeong H, Park J, Oh YM, Choi S, Choi KH. Predicting long-term outcomes after cardiac arrest by using serum neutrophil gelatinase-associated lipocalin. *Am J Emerg Med* 2018;**36**:660–4
Park	2018	Not a relevant type of population	Park SY, Eom JS, Lee JS, Ju YS, Park JY. Neutrophil Gelatinase-associated lipocalin as a predictor of acute kidney injury in patients during treatment with colistimethate sodium. *Infect Chemother* 2018;**50**:128–37
Park	2015	Not a relevant biomarker assay or test	Park CM, Kim JS, Moon HW, Park S, Kim H, Ji M, *et al.* Usefulness of plasma neutrophil gelatinase-associated lipocalin as an early marker of acute kidney injury after cardiopulmonary bypass in Korean cardiac patients: a prospective observational study. *Clin Biochem* 2015;**48**:44–9
Parr	2015	Not a relevant type of population	Parr SK, Clark AJ, Bian A, Shintani AK, Wickersham NE, Ware LB, *et al.* Urinary L-FABP predicts poor outcomes in critically ill patients with early acute kidney injury. *Kidney Int* 2015;**87**:640–8
Parravicini	2010	< 100 participants	Parravicini E, Nemerofsky SL, Michelson KA, Huynh TK, Sise ME, Bateman DA, *et al.* Urinary neutrophil gelatinase-associated lipocalin is a promising biomarker for late onset culture-positive sepsis in very low birth weight infants. *Pediatr Res* 2010;**67**:636–40

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Parravicini	2016	< 100 participants	Parravicini E, Locatelli C, Lorenz JM, Nemerofsky SL, Bateman DA. Is urinary neutrophil gelatinase-associated lipocalin able to predict acute kidney injury episodes in very low birth weight infants in clinical settings? *Pediatr Res* 2016;**80**:663–7
Passov	2019	Not a relevant biomarker assay or test	Passov A, Petäjä L, Pihlajoki M, Salminen US, Suojaranta R, Vento A, *et al.* The origin of plasma neutrophil gelatinase-associated lipocalin in cardiac surgery. *BMC Nephrol* 2019;**20**:182
Patel	2013	Not a relevant type of population	Patel M, Sachan R, Gangwar R, Sachan P, Natu S. Correlation of serum neutrophil gelatinase-associated lipocalin with acute kidney injury in hypertensive disorders of pregnancy. *Int J Nephrol Renovasc Dis* 2013;**6**:181–6
Patel	2016	Not a relevant biomarker assay or test	Patel ML, Sachan R, Shyam R, Kumar S, Kamal R, Misra A. Diagnostic accuracy of urinary neutrophil gelatinase-associated lipocalin in patients with septic acute kidney injury. *Int J Nephrol Renovasc Dis* 2016;**9**:161–9
Patschan	2014	< 100 participants	Patschan D, Heeg M, Brier M, Brandhorst G, Schneider S, Müller GA, Koziolek MJ. CD4+ lymphocyte adenosine triphosphate – a new marker in sepsis with acute kidney injury? *BMC Nephrol* 2014;**15**:203
Peco-Antić	2013	Not a relevant biomarker assay or test	Peco-Antić A, Ivanišević I, Vulićević I, Kotur-Stevuljević J, Ilić S, Ivanišević J, *et al.* Biomarkers of acute kidney injury in pediatric cardiac surgery. *Clin Biochem* 2013;**46**:1244–51
Pedersen	2010	< 100 participants	Pedersen KR, Ravn HB, Hjortdal VE, Nørregaard R, Povlsen JV. Neutrophil gelatinase-associated lipocalin (NGAL): validation of commercially available ELISA. *Scand J Clin Lab Invest* 2010;**70**:374–82
Pejović	2015	Not a relevant type of population	Pejović B, Erić-Marinković J, Pejović M, Kotur-Stevuljević J, Peco-Antić A. Detection of acute kidney injury in premature asphyxiated neonates by serum neutrophil gelatinase-associated lipocalin (sNGAL) – sensitivity and specificity of a potential new biomarker. *Biochem Med* 2015;**25**:450–9
Peralta	2014	Not a relevant type of population	Peralta CA, Scherzer R, Grunfeld C, Abraham A, Tien PC, Devarajan P, *et al.* Urinary biomarkers of kidney injury are associated with all-cause mortality in the Women's Interagency HIV Study (WIHS). *HIV Med* 2014;**15**:291–300
Peres	2014	< 100 participants	Peres LA, da Cunha AD, Assumpção RA, Schäfer A, da Silva AL, Gaspar AD, *et al.* Evaluation of the cisplatin nephrotoxicity using the urinary neutrophil gelatinase-associated lipocalin (NGAL) in patients with head and neck cancer. *J Bras Nefrol* 2014;**36**:280–8
Perrin	2013	Not a relevant type of population	Perrin T, Descombes E, Magnin JL, Gachet M, Hemett OM, Hayoz D, *et al.* Urinary neutrophil gelatinase-associated lipocalin (uNGAL) and contrast-induced acute kidney injury after coronary angiogram. *Swiss Med Wkly* 2013;**143**:13853

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Perrotti	2015	Not a relevant biomarker assay or test	Perrotti A, Miltgen G, Chevet-Noel A, Durst C, Vernerey D, Bardonnet K, *et al.* Neutrophil gelatinase-associated lipocalin as early predictor of acute kidney injury after cardiac surgery in adults with chronic kidney failure. *Ann Thorac Surg* 2015;**99**:864–9
Perry	2010	Not a relevant biomarker assay or test	Perry TE, Muehlschlegel JD, Liu KY, Fox AA, Collard CD, Shernan SK, Body SC, CABG Genomics Investigators. Plasma neutrophil gelatinase-associated lipocalin and acute postoperative kidney injury in adult cardiac surgical patients. *Anesth Analg* 2010;**110**:1541–7
Pesonen	2016	< 100 participants	Pesonen EJ, Suominen PK, Keski-Nisula J, Mattila IP, Rautiainen P, Jahnukainen T. The effect of methylprednisolone on plasma concentrations of neutrophil gelatinase-associated lipocalin in pediatric heart surgery. *Pediatr Crit Care Med* 2016;**17**:121–7
Petrovic	2013	< 100 participants	Petrovic S, Bogavac-Stanojevic N, Peco-Antic A, Ivanisevic I, Kotur-Stevuljevic J, Paripovic D, *et al.* Clinical application neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 as indicators of inflammation persistence and acute kidney injury in children with urinary tract infection. *Biomed Res Int* 2013;**2013**:947157
Pezeshgi	2018	< 100 participants	Pezeshgi A, Ghodrati S, Kiafar M, Kamali K, Asadi-Khiavi M. Study of neutrophil gelatinase-associated lipocalin in patients with cardiovascular shock. *J Ren Inj Prev* 2018;**7**:144–7
Piccoli	2012	Not a primary study	Piccoli GB, Ferraresi M, Aroasio E, Gonella S, De Pascale A, Veltri A. The search for perfect biomarkers in acute kidney damage: the case of NGAL, from AKI to acute pyelonephritis: back to the clinic? *Nephrol Dial Transplant* 2012;**27**:3665–6
Pickering	2013	< 100 participants	Pickering JW, Ralib AM, Endre ZH. Combining creatinine and volume kinetics identifies missed cases of acute kidney injury following cardiac arrest. *Crit Care* 2013;**17**:R7
Pickering	2013	Not a relevant biomarker assay or test	Pickering JW, Endre ZH. Linking injury to outcome in acute kidney injury: a matter of sensitivity. *PLOS ONE* 2013;**8**:e62691
Pickering	2013	Not a relevant biomarker assay or test	Pickering JW, Endre ZH. The clinical utility of plasma neutrophil gelatinase-associated lipocalin in acute kidney injury. *Blood Purif* 2013;**35**:295–302
Piirainen	2018	< 100 participants	Piirainen A, Huopio J, Kokki H, Holopainen A, Pajunen T, Pulkki K, Kokki M. Novel renal markers for the assessment of renal integrity in patients undergoing knee arthroplasty – a pilot study. *J Exp Orthop* 2018;**5**:40
Pilarczyk	2015	< 100 participants	Pilarczyk K, Edayadiyil-Dudasova M, Wendt D, Demircioglu E, Benedik J, Dohle DS, *et al.* Urinary [TIMP-2]*[IGFBP7] for early prediction of acute kidney injury after coronary artery bypass surgery. *Ann Intensive Care* 2015;**5**:1–11

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Pisano	2018	Not a primary study	Pisano DV, Joyce MF. Plasma neutrophil gelatinase-associated lipocalin: biomarker of the future or just another test? *J Clin Anesth* 2018;**45**:37–8
Plebani	2017	Not a primary study	Plebani M. Biomarkers of acute kidney injury: a step forward. *Clin Chem Lab Med* 2017;**55**:1071–3
Plewes	2014	Not a relevant type of population	Plewes K, Royakkers AA, Hanson J, Hasan MM, Alam S, Ghose A, *et al.* Correlation of biomarkers for parasite burden and immune activation with acute kidney injury in severe falciparum malaria. *Malar J* 2014;**13**:91
Polat	2013	< 100 participants	Polat M, Fidan K, Derinöz O, Gönen S, Söylemezoglu O. Neutrophil gelatinase-associated lipocalin as a follow-up marker in critically ill pediatric patients with established acute kidney injury. *Ren Fail* 2013;**35**:352–6
Poorshahbaz	2015	< 100 participants	Poorshahbaz F, Karami A, Jozpanahi M, Pezeshki A, Fagihzadeh S, Esmailzadeh A, *et al.* Comparison of changes in serum creatinine and PNGAL in predicting renal damage in brucellosis patients receiving gentamycin. *Crescent J Medical Biol Sci* 2015;**2**:116–20
Portal	2010	< 100 participants	Portal AJ, McPhail MJ, Bruce M, Coltart I, Slack A, Sherwood R, *et al.* Neutrophil gelatinase – associated lipocalin predicts acute kidney injury in patients undergoing liver transplantation. *Liver Transpl* 2010;**16**:1257–66
Prabhu	2010	< 100 participants	Prabhu A, Sujatha DI, Ninan B, Vijayalakshmi MA. Neutrophil gelatinase associated lipocalin as a biomarker for acute kidney injury in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. *Ann Vasc Surg* 2010;**24**:525–31
Prasad	2014	Not a primary study	Prasad A. Acute kidney injury following contrast administration in pediatric congenital heart disease patients: time to move beyond the serum creatinine. *Catheter Cardiovasc Interv* 2014;**84**:620–1
Prowle	2014	Not a primary study	Prowle JR, Kirwan CJ. Acute kidney injury after cardiac surgery: the injury that keeps on hurting? *Crit Care Med* 2014;**42**:2142–3
Prowle	2015	Not a primary study	Prowle JR. Measurement of AKI biomarkers in the ICU: still striving for appropriate clinical indications. *Intensive Care Med* 2015;**41**:541–3
Prowle	2015	< 100 participants	Prowle JR, Calzavacca P, Licari E, Ligabo EV, Echeverri JE, Bagshaw SM, *et al.* Combination of biomarkers for diagnosis of acute kidney injury after cardiopulmonary bypass. *Renal Fail* 2015;**37**:408–16
Przybylowski	2010	No focus on DTA for AKI	Przybylowski P, Malyszko J, Malyszko JS. Serum neutrophil gelatinase-associated lipocalin correlates with kidney function in heart allograft recipients. *Transplant Proc* 2010;**42**:1797–802
Przybylowski	2011	Not a relevant type of population	Przybylowski P, Koc-Zorawska E, Malyszko JS, Kozlowska S, Mysliwiec M, Malyszko J. Liver fatty-acid-binding protein in heart and kidney allograft recipients in relation to kidney function. *Transplant Proc* 2011;**43**:3064–7

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Puiac	2017	< 100 participants	Puiac C, Szederjesi J, Lazăr A, Bad C, Puşcaşiu L. Neutrophil gelatinase-associated lipocalin as a marker for renal dysfunction detection in critically ill patients with increased intraabdominal pressure. *J Crit Care Med* 2017;**3**:24–8
Puthumana	2017	Meta-analysis – retained as background material	Puthumana J, Ariza X, Belcher JM, Graupera I, Ginès P, Parikh CR. Urine interleukin 18 and lipocalin 2 are biomarkers of acute tubular necrosis in patients with cirrhosis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2017;**15**:1003–13.e3
Pynn	2015	No focus on DTA for AKI	Pynn JM, Parravicini E, Saiman L, Bateman DA, Barasch JM, Lorenz JM. Urinary neutrophil gelatinase-associated lipocalin: potential biomarker for late-onset sepsis. *Pediatr Res* 2015;**78**:76–81
Qasem	2014	Not a relevant biomarker assay or test	Qasem AA, Farag SE, Hamed E, Emara M, Bihery A, Pasha H. Urinary biomarkers of acute kidney injury in patients with liver cirrhosis. *ISRN Nephrol* 2014;**2014**:376795
Qiao	2015	Not a relevant type of population	Qiao B, Deng J, Li Y, Wang X, Han Y. Rosuvastatin attenuated contrast-induced nephropathy in diabetes patients with renal dysfunction. *Int J Clin Exp Med* 2015;**8**:2342–9
Quartin	2013	Not a primary study	Quartin A, Schein R, Cely C. Accuracy of plasma neutrophil gelatinase-associated lipocalin in the early diagnosis of contrast-induced acute kidney injury in critical illness. *Intensive Care Med* 2013;**39**:1670
Quintavalle	2015	Not a relevant type of population	Quintavalle C, Anselmi CV, De Micco F, Roscigno G, Visconti G, Golia B, *et al.* Neutrophil gelatinase-associated lipocalin and contrast-induced acute kidney injury. *Circ Cardiovasc Interv* 2015;**8**:e002673
Radovic	2019	No relevant outcome	Radovic M, Bojic S, Kotur-Stevuljevic J, Lezaic V, Milicic B, Velinovic M, *et al.* Serum lactate as reliable biomarker of acute kidney injury in low-risk cardiac surgery patients. *J Med Biochem* 2019;**38**:118–25
Rafiei	2015	< 100 participants	Rafiei A, Mohammadjafari H, Bazi S, Mirabi AM. Urinary neutrophil gelatinase-associated lipocalin (NGAL) might be an independent marker for anticipating scar formation in children with acute pyelonephritis. *J Renal Inj Prev* 2015;**4**:39–44
Raggal	2013	< 100 participants	Raggal NE, Khafagy SM, Mahmoud NH, Beltagy SE. Serum neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury in asphyxiated neonates. *Indian Pediatr* 2013;**50**:459–62
Rakkolainen	2016	< 100 participants	Rakkolainen I, Vuola J. Plasma NGAL predicts early acute kidney injury no earlier than s-creatinine or cystatin C in severely burned patients. *Burns* 2016;**42**:322–8
Ralib	2011	Not a primary study	Ralib AM, Pickering JW, Endre ZH. Predictor of early diagnosis, diagnosis, or progression of acute kidney injury. *Ann Emerg Med* 2011;**57**:75–6
Ralib	2012	Not a relevant biomarker assay or test	Ralib AM, Pickering JW, Shaw GM, Devarajan P, Edelstein CL, Bonventre JV, Endre ZH. Test characteristics of urinary biomarkers depend on quantitation method in acute kidney injury. *J Am Soc Nephrol* 2012;**23**:322–33

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Ralib	2014	< 100 participants	Ralib AM, Pickering JW, Shaw GM, Than MP, George PM, Endre ZH. The clinical utility window for acute kidney injury biomarkers in the critically ill. *Crit Care* 2014;**18**:601
Ralib	2017	Not a relevant type of population	Ralib AM, Nanyan S, Mat Nor MB. Dynamic changes of plasma neutrophil gelatinase-associated lipocalin predicted mortality in critically ill patients with systemic inflammatory response syndrome. *Indian J Crit Care Med* 2017;**21**:23–9
Ramchandran	2013	Not a primary study	Ramachandran B. Acute kidney injury in critically ill children: More than just urine output. *Indian J Crit Care Med* 2013;**17**:203–4
Rampoldi	2018	< 100 participants	Rampoldi B, Tessarolo S, Giubbilini P, Gaia P, Corino SD, Mazza S, *et al.* Neutrophil gelatinase-associated lipocalin and acute kidney injury in endovascular aneurysm repair or open aortic repair: a pilot study. *Biochemia Medica* 2018;**28**:010904
Rauen	2011	Not a primary study	Rauen T, Weiskirchen R, Floege J. In search of early events in the development of chronic kidney disease: the emerging role for lipocalin-2/NGAL. *Nephrol Dial Transplant* 2011;**26**:445–7
Redding	2013	Not a primary study	Redding S. Distinct injury markers for the early detection and prognosis of incident acute kidney injury in critically ill adults with preserved kidney function. *Ann Clin Biochem* 2013;**50**:625–6
Reiter	2018	< 100 participants	Reiter K, Balling G, Bonelli V, Pabst Von Ohain J, Braun SL, Ewert P, Ruf B. Neutrophil gelatinase-associated lipocalin reflects inflammation and is not a reliable renal biomarker in neonates and infants after cardiopulmonary bypass: a prospective case-control study. *Cardiol Young* 2018;**28**:243–51
Renhua	2014	Not a relevant type of population	Renhua L, Miaolin C, Junlin W, Qingwei W, Xiaoping X, Huili D, *et al.* The level of the biomarkers at the time of nephrology consultation might predict the prognosis of acute kidney injury in hospitalized patients. *Blood Purif* 2014;**38**:89–95
Rewa	2015	Not a relevant biomarker assay or test	Rewa O, Wald R, Adhikari NK, Hladunewich M, Lapinsky S, Muscedere J, *et al.* Whole-blood neutrophil gelatinase-associated lipocalin to predict adverse events in acute kidney injury: a prospective observational cohort study. *J Crit Care* 2015;**30**:1359–64
Ribitsch	2011	Not a primary study	Ribitsch W, Rosenkranz AR. Biomarkers in acute kidney injury: a never ending story? *Crit Care Med* 2011;**39**:2570–1
Ribitsch	2017	Not a relevant type of population	Ribitsch W, Schilcher G, Quehenberger F, Pilz S, Portugaller RH, Truschnig-Wilders M, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) fails as an early predictor of contrast induced nephropathy in chronic kidney disease (ANTI-CI-AKI study). *Sci Rep* 2017;**7**:41300

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Ricci	2012	Not a relevant biomarker assay or test	Ricci Z, Netto R, Garisto C, Iacoella C, Favia I, Cogo P. Whole blood assessment of neutrophil gelatinase-associated lipocalin versus pediatricRIFLE for acute kidney injury diagnosis and prognosis after pediatric cardiac surgery: cross-sectional study. *Pediatr Crit Care Med* 2012;**13**:667–70
Ricci	2015	No focus on DTA for AKI	Ricci Z, Haiberger R, Pezzella C, Garisto C, Favia I, Cogo P. Furosemide versus ethacrynic acid in pediatric patients undergoing cardiac surgery: a randomized controlled trial. *Crit Care* 2015;**19**:2
Roberts	2011	Not a relevant type of population	Roberts DM, Wilks MF, Roberts MS, Swaminathan R, Mohamed F, Dawson AH, Buckley NA. Changes in the concentrations of creatinine, cystatin C and NGAL in patients with acute paraquat self-poisoning. *Toxicol Lett* 2011;**202**:69–74
Robertson	2019	< 100 participants	Robertson FP, Yeung AC, Male V, Rahman S, Mallett S, Fuller BJ, Davidson BR. Urinary neutrophil gelatinase associated lipocalins (NGALs) predict acute kidney injury post liver transplant. *HPB* 2019;**21**:473–81
Rocha	2015	< 100 participants	Rocha PN, Macedo MN, Kobayashi CD, Moreno L, Guimarães LH, Machado PR, *et al.* Role of urine neutrophil gelatinase-associated lipocalin in the early diagnosis of amphotericin B-induced acute kidney injury. *Antimicrob Agents Chemother* 2015;**59**:6913–21
Ronco	2008	Not a primary study	Ronco C. NGAL: an emerging biomarker of acute kidney injury. *Int J Artif Organs* 2008;**31**:199–200
Ronco	2013	Not a primary study	Ronco C. Kidney attack: overdiagnosis of acute kidney injury or comprehensive definition of acute kidney syndromes? *Blood Purif* 2013;**36**:65–8
Ronco	2017	Not a primary study	Ronco C, Rizo-Topete L, Serrano-Soto M, Kashani K. Pro: Prevention of acute kidney injury: time for teamwork and new biomarkers. *Nephrol Dial Transplant* 2017;**32**:408–13
Rostami	2010	Not a primary study	Rostami Z, Lessan-Pezeshki M. Role of NGAL for the early detection of acute kidney injury. *Int J Nephrol Urol* 2010;**2**:387–9
Roudkenar	2008	< 100 participants	Roudkenar MH, Halabian R, Oodi A, Roushandeh AM, Yaghmai P, Najar MR, *et al.* Upregulation of neutrophil gelatinase-associated lipocalin, NGAL/Lcn2, in beta-thalassemia patients. *Arch Med Res* 2008;**39**:402–7
Roudkenar	2008	No focus on DTA for AKI	Roudkenar MH, Halabian R, Ghasemipour Z, Roushandeh AM, Rouhbakhsh M, Nekogoftar M, *et al.* Neutrophil gelatinase-associated lipocalin acts as a protective factor against H_2O_2 toxicity. *Arch Med Res* 2008;**39**:560–6
Rouve	2018	< 100 participants	Rouve E, Lakhal K, Salmon GandonnièreC, Jouan Y, Bodet-Contentin L, Ehrmann S. Lack of impact of iodinated contrast media on kidney cell-cycle arrest biomarkers in critically ill patients. *BMC Nephrol* 2018;**19**:308
Royakkers	2012	Not a relevant biomarker assay or test	Royakkers AA, Bouman CS, Stassen PM, Korevaar JC, Binnekade JM, van de Hoek W, *et al.* Systemic and urinary neutrophil gelatinase-associated lipocalins are poor predictors of acute kidney injury in unselected critically ill patients. *Crit Care Res Pract* 2012;**2012**:712695

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Ruf	2015	< 100 participants	Ruf B, Bonelli V, Balling G, Hörer J, Nagdyman N, Braun SL, *et al.* Intraoperative renal near-infrared spectroscopy indicates developing acute kidney injury in infants undergoing cardiac surgery with cardiopulmonary bypass: a case-control study. *Crit Care* 2015;**19**:27
Saad	2016	< 100 participants	Saad A, Wang W, Herrmann SM, Glockner JF, Mckusick MA, Misra S, *et al.* Atherosclerotic renal artery stenosis is associated with elevated cell cycle arrest markers related to reduced renal blood flow and postcontrast hypoxia. *Nephrol Dial Transplant* 2016;**31**:1855–63
Sagatov	2019	No focus on DTA for AKI	Sagatov IY, Medeubekov US. Dynamics of urine neutrophil gelatinase-associated lipocalin in cardiac surgery patients in the near term after surgery. *Chirurgia* 2019;**32**:59–61
Saleena	2015	Not a relevant type of population	Saleena UV, Nalini K, Gopalakrishna K, Prabhu R, Vadhiraja BM, Athiyamaan MS, *et al.* Early prediction of cisplatin nephrotoxicity in head and neck cancer patients – an evaluation with urinary biomarkers. *Int J Pharm Sci Res* 2015;**6**:2893–901
Saleh	2017	Not a relevant biomarker assay or test	Saleh NY, Abo El Fotoh WMM, El-Hawy MA. Serum Neutrophil gelatinase-associated lipocalin: a diagnostic marker in pediatric sepsis. *Pediatr Crit Care Med* 2017;**18**:e245–e252
Sarafidis	2012	< 100 participants	Sarafidis K, Tsepkentzi E, Agakidou E, Diamanti E, Taparkou A, Soubasi V, *et al.* Serum and urine acute kidney injury biomarkers in asphyxiated neonates. *Pediatr Nephrol* 2012;**27**:1575–82
Sarafidis	2014	< 100 participants	Sarafidis K, Tsepkentzi E, Diamanti E, Agakidou E, Taparkou A, Soubasi V, *et al.* Urine neutrophil gelatinase-associated lipocalin to predict acute kidney injury in preterm neonates. A pilot study. *Pediatr Nephrol* 2014;**29**:305–10
Sargentini	2012	< 100 participants	Sargentini V, Mariani P, D'Alessandro M, Pistolesi V, Lauretta MP, Pacini F, *et al.* Assessment of NGAL as an early biomarker of acute kidney injury in adult cardiac surgery patients. *J Biol Regul Homeost Agents* 2012;**26**:485–93
Sarlak	2014	Not a primary study	Sarlak H, Dinc M, Balta S, Cakar M, Arslan E, Demirbas S. Early detection of urinary NGAL and plasma CysC may prevent progression to overt acute renal failure. *Swiss Med Wkly* 2014;**144**:w13949
Sarnak	2014	Not a relevant type of population	Sarnak MJ, Katz R, Newman A, Harris T, Peralta CA, Devarajan P, *et al.* Association of urinary injury biomarkers with mortality and cardiovascular events. *J Am Soc Nephrol* 2014;**25**:1545–53
Satirapoj	2016	Not a relevant type of population	Satirapoj B, Aramsaowapak K, Tangwonglert T, Supasyndh O. Novel tubular biomarkers predict renal progression in type 2 diabetes mellitus: a prospective cohort study. *J Diabetes Res* 2016;**2016**:3102962

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Savran Karadeniz	2019	< 100 participants	Savran Karadeniz M, Alp Enişte I, Şentürk Çiftçi H, Usta S, Tefik T, Şanlı Ö, *et al.* Neutrophil gelatinase-associated lipocalin significantly correlates with ischemic damage in patients undergoing laparoscopic partial nephrectomy. *Balkan Med J* 2019;**36**:121–8
Saydam	2018	< 100 participants	Saydam O, Türkmen E, Portakal O, Arıcı M, Doğan R, Demircin M, *et al.* Emerging biomarker for predicting acute kidney injury after cardiac surgery: cystatin C. *Turk J Med Sci* 2018;**48**:1096–103
Sayed	2015	< 100 participants	Sayed S, Idriss NK, Blann A, Sayyed HG, Raafat DM, Fouad D, Tawfeek MS. The number of GT(n) repeats in the hemeoxygenase-1 gene promoter is increased in pediatric heart failure but is unrelated to renal, antioxidant and anti-inflammatory markers. *Pediatr Cardiol* 2015;**36**:1204–11
Scazzochio	2014	< 100 participants	Scazzochio E, Munmany M, Garcia L, Meler E, Crispi F, Gratacos E, Figueras F. Prognostic role of maternal neutrophil gelatinase-associated lipocalin in women with severe early-onset preeclampsia. *Fetal Diagn Ther* 2014;**35**:127–32
Schanz	2017	< 100 participants	Schanz M, Shi J, Wasser C, Alscher MD, Kimmel M. Urinary [TIMP-2] × [IGFBP7] for risk prediction of acute kidney injury in decompensated heart failure. *Clin Cardiol* 2017;**40**:485–91
Schanz	2018	Not a relevant type of population	Schanz M, Wasser C, Allgaeuer S, Schricker S, Dippon J, Alscher MD, Kimmel M. Urinary [TIMP-2] × [IGFBP7]-guided randomized controlled intervention trial to prevent acute kidney injury in the emergency department. *Nephrol Dial Transplant* 2018;**34**:1902–9
Schanz	2017	< 100 participants	Schanz M, Hoferer A, Shi J, Alscher MD, Kimmel M. Urinary TIMP2.IGFBP7 for the prediction of platinum-induced acute renal injury. *Int J Nephrol Renovasc Dis* 2017;**10**:175–81
Schaub	2015	No focus on DTA for AKI	Schaub JA, Garg AX, Coca SG, Testani JM, Shlipak MG, Eikelboom J, *et al.* Perioperative heart-type fatty acid binding protein is associated with acute kidney injury after cardiac surgery. *Kidney Int* 2015;**88**:576–83
Schetz	2018	Not a primary study	Schetz M, Prowle J. Focus on acute kidney injury 2017. *Intensive Care Med* 2018;**44**:1992–4
Schilcher	2011	Not a primary study	Schilcher G, Ribitsch W, Otto R, Portugaller RH, Quehenberger F, Truschnig-Wilders M, *et al.* Early detection and intervention using neutrophil gelatinase-associated lipocalin (NGAL) may improve renal outcome of acute contrast media induced nephropathy: a randomized controlled trial in patients undergoing intra-arterial angiography (ANTI-CIN Study). *BMC Nephrol* 2011;**12**:39
Schinstock	2013	No relevant outcome	Schinstock CA, Semret MH, Wagner SJ, Borland TM, Bryant SC, Kashani KB, *et al.* Urinalysis is more specific and urinary neutrophil gelatinase-associated lipocalin is more sensitive for early detection of acute kidney injury. *Nephrol Dial Transplant* 2013;**28**:1175–85

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Schley	2015	Poster presentation – may be the same study as Schley[61]	Schley G, Koberle C, Manuilova E, Rutz S, Kientsch-Engel R, Eckardt KU, Willam C. Comparative analysis of diagnostic and predictive performance of novel renal biomarkers in plasma and urine of acute kidney injury patients. *Intensive Care Med Exp* 2015;**3**(Suppl. 1):A258
Schneider	2013	Not a primary study	Schneider AG, Bellomo R. Acute kidney injury: new studies. *Intensive Care Med* 2013;**39**:569–71
Schneider	2018	Not a primary study	Schneider AG, Mongardon N, Muller L. Biomarkers of renal injury, time for a grey-zone approach? *Anaesth Crit Care Pain Med* 2018;**37**:307–9
Schutz	2017	Not a relevant type of population	Schutz C, Boulware DR, Huppler-Hullsiek K, von Hohenberg M, Rhein J, Taseera K, *et al.* Acute kidney injury and urinary biomarkers in human immunodeficiency virus-associated cryptococcal meningitis. *Open Forum Infect Dis* 2017;**4**:ofx127
Seibert	2013	< 100 participants	Seibert FS, Pagonas N, Arndt R, Heller F, Dragun D, Persson P, *et al.* Calprotectin and neutrophil gelatinase-associated lipocalin in the differentiation of pre-renal and intrinsic acute kidney injury. *Acta Physiol* 2013;**207**:700–8
Seibert	2018	No focus on DTA for AKI	Seibert FS, Sitz M, Passfall J, Haesner M, Laschinski P, Buhl M, *et al.* Prognostic value of urinary calprotectin, NGAL and KIM-1 in chronic kidney disease. *Kidney Blood Press Res* 2018;**43**:1255–62
Se-Jun	2017	< 100 participants	Se-Jun P, Hoseok KOO, Kyoung-Jin LEE, Seo-Hyun KIM, Seo-Young YUN, Seunghyup KIM, *et al.* Usefulness of neutrophil gelatinase-associated lipocalin (NGAL) to confirm subclinical acute kidney injury and renal prognosis in patients following surgery. *Kosin Med J* 2017;**23**:212–20
Seker	2015	< 100 participants	Seker MM, Deveci K, Seker A, Sancakdar E, Yilmaz A, Turesin AK, *et al.* Predictive role of neutrophil gelatinase-associated lipocalin in early diagnosis of platin-induced renal injury. *Asian Pac J Cancer Prev* 2015;**16**:407–10
Self	2010	Not a primary study	Self WH, Barrett TW. Novel biomarkers: help or hindrance to patient care in the emergency department? *Ann Emerg Med* 2010;**56**:60–1
Sellmer	2017	No focus on DTA for AKI	Sellmer A, Bech BH, Bjerre JV, Schmidt MR, Hjortdal VE, Esberg G, *et al.* Urinary neutrophil gelatinase-associated lipocalin in the evaluation of patent ductus arteriosus and AKI in very preterm neonates: a cohort study. *BMC Pediatr* 2017;**17**:7
Sen	2015	< 100 participants	Sen S, Godwin ZR, Palmieri T, Greenhalgh D, Steele AN, Tran NK. Whole blood neutrophil gelatinase-associated lipocalin predicts acute kidney injury in burn patients. *J Surg Res* 2015;**196**:382–7
Şen	2015	Not a relevant type of population	Şen V, Ece A, Uluca Ü, Söker M, Güneş A, Kaplan İ, *et al.* Urinary early kidney injury molecules in children with beta-thalassemia major. *Ren Fail* 2015;**37**:607–13

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Seo	2014	< 100 participants	Seo WH, Nam SW, Lee EH, Je BK, Yim HE, Choi BM. A rapid plasma neutrophil gelatinase-associated lipocalin assay for diagnosis of acute pyelonephritis in infants with acute febrile urinary tract infections: a preliminary study. *Eur J Pediatr* 2014;**173**:229–32
Shahbazi	2015	Not a relevant type of population	Shahbazi F, Sadighi S, Dashti-Khavidaki S, Shahi F, Mirzania M, Abdollahi A, Ghahremani MH. Effect of silymarin administration on cisplatin nephrotoxicity: report from a pilot, randomized, double-blinded, placebo-controlled clinical trial. *Phytother Res* 2015;**29**:1046–53
Shahbazi	2015	Not a relevant type of population	Shahbazi F, Sadighi S, Dashti-Khavidaki S, Shahi F, Mirzania M. Urine ratio of neutrophil gelatinase-associated lipocalin to creatinine as a marker for early detection of cisplatin-associated nephrotoxicity. *Iran J Kidney Dis* 2015;**9**:305–10
Shaker	2010	< 100 participants	Shaker OG, El-Shehaby A, El-Khatib M. Early diagnostic markers for contrast nephropathy in patients undergoing coronary angiography. *Angiology* 2010;**61**:731–6
Shaker	2018	< 100 participants	Shaker AM, El Mohamed E, Samir HH, Elnokeety MM, Sayed HA, Ramzy TA. Fibroblast growth factor-23 as a predictor biomarker of acute kidney injury after cardiac surgery. *Saudi J Kidney Dis Transpl* 2018;**29**:531–9
Shao	2017	Not a relevant type of population	Shao Y, Fan Y, Xie Y, Yin L, Zhang Y, Deng L, *et al.* Effect of continuous renal replacement therapy on kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin in patients with septic acute kidney injury. *Exp Ther Med* 2017;**13**:3594–602
Shapiro	2010	Not a relevant biomarker assay or test	Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM, *et al.* The diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin in the prediction of acute kidney injury in emergency department patients with suspected sepsis. *Ann Emerg Med* 2010;**56**:52–9.e1
Sharma	2017	Not a relevant type of population	Sharma A, Demissei BG, Tromp J, Hillege HL, Cleland JG, O'Connor CM, *et al.* A network analysis to compare biomarker profiles in patients with and without diabetes mellitus in acute heart failure. *Eur J Heart Fail* 2017;**19**:1310–20
Shavit	2011	< 100 participants	Shavit L, Dolgoker I, Ivgi H, Assous M, Slotki I. Neutrophil gelatinase-associated lipocalin as a predictor of complications and mortality in patients undergoing non-cardiac major surgery. *Kidney Blood Press Res* 2011;**34**:116–24
Shavit	2013	Not a relevant type of population	Shavit L, Manilov R, Wiener-Well Y, Algur N, Slotki I. Urinary neutrophil gelatinase-associated lipocalin for early detection of acute kidney injury in geriatric patients with urinary tract infection treated by colistin. *Clin Nephrol* 2013;**80**:405–16
Shaw	2011	Cost-effectiveness – retained as background material	Shaw AD, Chalfin DB, Kleintjens J. The economic impact and cost-effectiveness of urinary neutrophil gelatinase-associated lipocalin after cardiac surgery. *Clin Ther* 2011;**33**:1713–25

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Shema-Didi	2016	Not a relevant type of population	Shema-Didi L, Kristal B, Eizenberg S, Marzuq N, Sussan M, Feldman-Idov Y, *et al.* Prevention of contrast-induced nephropathy with single bolus erythropoietin in patients with diabetic kidney disease: a randomized controlled trial. *Nephrology* 2016;**21**:295–300
Shen	2014	< 100 participants	Shen SJ, Hu ZX, Li QH, Wang SM, Song CJ, Wu DD, *et al.* Implications of the changes in serum neutrophil gelatinase-associated lipocalin and cystatin C in patients with chronic kidney disease. *Nephrology* 2014;**19**:129–35
Shin	2017	< 100 participants	Shin SY, Ha JY, Lee SL, Lee WM, Park JH. Increased urinary neutrophil gelatinase-associated lipocalin in very-low-birth-weight infants with oliguria and normal serum creatinine. *Pediatr Nephrol* 2017;**32**:1059–65
Shinke	2015	Not a relevant type of population	Shinke H, Masuda S, Togashi Y, Ikemi Y, Ozawa A, Sato T, *et al.* Urinary kidney injury molecule-1 and monocyte chemotactic protein-1 are noninvasive biomarkers of cisplatin-induced nephrotoxicity in lung cancer patients. *Cancer Chemother Pharmacol* 2015;**76**:989–96
Shirakabe	2015	Not a relevant biomarker assay or test	Shirakabe A, Hata N, Kobayashi N, Okazaki H, Shinada T, Tomita K, *et al.* Serum heart-type fatty acid-binding protein level can be used to detect acute kidney injury on admission and predict an adverse outcome in patients with acute heart failure. *Circ J* 2015;**79**:119–28
Shirakabe	2019	Not a relevant biomarker assay or test	Shirakabe A, Hata N, Kobayashi N, Okazaki H, Matsushita M, Shibata Y, *et al.* Worsening renal failure in patients with acute heart failure: the importance of cardiac biomarkers. *ESC Heart Fail* 2019;**6**:416–27
Shlipak	2012	Not a relevant type of population	Shlipak MG, Scherzer R, Abraham A, Tien PC, Grunfeld C, Peralta CA, *et al.* Urinary markers of kidney injury and kidney function decline in HIV-infected women. *J Acquir Immune Defic Syndr* 2012;**61**:565–73
Shoaib	2019	< 100 participants	Shoaib M, Mahmud SN, Safdar M. Early diagnosis of acute kidney injury by urinary neutrophil gelatinase associated lipocalin in adult critically ill patients. *J Ayub Med Coll Abbottabad* 2019;**31**:12–15
Shrestha	2011	No relevant outcome	Shrestha K, Borowski AG, Troughton RW, Thomas JD, Klein AL, Tang WH. Renal dysfunction is a stronger determinant of systemic neutrophil gelatinase-associated lipocalin levels than myocardial dysfunction in systolic heart failure. *J Card Fail* 2011;**17**:472–8
Shrestha	2012	< 100 participants	Shrestha K, Shao Z, Singh D, Dupont M, Tang WH. Relation of systemic and urinary neutrophil gelatinase-associated lipocalin levels to different aspects of impaired renal function in patients with acute decompensated heart failure. *Am J Cardiol* 2012;**110**:1329–35

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Shukla	2017	Not a relevant type of population	Shukla A, Rai MK, Prasad N, Agarwal V. Short-term non-steroid anti-inflammatory drug use in spondyloarthritis patients induces subclinical acute kidney injury: biomarkers study. *Nephron* 2017;**135**:277–86
Shulkina	2016	< 100 participants	Shulkina SG, Schekotov VV, Smirnova EN, Antipova AA. Vascular endothelial growth factor and lipocalin-2 as markers of early nephron damage in patients with hypertension and obesity. *Sovrem Tehnologii Med* 2016;**8**:148–51
Shum	2015	Not a relevant biomarker assay or test	Shum HP, Leung NY, Chang LL, Tam OY, Kwan AM, Chan KC, *et al.* Predictive value of plasma neutrophil gelatinase-associated lipocalin for acute kidney injury in intensive care unit patients after major non-cardiac surgery. *Nephrology* 2015;**20**:375–82
Shyam	2017	< 100 participants	Shyam R, Patel ML, Sachan R, Kumar S, Pushkar DK. Role of urinary neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury in patients with circulatory shock. *Indian J Crit Care Med* 2017;**21**:740–5
Nga	2015	Not a relevant biomarker assay or test	Nga HS, Medeiros P, Menezes P, Bridi R, Balbi A, Ponce D. Sepsis and AKI in clinical emergency room patients: the role of urinary NGAL. *Biomed Res Int* 2015;**2015**:413751
Nga	2015	Not a relevant biomarker assay or test	Nga HS, Medeiros P, Menezes P, Bridi R, Balbi A, Ponce D. Sepsis and AKI in clinical emergency room patients: the role of urinary NGAL. *Biomed Res Int* 2015;**2015**:413751
Siddappa	2019	< 100 participants	Siddappa PK, Kochhar R, Sarotra P, Medhi B, Jha V, Gupta V. Neutrophil gelatinase-associated lipocalin: an early biomarker for predicting acute kidney injury and severity in patients with acute pancreatitis. *JGH Open* 2019;**3**:105–10
Sidoti	2014	< 100 participants	Sidoti A, Giacalone M, Abramo A, Anselmino M, Donadio C, Salvo CD, *et al.* Early identification of acute kidney injury after bariatric surgery: role of NGAL and cystatin C. *Open Obes J* 2014;**6**:50–9
Siew	2009	Not a relevant biomarker assay or test	Siew ED, Ware LB, Gebretsadik T, Shintani A, Moons KG, Wickersham N, *et al.* Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. *J Am Soc Nephrol* 2009;**20**:1823–32
Siew	2010	Not a relevant biomarker assay or test	Siew ED, Ikizler TA, Gebretsadik T, Shintani A, Wickersham N, Bossert F, *et al.* Elevated urinary IL-18 levels at the time of ICU admission predict adverse clinical outcomes. *Clin J Am Soc Nephrol* 2010;**5**:1497–505
Siew	2013	Not a relevant biomarker assay or test	Siew ED, Ware LB, Bian A, Shintani A, Eden SK, Wickersham N, *et al.* Distinct injury markers for the early detection and prognosis of incident acute kidney injury in critically ill adults with preserved kidney function. *Kidney Int* 2013;**84**:786–94

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Silvetti	2014	< 100 participants	Silvetti S, Meroni R, Bignami E, Bove T, Landoni G, Zangrillo A, *et al.* Preoperative urinary neutrophil gelatinase-associated lipocalin and outcome in high-risk heart failure patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2014;**28**:323–7
Sim	2015	Not a relevant type of population	Sim JH, Yim HE, Choi BM, Lee JH, Yoo KH. Plasma neutrophil gelatinase-associated lipocalin predicts acute pyelonephritis in children with urinary tract infections. *Pediatr Res* 2015;**78**:48–55
Simonazzi	2015	< 100 participants	Simonazzi G, Capelli I, Curti A, Comai G, Rizzo N, La Manna G. Serum and urinary neutrophil gelatinase-associated lipocalin monitoring in normal pregnancy versus pregnancies complicated by pre-eclampsia. *In Vivo* 2015;**29**:117–21
Singal	2018	No focus on DTA for AKI	Singal AK, Jackson B, Pereira GB, Russ KB, Fitzmorris PS, Kakati D, *et al.* Biomarkers of renal injury in cirrhosis: association with acute kidney injury and recovery after liver transplantation. *Nephron* 2018;**138**:1–12
Singer	2016	Not a relevant type of population	Singer E, Schrezenmeier EV, Elger A, Seelow ER, Krannich A, Luft FC, Schmidt-Ott KM. Urinary NGAL-positive acute kidney injury and poor long-term outcomes in hospitalized patients. *Kidney Int Rep* 2016;**1**:114–24
Balbir Singh	2016	Not a relevant type of population	Balbir Singh G, Ann SH, Park J, Chung HC, Lee JS, Kim ES, *et al.* Remote Ischemic Preconditioning for the prevention of contrast-induced acute kidney injury in diabetics receiving elective percutaneous coronary intervention. *PLOS ONE* 2016;**11**:e0164256
Singh	2018	Not a relevant type of population	Singh A, Kamal R, Tiwari R, Gaur VK, Bihari V, Satyanarayana GNV, *et al.* Association between PAHs biomarkers and kidney injury biomarkers among kitchen workers with microalbuminuria: a cross-sectional pilot study. *Clin Chim Acta* 2018;**487**:349–56
Sinna	2019	< 100 participants	Sinna MM, Altaf FM, Mosa OF. Serum and urinary NGAL and cystatin C levels as diagnostic tools for for acute kidney injury and chronic kidney disease: a histobiochemical comparative study. *Curr Pharm Des* 2019;**25**:1122–33
Sirisopha	2016	< 100 participants	Sirisopha A, Vanavanan S, Chittamma A, Phakdeekitcharoen B, Thakkinstian A, Lertrit A, *et al.* Effects of therapy on urine neutrophil gelatinase-associated lipocalin in nondiabetic glomerular diseases with proteinuria. *Int J Nephrol* 2016;**2016**:4904502
Sirota	2013	< 100 participants	Sirota JC, Walcher A, Faubel S, Jani A, McFann K, Devarajan P, *et al.* Urine IL-18, NGAL, IL-8 and serum IL-8 are biomarkers of acute kidney injury following liver transplantation. *BMC Nephrol* 2013;**14**:17
Sise	2009	Not a primary study	Sise ME, Barasch J, Devarajan P, Nickolas TL. Elevated urine neutrophil gelatinase-associated lipocalin can diagnose acute kidney injury in patients with chronic kidney diseases. *Kidney Int* 2009;**75**:115–16

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Slack	2013	< 100 participants	Slack AJ, McPhail MJ, Ostermann M, Bruce M, Sherwood R, Musto R, *et al.* Predicting the development of acute kidney injury in liver cirrhosis – an analysis of glomerular filtration rate, proteinuria and kidney injury biomarkers. *Aliment Pharmacol Ther* 2013;**37**:989–97
Smertka	2014	< 100 participants	Smertka M, Wroblewska J, Suchojad A, Majcherczyk M, Jadamus-Niebroj D, Owsianka-Podlesny T, *et al.* Serum and urinary NGAL in septic newborns. *BioMed Res Int* 2014;**2014**:717318
Sokolski	2017	Not a relevant biomarker assay or test	Sokolski M, Zymliński R, Biegus J, Siwołowski P, Nawrocka-Millward S, Todd J, *et al.* Urinary levels of novel kidney biomarkers and risk of true worsening renal function and mortality in patients with acute heart failure. *Eur J Heart Fail* 2017;**19**:760–7
Solak	2015	Not a relevant biomarker assay or test	Solak Y, Yilmaz MI, Siriopol D, Saglam M, Unal HU, Yaman H, *et al.* Serum neutrophil gelatinase-associated lipocalin is associated with cardiovascular events in patients with chronic kidney disease. *Int Urol Nephrol* 2015;**47**:1993–2001
Song	2017	Meta-analysis – retained as background material	Song Z, Ma Z, Qu K, Liu S, Niu W, Lin T. Diagnostic prediction of urinary [TIMP-2] x [IGFBP7] for acute kidney injury: a meta-analysis exploring detection time and cutoff levels. *Oncotarget* 2017;**8**:100631–100639
Song	2017	Not a relevant type of population	Song Y, Sun S, Yu Y, Li G, Song J, Zhang H, Yan C. Diagnostic value of neutrophil gelatinase-associated lipocalin for renal injury in asphyxiated preterm infants. *Exp Ther Med* 2017;**13**:1245–8
Song	2019	No focus on DTA for AKI	Song Y, Kim DH, Kwon TD, Han DW, Baik SH, Jung HH, Kim JY. Effect of intraoperative dexmedetomidine on renal function after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a randomized, placebo-controlled trial. *Int J Hyperthermia* 2019;**36**:1–8
Soto	2013	Not a relevant biomarker assay or test	Soto K, Papoila AL, Coelho S, Bennett M, Ma Q, Rodrigues B, *et al.* Plasma NGAL for the diagnosis of AKI in patients admitted from the emergency department setting. *Clin J Am Soc Nephrol* 2013;**8**:2053–63
Soto	2016	Not a relevant biomarker assay or test	Soto K, Campos P, Pinto I, Rodrigues B, Frade F, Papoila AL, Devarajan P. The risk of chronic kidney disease and mortality are increased after community-acquired acute kidney injury. *Kidney Int* 2016;**90**:1090–9
Souza	2015	Not a relevant type of population	Souza DF, Reis SS, Botelho RV, Ferreira-Filho SR. Relative and absolute changes in urinary neutrophil gelatinase-associated lipocalin and correlation with small increases in serum creatinine levels after coronary angiography: an observational study. *Nephron* 2015;**129**:84–90
Soyler	2015	Not a relevant biomarker assay or test	Soyler C, Tanriover MD, Ascioglu S, Aksu NM, Arici M. Urine neutrophil gelatinase-associated lipocalin levels predict acute kidney injury in acute decompensated heart failure patients. *Ren Fail* 2015;**37**:772–6

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Spasojević-Dimitrijeva	2017	Not a relevant type of population	Spasojević-Dimitrijeva B, Kotur-Stevuljević J, Đukić M, Paripović D, Miloševski-Lomić G, Spasojević-Kalimanovska V, *et al.* Serum neutrophil gelatinase-associated lipocalin and urinary kidney injury molecule-1 as potential biomarkers of subclinical nephrotoxicity after gadolinium-based and iodinated-based contrast media exposure in pediatric patients with normal kidney function. *Med Sci Monit* 2017;**23**:4299–305
Sporek	2016	< 100 participants	Sporek M, Gala-Błądzińska A, Dumnicka P, Mazur-Laskowska M, Kielczewski S, Walocha J, *et al.* Urine NGAL is useful in the clinical evaluation of renal function in the early course of acute pancreatitis. *Folia Med Cracov* 2016;**56**:13–25
Sprenkle	2013	No focus on DTA for AKI	Sprenkle PC, Wren J, Maschino AC, Feifer A, Power N, Ghoneim T, *et al.* Urine neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after kidney surgery. *J Urol* 2013;**190**:159–64
Srisawat	2011	Not a relevant type of population	Srisawat N, Murugan R, Lee M, Kong L, Carter M, Angus DC, Kellum JA, Genetic and Inflammatory Markers of Sepsis (GenIMS) Study Investigators. Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. *Kidney Int* 2011;**80**:545–52
Srisawat	2015	Not a relevant type of population	Srisawat N, Praditpornsilpa K, Patarakul K, Techapornrung M, Daraswang T, Sukmark T, *et al.* Neutrophil gelatinase associated lipocalin (NGAL) in leptospirosis acute kidney injury: a multicenter study in Thailand. *PLOS ONE* 2015;**10**:e0143367
Srisawat	2018	< 100 participants	Srisawat N, Laoveeravat P, Limphunudom P, Lumlertgul N, Peerapornratana S, Tiranathanagul K, *et al.* The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: a feasibility study. *J Crit Care* 2018;**43**:36–41 [4627]
Srisawat	2018	< 100 participants	Srisawat N, Kongwibulwut M, Laoveeravat P, Lumplertgul N, Chatkaew P, Saeyub P, *et al.* The role of intraoperative parameters on predicting laparoscopic abdominal surgery associated acute kidney injury. *BMC Nephrol* 2018;**19**:289
Srisawat	2018	< 100 participants	Srisawat N, Laoveeravat P, Limphunudom P, Lumlertgul N, Peerapornratana S, Tiranathanagul K, *et al.* The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: a feasibility study. *J Crit Care* 2018;**43**:36–41
Srisawat	2018	Not a primary study	Srisawat N, Tangvoraphonkchai K, Lumlertgul N, Tungsanga K, Eiam-Ong S. Role of acute kidney injury biomarkers to guide renal replacement therapy initiation, what we learn from EARLY-RRT trial and FST trial? *J Thorac Dis* 2018;**10**:E835–E838

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Stads	2019	< 100 participants	Stads S, Kant KM, de Jong MFC, de Ruijter W, Cobbaert CM, Betjes MGH, *et al.* Predictors of short-term successful discontinuation of continuous renal replacement therapy: results from a prospective multicentre study. *BMC Nephrol* 2019;**20**:129
Sterling	2017	< 100 participants	Sterling M, Al-Ismaili Z, McMahon KR, Piccioni M, Pizzi M, Mottes T, *et al.* Urine biomarkers of acute kidney injury in noncritically ill, hospitalized children treated with chemotherapy. *Pediatr Blood Cancer* 2017;**64**:e26538
Stewart	2015	< 100 participants	Stewart IJ, Glass KR, Howard JT, Morrow BD, Sosnov JA, Siew ED, *et al.* The potential utility of urinary biomarkers for risk prediction in combat casualties: a prospective observational cohort study. *Crit Care* 2015;**19**:252
Strazzulla	2016	< 100 participants	Strazzulla A, Coppolino G, Di Fatta C, Giancotti F, D'Onofrio G, Postorino MC, *et al.* Is neutrophil gelatinase associated lipocalin useful in hepatitis C virus infection? *World J Hepatol* 2016;**8**:815–24
Stypmann	2015	No focus on DTA for AKI	Stypmann J, Fobker M, Rosing K, Engelen M, Gunia S, Dell'Aquila AM, Nofer JR. Neutrophil gelatinase-associated lipocalin (NGAL) in heart transplant recipients after conversion to everolimus therapy. *J Cardiol* 2015;**66**:347–52
Su	2017	Meta-analysis – retained as background material	Su Y, Gong Z, Wu Y, Tian Y, Liao X. Diagnostic value of urine tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 for acute kidney injury: a meta-analysis. *PLOS ONE* 2017;**12**:e0170214
Su	2018	Meta-analysis – retained as background material	Su LJ, Li YM, Kellum JA, Peng ZY. Predictive value of cell cycle arrest biomarkers for cardiac surgery-associated acute kidney injury: a meta-analysis. *Br J Anaesth* 2018;**121**:350–7
Suchojad	2015	< 100 participants	Suchojad A, Tarko A, Smertka M, Majcherczyk M, Brzozowska A, Wroblewska J, Maruniak-Chudek I. Factors limiting usefulness of serum and urinary NGAL as a marker of acute kidney injury in preterm newborns. *Ren Fail* 2015;**37**:439–45
Sueud	2019	< 100 participants	Sueud T, Hadi NR, Abdulameer R, Jamil DA, Al-Aubaidy HA. Assessing urinary levels of IL-18, NGAL and albumin creatinine ratio in patients with diabetic nephropathy. *Diabetes Metab Syndr* 2019;**13**:564–8
Sumida	2014	< 100 participants	Sumida M, Doi K, Kinoshita O, Kimura M, Ono M, Hamasaki Y, *et al.* Perioperative plasma neutrophil gelatinase-associated lipocalin measurement in patients who undergo left ventricular assist device implantation surgery. *Circ J* 2014;**78**:1891–9
Sun	2017	Not a relevant type of population	Sun IO, Shin SH, Cho AY, Yoon HJ, Chang MY, Lee KY. Clinical significance of NGAL and KIM-1 for acute kidney injury in patients with scrub typhus. *PLOS ONE* 2017;**12**:e0175890

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Surmiak	2015	< 100 participants	Surmiak P, Baumert M, Fiala M, Walencka Z, Więcek A. Umbilical neutrophil gelatinase-associated lipocalin level as an early predictor of acute kidney injury in neonates with hypoplastic left heart syndrome. *Biomed Res Int* 2015;**2015**:360209
Suzuki	2008	< 100 participants	Suzuki M, Wiers KM, Klein-Gitelman MS, Haines KA, Olson J, Onel KB, *et al.* Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis. *Pediatr Nephrol* 2008;**23**:403–12
Sweetman	2016	< 100 participants	Sweetman DU, Onwuneme C, Watson WR, O'Neill A, Murphy JF, Molloy EJ. Renal function and novel urinary biomarkers in infants with neonatal encephalopathy. *Acta Paediatr* 2016;**105**:e513–e519
Szeto	2010	< 100 participants	Szeto CC, Kwan BC, Lai KB, Lai FM, Chow KM, Wang G, *et al.* Urinary expression of kidney injury markers in renal transplant recipients. *Clin J Am Soc Nephrol* 2010;**5**:2329–37
Szewczyk	2009	< 100 participants	Szewczyk M, Wielkoszyński T, Zakliczyński M, Zembala M. Plasma neutrophil gelatinase-associated lipocalin (NGAL) correlations with cystatin C, serum creatinine, and glomerular filtration rate in patients after heart and lung transplantation. *Transplant Proc* 2009;**41**:3242–3
Taghizadeh-Ghehi	2015	< 100 participants	Taghizadeh-Ghehi M, Sarayani A, Ashouri A, Ataei S, Moslehi A, Hadjibabaie M. Urine neutrophil gelatinase associated lipocalin as an early marker of acute kidney injury in hematopoietic stem cell transplantation patients. *Ren Fail* 2015;**37**:994–8
Tai	2020	Meta-analysis – retained as background material	Tai Q, Yi H, Wei X, Xie W, Zeng O, Zheng D, *et al.* The accuracy of urinary TIMP-2 and IGFBP7 for the diagnosis of cardiac surgery-associated acute kidney injury: a systematic review and meta-analysis. *J Intensive Care Med* 2020;**35**:1013–25
Takahashi	2016	< 100 participants	Takahashi G, Shibata S, Fukui Y, Okamura Y, Inoue Y. Diagnostic accuracy of procalcitonin and presepsin for infectious disease in patients with acute kidney injury. *Diagn Microbiol Infect Dis* 2016;**86**:205–10
Tamimi	2018	< 100 participants	Tamimi A, Kord E, Rappaport YH, Cooper A, Abu Hamad R, Efrati S, *et al.* Salivary neutrophil gelatinase-associated lipocalin sampling feasibility in acute renal colic. *J Endourol* 2018;**32**:566–71
Tanigasalam	2016	Not a relevant biomarker assay or test	Tanigasalam V, Bhat BV, Adhisivam B, Sridhar MG, Harichandrakumar KT. Predicting severity of acute kidney injury in term neonates with perinatal asphyxia using urinary neutrophil gelatinase associated lipocalin. *Indian J Pediatr* 2016;**83**:1374–8
Tanzil	2016	< 100 participants	Tanzil WL, Wilar R, Mantik MFJ, Umboh A, Tatura SNN. Comparison of urine neutrophil gelatinase-associated lipocalin to serum creatinine to assess kidney function in neonatal asphyxia. *Paediatr Indones* 2016;**56**:356–9

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Tasanarong	2013	Not a relevant type of population	Tasanarong A, Hutayanon P, Piyayotai D. Urinary neutrophil gelatinase-associated lipocalin predicts the severity of contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. *BMC Nephrol* 2013;**14**:270
Tavakoli	2018	Not a primary study	Tavakoli R, Lebreton G. Biomarkers for early detection of cardiac surgery-associated acute kidney injury. *J Thorac Dis* 2018;**10**(Suppl. 33):S3914–18
Tawfik	2015	< 100 participants	Tawfik Y, Shaat RM, El-Bassiony SR, Hawas S, Effat N. Urinary and serum neutrophil gelatinase-associated lipocalin as a biomarker in Egyptian systemic lupus erythematosus patients: relation to lupus nephritis and disease activity. *Egypt Rheumatol* 2015;**37**:S25–S31
ter Maaten	2016	No focus on DTA for AKI	ter Maaten JM, Valente MAE, Metra M, Bruno N, O'Connor CM, Ponikowski P, *et al.* A combined clinical and biomarker approach to predict diuretic response in acute heart failure. *Clin Res Cardiol* 2016;**105**:145–53
Torres-Salido	2014	Not a relevant type of population	Torres-Salido MT, Cortés-Hernández J, Vidal X, Pedrosa A, Vilardell-Tarres M, Ordi-Ros J. Neutrophil gelatinase-associated lipocalin as a biomarker for lupus nephritis. *Nephrol Dial Transplant* 2014;**29**:1740–9
Testani	2013	Not a primary study	Testani JM, Tang WH. Biomarkers of acute kidney injury in chronic heart failure: what do the signals mean? *JACC Heart Fail* 2013;**1**:425–6
Tiranathanagul	2013	< 100 participants	Tiranathanagul K, Amornsuntorn S, Avihingsanon Y, Srisawat N, Susantitaphong P, Praditpornsilpa K, *et al.* Potential role of neutrophil gelatinase-associated lipocalin in identifying critically ill patients with acute kidney injury stage 2–3 who subsequently require renal replacement therapy. *Ther Apher Dial* 2013;**17**:332–8
Tkaczyk	2018	< 100 participants	Tkaczyk M, Tomczyk D, Jander A, Góreczny S, Moszura T, Dryżek P, *et al.* Glomerular filtration decrease after diagnostic cardiac catheterisation in children with congenital cardiac malformation – the role of serum creatinine, cystatin C, neutrophil gelatinase and urine output monitoring. *Postepy Kardiol Interwencyjnej* 2018;**14**:67–74
Tomczyk	2016	< 100 participants	Tomczyk D, Jander A, Chrul S, Moszura T, Dryzek P, Krajewski W, *et al.* Contrast-induced acute kidney injury in children with cardiovascular defects – results of a pilot study. *Pediatria i Med Rodz* 2016;**12**:436–44
Tong	2015	Meta-analysis – retained as background material	Tong J, Li H, Zhang H, Luo Z, Huang Y, Huang J, *et al.* Neutrophil gelatinase-associated lipocalin in the prediction of contrast-induced nephropathy: a systemic review and meta-analysis. *J Cardiovasc Pharmacol* 2015;**66**:239–45
Toprak	2017	Not a relevant type of population	Toprak Z, Cebeci E, Helvaci SA, Toprak ID, Kutlu Y, Sakin A, Tukek T. Cisplatin nephrotoxicity is not detected by urinary cell-cycle arrest biomarkers in lung cancer patients. *Int Urol Nephrol* 2017;**49**:1041–7

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Torregrosa	2012	Not a relevant biomarker assay or test	Torregrosa I, Montoliu C, Urios A, Elmlili N, Juan I, Puchades MJ, *et al.* Early biomarkers of acute kidney failure after heart angiography or heart surgery in patients with acute coronary syndrome or acute heart failure. *Nefrologia* 2012;**32**:44–52
Torregrosa	2015	Not a relevant type of population	Torregrosa I, Montoliu C, Urios A, Andrés-Costa MJ, Giménez-Garzó C, Juan I, *et al.* Urinary KIM-1, NGAL and L-FABP for the diagnosis of AKI in patients with acute coronary syndrome or heart failure undergoing coronary angiography. *Heart Vessels* 2015;**30**:703–11
Trachtman	2006	< 100 participants	Trachtman H, Christen E, Cnaan A, Patrick J, Mai V, Mishra J, *et al.* Urinary neutrophil gelatinase-associated lipocalcin in D+HUS: a novel marker of renal injury. *Pediatr Nephrol* 2006;**21**:989–94 [4024]
Tsuchimoto	2014	< 100 participants	Tsuchimoto A, Shinke H, Uesugi M, Kikuchi M, Hashimoto E, Sato T, *et al.* Urinary neutrophil gelatinase-associated lipocalin: a useful biomarker for tacrolimus-induced acute kidney injury in liver transplant patients. *PLOS ONE* 2014;**9**:e110527
Tugba Kos	2013	< 100 participants	Tugba Kos F, Sendur MAN, Aksoy S, Celik HT, Sezer S, Civelek B, *et al.* Evaluation of renal function using the level of neutrophil gelatinase-associated lipocalin is not predictive of nephrotoxicity associated with cisplatin-based chemotherapy. *Asian Pac J Cancer Prev* 2013;**14**:1111–14
Tuladhar	2009	< 100 participants	Tuladhar SM, Püntmann VO, Soni M, Punjabi PP, Bogle RG. Rapid detection of acute kidney injury by plasma and urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass. *J Cardiovasc Pharmacol* 2009;**53**:261–6
Tuladhar	2009	< 100 participants	Tuladhar SM, Püntmann VO, Soni M, Punjabi PP, Bogle RG. Rapid detection of acute kidney injury by plasma and urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass. *J Cardiovasc Pharmacol* 2009;**53**:261–6
Tung	2015	Not a relevant type of population	Tung YC, Chang CH, Chen YC, Chu PH. Combined biomarker analysis for risk of acute kidney injury in patients with ST-segment elevation myocardial infarction. *PLOS ONE* 2015;**10**:e0125282
Tyagi	2018	< 100 participants	Tyagi A, Luthra A, Kumar M, Das S. Epidemiology of acute kidney injury and the role of urinary [TIMP-2]·[IGFBP7]: a prospective cohort study in critically ill obstetric patients. *Int J Obstet Anesth* 2018;**36**:77–84
Tyagi	2018	< 100 participants	Tyagi A, Lahan S, Verma G, Das S, Kumar M. Role of intra-abdominal pressure in early acute kidney injury: a prospective cohort study in critically ill obstetric patients. *Indian J Crit Care Med* 2018;**22**:602–7
Tziakas	2015	Not a relevant biomarker assay or test	Tziakas D, Chalikias G, Kareli D, Tsigalou C, Risgits A, Kikas P, *et al.* Spot urine albumin to creatinine ratio outperforms novel acute kidney injury biomarkers in patients with acute myocardial infarction. *Int J Cardiol* 2015;**197**:48–55

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Uehara	2009	Not a relevant type of population	Uehara Y, Makino H, Seiki K, Urade Y, L-PGDS Clinical Research Group of Kidney. Urinary excretions of lipocalin-type prostaglandin D synthase predict renal injury in type-2 diabetes: a cross-sectional and prospective multicentre study. *Nephrol Dial Transplant* 2009;**24**:475–82
Ueta	2014	< 100 participants	Ueta K, Watanabe M, Iguchi N, Uchiyama A, Shirakawa Y, Kuratani T, *et al.* Early prediction of acute kidney injury biomarkers after endovascular stent graft repair of aortic aneurysm: a prospective observational study. *J Intensive Care* 2014;**2**:45
Uettwiller-Geiger	2016	< 100 participants	Uettwiller-Geiger DL, Vijayendran R, Kellum JA, Fitzgerald RL. Analytical characteristics of a biomarker-based risk assessment test for acute kidney injury (AKI). *Clin Chim Acta* 2016;**455**:93–8
Urbschat	2014	No focus on DTA for AKI	Urbschat A, Gauer S, Paulus P, Reissig M, Weipert C, Ramos-Lopez E, *et al.* Serum and urinary NGAL but not KIM-1 raises in human postrenal AKI. *Eur J Clin Invest* 2014;**44**:652–9
Vaidya	2008	Not a relevant type of population	Vaidya VS, Waikar SS, Ferguson MA, Collings FB, Sunderland K, Gioules C, *et al.* Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. *Clin Transl Sci* 2008;**1**:200–8
Valero	2016	Not a relevant type of population	Valero E, Rodríguez JC, Moyano P, Miñana G, Sanchis J, Núñez J. Role of neutrophil gelatinase-associated lipocalin in the detection of contrast-induced nephropathy in patients undergoing a coronary angiography. *Rev Esp Cardiol* 2016;**69**:524–5
Valette	2013	< 100 participants	Valette X, Savary B, Nowoczyn M, Daubin C, Pottier V, Terzi N, *et al.* Accuracy of plasma neutrophil gelatinase-associated lipocalin in the early diagnosis of contrast-induced acute kidney injury in critical illness. *Intensive Care Med* 2013;**39**:857–65
Van Biesen	2012	Not a primary study	Van Biesen W, Van Massenhove J, Lameire N, Vanholder R. Does urinary neutrophil gelatinase-associated lipocalin really solve the issue of discriminating prerenal from intrinsic acute kidney injury? *Kidney Int* 2012;**81**:321
van Deursen	2014	No focus on DTA for AKI	van Deursen VM, Damman K, Voors AA, van der Wal MH, Jaarsma T, van Veldhuisen DJ, Hillege HL. Prognostic value of plasma neutrophil gelatinase-associated lipocalin for mortality in patients with heart failure. *Circ Heart Fail* 2014;**7**:35–42
van Wolfswinkel	2016	< 100 participants	van Wolfswinkel ME, Koopmans LC, Hesselink DA, Hoorn EJ, Koelewijn R, van Hellemond JJ, van Genderen PJ. Neutrophil gelatinase-associated lipocalin (NGAL) predicts the occurrence of malaria-induced acute kidney injury. *Malar J* 2016;**15**:464
Vandenberghe	2017	Review – retained as background material	Vandenberghe W, De Loor J, Hoste EA. Diagnosis of cardiac surgery-associated acute kidney injury from functional to damage biomarkers. *Curr Opin Anaesthesiol* 2017;**30**:66–75

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Vanmassenhove	2013	No relevant outcome	Vanmassenhove J, Glorieux G, Hoste E, Dhondt A, Vanholder R, Van Biesen W. Urinary output and fractional excretion of sodium and urea as indicators of transient versus intrinsic acute kidney injury during early sepsis. *Crit Care* 2013;**17**:R234
Vanmassenhove	2014	No focus on DTA for AKI	Vanmassenhove J, Glorieux G, Hoste E, Dhondt A, Vanholder R, Van Biesen W. AKI in early sepsis is a continuum from transient AKI without tubular damage over transient AKI with minor tubular damage to intrinsic AKI with severe tubular damage. *Int Urol Nephrol* 2014;**46**:2003–8
Vanmassenhove	2015	No focus on DTA for AKI	Vanmassenhove J, Glorieux G, Lameire N, Hoste E, Dhondt A, Vanholder R, Van Biesen W. Influence of severity of illness on neutrophil gelatinase-associated lipocalin performance as a marker of acute kidney injury: a prospective cohort study of patients with sepsis. *BMC Nephrol* 2015;**16**:18
Varela	2015	< 100 participants	Varela CF, Greloni G, Schreck C, Bratti G, Medina A, Marenchino R, *et al.* Assessment of fractional excretion of urea for early diagnosis of cardiac surgery associated acute kidney injury. *Ren Fail* 2015;**37**:327–31
Varnell	2017	Not a primary study	Varnell CD, Goldstein SL, Devarajan P, Basu RK. Impact of near real-time urine neutrophil gelatinase-associated lipocalin assessment on clinical practice. *Kidney Int Rep* 2017;**2**:1243–9
Verbrugge	2013	< 100 participants	Verbrugge FH, Dupont M, Shao Z, Shrestha K, Singh D, Finucan M, *et al.* Novel urinary biomarkers in detecting acute kidney injury, persistent renal impairment, and all-cause mortality following decongestive therapy in acute decompensated heart failure. *J Card Fail* 2013;**19**:621–8
Vermi	2014	< 100 participants	Vermi AC, Costopoulos C, Latib A, Piraino D, Maisano F, Naim C, *et al.* Urinary neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury after transcatheter aortic valve implantation. *Hellenic J Cardiol* 2014;**55**:77–9
Vesnina	2016	< 100 participants	Vesnina ZV, Lishmanov YB, Alexandrova EA, Nesterov EA. Evaluation of nephroprotective efficacy of hypoxic preconditioning in patients undergoing coronary artery bypass surgery. *Cardiorenal Med* 2016;**6**:328–36
Virzì	2015	< 100 participants	Virzì GM, de Cal M, Day S, Brocca A, Cruz DN, Castellani C, *et al.* Pro-apoptotic effects of plasma from patients with cardiorenal syndrome on human tubular cells. *Am J Nephrol* 2015;**41**:474–84
Virzì	2018	< 100 participants	Virzì GM, Breglia A, Brocca A, de Cal M, Bolin C, Vescovo G, Ronco C. Levels of proinflammatory cytokines, oxidative stress, and tissue damage markers in patients with acute heart failure with and without cardiorenal syndrome type 1. *Cardiorenal Med* 2018;**8**:321–31
Vives	2012	Not a primary study	Vives M, Lockwood G, Punjabi PP, Krahne D. Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. *Anesthesiology* 2012;**116**:490–1

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Volovelsky	2018	< 100 participants	Volovelsky O, Gist KM, Terrell TC, Bennett MR, Cooper DS, Alten JA, Goldstein SL. Early postoperative measurement of fibroblast growth factor 23 predicts severe acute kidney injury in infants after cardiac surgery. *Clin Nephrol* 2018;**90**:165–71
von Jeinsen	2017	No relevant outcome	von Jeinsen B, Kraus D, Palapies L, Tzikas S, Zeller T, Schauer A, *et al.* Urinary neutrophil gelatinase-associated lipocalin and cystatin C compared to the estimated glomerular filtration rate to predict risk in patients with suspected acute myocardial infarction. *Int J Cardiol* 2017;**245**:6–12
Wagener	2008	Not a relevant biomarker assay or test	Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT. Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. *Am J Kidney Dis* 2008;**52**:425–33
Wagener	2008	Not a primary study	Wagener G, Lee HT. Aprotinin and urinary neutrophil gelatinase-associated lipocalin after cardiac surgery. *Anesth Analg* 2008;**106**:1593
Wagener	2011	< 100 participants	Wagener G, Minhaz M, Mattis FA, Kim M, Emond JC, Lee HT. Urinary neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after orthotopic liver transplantation. *Nephrol Dial Transplant* 2011;**26**:1717–23
Wagener	2006	< 100 participants	Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, Lee HT. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. *Anesthesiology* 2006;**105**:485–91
Wai	2013	< 100 participants	Wai K, Soler-García AA, Perazzo S, Mattison P, Ray PE. A pilot study of urinary fibroblast growth factor-2 and epithelial growth factor as potential biomarkers of acute kidney injury in critically ill children. *Pediatr Nephrol* 2013;**28**:2189–98
Waldherr	2019	< 100 participants	Waldherr S, Fichtner A, Beedgen B, Bruckner T, Schaefer F, Tönshoff B, *et al.* Urinary acute kidney injury biomarkers in very low-birth-weight infants on indomethacin for patent ductus arteriosus. *Pediatr Res* 2019;**85**:678–86
Wang	2014	Not a relevant biomarker assay or test	Wang M, Zhang Q, Zhao X, Dong G, Li C. Diagnostic and prognostic value of neutrophil gelatinase-associated lipocalin, matrix metalloproteinase-9, and tissue inhibitor of matrix metalloproteinases-1 for sepsis in the emergency department: an observational study. *Crit Care* 2014;**18**:634
Wang	2015	Not a relevant biomarker assay or test	Wang B, Chen G, Zhang J, Xue J, Cao Y, Wu Y. Increased neutrophil gelatinase-associated lipocalin is associated with mortality and multiple organ dysfunction syndrome in severe sepsis and septic shock. *Shock* 2015;**44**:234–8
Wang	2016	< 100 participants	Wang W, Saad A, Herrmann SM, Eirin Massat A, McKusick MA, Misra S, *et al.* Changes in inflammatory biomarkers after renal revascularization in atherosclerotic renal artery stenosis. *Nephrol Dial Transplant* 2016;**31**:1437–43

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Wang	2016	No focus on DTA for AKI	Wang Z, Ma S, Zappitelli M, Parikh C, Wang CY, Devarajan P. Penalized count data regression with application to hospital stay after pediatric cardiac surgery. *Stat Methods Med Res* 2016;**25**:2685–703
Wang	2017	Not a relevant biomarker assay or test	Wang C, Zhang J, Han J, Yang Q, Liu J, Liang B. The level of urinary IL-18 in acute kidney injury after cardiopulmonary bypass. *Exp Ther Med* 2017;**14**:6047–51
Wang	2017	< 100 participants	Wang Y, Zou Z, Jin J, Teng J, Xu J, Shen B, *et al.* Urinary TIMP-2 and IGFBP7 for the prediction of acute kidney injury following cardiac surgery. *BMC Nephrol* 2017;**18**:177
Wang	2017	Not a relevant type of population	Wang HJ, Wang P, Li N, Wan C, Jiang CM, He JS, *et al.* Effects of continuous renal replacement therapy on serum cytokines, neutrophil gelatinase-associated lipocalin, and prognosis in patients with severe acute kidney injury after cardiac surgery. *Oncotarget* 2017;**8**:10628–36
Wang	2018	Not a relevant biomarker assay or test	Wang JJ, Chi NH, Huang TM, Connolly R, Chen LW, Chueh SJ, *et al.* Urinary biomarkers predict advanced acute kidney injury after cardiovascular surgery. *Crit Care* 2018;**22**:108
Washino	2019	< 100 participants	Washino S, Hosohata K, Oshima M, Okochi T, Konishi T, Nakamura Y, *et al.* A novel biomarker for acute kidney injury, vanin-1, for obstructive nephropathy: a prospective cohort pilot study. *Int J Mol Sci* 2019;**20**:899
Wasilewska	2010	< 100 participants	Wasilewska A, Zoch-Zwierz W, Taranta-Janusz K, Michaluk-Skutnik J. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of cyclosporine nephrotoxicity? *Pediatr Nephrol* 2010;**25**:889–97
Watanabe	2014	< 100 participants	Watanabe M, Silva GF, Fonseca CD, Vattimo Mde F. Urinary NGAL in patients with and without acute kidney injury in a cardiology intensive care unit. *Rev Bras Ter Intensiva* 2014;**26**:347–54
Weber	2011	Not a relevant type of population	Weber CL, Bennett M, Er L, Bennett MT, Levin A. Urinary NGAL levels before and after coronary angiography: a complex story. *Nephrol Dial Transplant* 2011;**26**:3207–11
Wen	2017	Non-English-language publication	Wen Y, Li Z, Chang C, Zhang P, Lyu Y. [Diagnostic significance of urinary neutrophil gelatin enzyme-related lipid delivery protein and kidney injury molecule-1 in acute kidney injury after cardiac operation with cardiopulmonary bypass operation in children.] *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2017;**29**:1112–16
Westhoff	2015	< 100 participants	Westhoff JH, Tönshoff B, Waldherr S, Pöschl J, Teufel U, Westhoff TH, Fichtner A. Urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) • insulin-like growth factor-binding protein 7 (IGFBP7) predicts adverse outcome in pediatric acute kidney injury. *PLOS ONE* 2015;**10**:e0143628

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Westhoff	2016	< 100 participants	Westhoff JH, Fichtner A, Waldherr S, Pagonas N, Seibert FS, Babel N, *et al.* Urinary biomarkers for the differentiation of prerenal and intrinsic pediatric acute kidney injury. *Pediatr Nephrol* 2016;**31**:2353–63
Westhoff	2017	< 100 participants	Westhoff JH, Seibert FS, Waldherr S, Bauer F, Tönshoff B, Fichtner A, Westhoff TH. Urinary calprotectin, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin for the prediction of adverse outcome in pediatric acute kidney injury. *Eur J Pediatr* 2017;**176**:745–55
Wetz	2015	< 100 participants	Wetz AJ, Richardt EM, Wand S, Kunze N, Schotola H, Quintel M, *et al.* Quantification of urinary TIMP-2 and IGFBP-7: an adequate diagnostic test to predict acute kidney injury after cardiac surgery? *Crit Care* 2015;**19**:3
Wheeler	2008	Not a relevant biomarker assay or test	Wheeler DS, Devarajan P, Ma Q, Harmon K, Monaco M, Cvijanovich N, Wong HR. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. *Crit Care Med* 2008;**36**:1297–303
Wijerathna	2018	< 100 participants	Wijerathna TM, Mohamed F, Dissanayaka D, Gawarammana I, Palangasinghe C, Shihana F, *et al.* Albuminuria and other renal damage biomarkers detect acute kidney injury soon after acute ingestion of oxalic acid and potassium permanganate. *Toxicol Lett* 2018;**299**:182–90
Wijerathna	2019	Not a relevant type of population	Wijerathna TM, Gawarammana IB, Mohamed F, Dissanayaka DM, Dargan PI, Chathuranga U, *et al.* Epidemiology, toxicokinetics and biomarkers after self-poisoning with *Gloriosa superba*. *Clin Toxicol (Phila)* 2019;**57**:1080–6
Woitas	2017	Not a relevant type of population	Woitas RP, Scharnagl H, Kleber ME, Delgado GE, Grammer TB, Pichler M, *et al.* Neutrophil gelatinase-associated lipocalin levels are U-shaped in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study-Impact for mortality. *PLOS ONE* 2017;**12**:e0171574
Wong	2014	Not a primary study	Wong F, Murray P. Kidney damage biomarkers: Novel tools for the diagnostic assessment of acute kidney injury in cirrhosis. *Hepatology* 2014;**60**:455–7
Woo	2012	Not a relevant type of population	Woo KS, Choi JL, Kim BR, Kim JE, An WS, Han JY. Urinary neutrophil gelatinase-associated lipocalin levels in comparison with glomerular filtration rate for evaluation of renal function in patients with diabetic chronic kidney disease. *Diabetes Metab J* 2012;**36**:307–13
Wu	2010	< 100 participants	Wu Y, Su T, Yang L, Zhu SN, Li XM. Urinary neutrophil gelatinase-associated lipocalin: a potential biomarker for predicting rapid progression of drug-induced chronic tubulointerstitial nephritis. *Am J Med Sci* 2010;**339**:537–42
Wu	2013	Not a relevant type of population	Wu J, Ding Y, Zhu C, Shao X, Xie X, Lu K, Wang R. Urinary TNF-alpha and NGAL are correlated with the progression of nephropathy in patients with type 2 diabetes. *Exp Ther Med* 2013;**6**:1482–8

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Wu	2018	Not a relevant type of population	Wu VC, Shiao CC, Chi NH, Wang CH, Chueh SCJ, Liou HH, *et al.* Outcome prediction of acute kidney injury biomarkers at initiation of dialysis in critical units. *J Clin Med* 2018;**7**:202
Xiao	2013	< 100 participants	Xiao J, Niu J, Ye X, Yu Q, Gu Y. Combined biomarkers evaluation for diagnosing kidney injury in preeclampsia. *Hypertens Pregnancy* 2013;**32**:439–49
Xiao	2015	< 100 participants	Xiao N, Devarajan P, Inge TH, Jenkins TM, Bennett M, Mitsnefes MM. Subclinical kidney injury before and 1 year after bariatric surgery among adolescents with severe obesity. *Obesity* 2015;**23**:1234–8
Xiao	2019	Not a relevant biomarker assay or test	Xiao W, Chen W, Hu H, Huang X, Luo Y. The clinical significance of neutrophil gelatinase-associated lipocalin in ischemic stroke patients with acute kidney injury. *J Clin Lab Anal* 2019;**33**:e22907
Xie	2014	< 100 participants	Xie Y, Xu W, Wang Q, Shao X, Ni Z, Mou S. Urinary excretion of liver-type FABP as a new clinical marker for the progression of obstructive nephropathy. *Biomark Med* 2014;**8**:543–56
Ximenes	2015	< 100 participants	Ximenes RO, Farias AQ, Helou CM. Early predictors of acute kidney injury in patients with cirrhosis and bacterial infection: urinary neutrophil gelatinase-associated lipocalin and cardiac output as reliable tools. *Kidney Res Clin Pract* 2015;**34**:140–5
Xin	2013	< 100 participants	Xin C, Yulong X, Yu C, Changchun C, Feng Z, Xinwei M. Urine neutrophil gelatinase-associated lipocalin and interleukin-18 predict acute kidney injury after cardiac surgery. *Renal Fail* 2013;**30**:904–13
Xue	2014	< 100 participants	Xue W, Xie Y, Wang Q, Xu W, Mou S, Ni Z. Diagnostic performance of urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin for acute kidney injury in an obstructive nephropathy patient. *Nephrology* 2014;**19**:186–94
Yamanouchi	2018	< 100 participants	Yamanouchi S, Kimata T, Kino J, Kitao T, Suruda C, Tsuji S, *et al.* Urinary C-megalin for screening of renal scarring in children after febrile urinary tract infection. *Pediatr Res* 2018;**83**:662–8
Yamashita	2014	< 100 participants	Yamashita T, Doi K, Hamasaki Y, Matsubara T, Ishii T, Yahagi N, *et al.* Evaluation of urinary tissue inhibitor of metalloproteinase-2 in acute kidney injury: a prospective observational study. *Crit Care* 2014;**18**:716
Yamashita	2016	< 100 participants	Yamashita T, Noiri E, Hamasaki Y, Matsubara T, Ishii T, Yahagi N, *et al.* Erythropoietin concentration in acute kidney injury is associated with insulin-like growth factor-binding protein-1. *Nephrology* 2016;**21**:693–9
Yang	2009	Not a relevant type of population	Yang YH, He XJ, Chen SR, Wang L, Li EM, Xu LY. Changes of serum and urine neutrophil gelatinase-associated lipocalin in type-2 diabetic patients with nephropathy: one year observational follow-up study. *Endocrine* 2009;**36**:45–51

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Yang	2012	< 100 participants	Yang CC, Hsieh SC, Li KJ, Wu CH, Lu MC, Tsai CY, Yu CL. Urinary neutrophil gelatinase-associated lipocalin is a potential biomarker for renal damage in patients with systemic lupus erythematosus. *J Biomed Biotechnol* 2012;**2012**:759313
Yang	2014	< 100 participants	Yang HT, Yim H, Cho YS, Kym D, Hur J, Kim JH, *et al.* Assessment of biochemical markers in the early post-burn period for predicting acute kidney injury and mortality in patients with major burn injury: comparison of serum creatinine, serum cystatin-C, plasma and urine neutrophil gelatinase-associated lipocalin. *Crit Care* 2014;**18**:R151
Yang	2015	Not a relevant biomarker assay or test	Yang X, Chen C, Tian J, Zha Y, Xiong Y, Sun Z, *et al.* Urinary angiotensinogen level predicts AKI in acute decompensated heart failure: a prospective, two-stage study. *J Am Soc Nephrol* 2015;**26**:2032–41
Yang	2016	Not a relevant biomarker assay or test	Yang CH, Chang CH, Chen TH, Fan PC, Chang SW, Chen CC, *et al.* Combination of urinary biomarkers improves early detection of acute kidney injury in patients with heart failure. *Circ J* 2016;**80**:1017–23
Yang	2017	< 100 participants	Yang J, Lim SY, Kim MG, Jung CW, Cho WY, Jo SK. Urinary tissue inhibitor of metalloproteinase and insulin-like growth factor-7 as early biomarkers of delayed graft function after kidney transplantation. *Transplant Proc* 2017;**49**:2050–4
Yap	2017	< 100 participants	Yap DY, Seto WK, Fung J, Chok SH, Chan SC, Chan GC, *et al.* Serum and urinary biomarkers that predict hepatorenal syndrome in patients with advanced cirrhosis. *Dig Liver Dis* 2017;**49**:202–6
Yavas	2013	< 100 participants	Yavas H, Sahin OZ, Ersoy R, Taşlı F, Gibyeli Genek D, Uzum A, Cirit M. Prognostic value of NGAL staining in patients with IgA nephropathy. *Ren Fail* 2013;**35**:472–6
Yavuz	2014	< 100 participants	Yavuz S, Anarat A, Acartürk S, Dalay AC, Kesiktaş E, Yavuz M, Acartürk TO. Neutrophil gelatinase associated lipocalin as an indicator of acute kidney injury and inflammation in burned children. *Burns* 2014;**40**:648–54
Ye	2018	Not a relevant type of population	Ye HH, Shen G, Luo Q, Zhou FF, Xie XL, Wang CY, Han LN. Early diagnosis of acute kidney injury in aged patients undergoing percutaneous coronary intervention. *J Zhejiang Univ Sci B* 2018;**19**:342–8
Yegenaga	2018	Not a relevant biomarker assay or test	Yegenaga I, Kamis F, Baydemir C, Erdem E, Celebi K, Eren N, Baykara N. Neutrophil gelatinase-associated lipocalin is a better biomarker than cystatin C for the prediction of imminent acute kidney injury in critically ill patients. *Ann Clin Biochem* 2018;**55**:190–7
Yeh	2013	< 100 participants	Yeh YH, Chang JL, Hsiao PC, Tsao SM, Lin CH, Kao SJ, *et al.* Circulating level of lipocalin 2 as a predictor of severity in patients with community-acquired pneumonia. *J Clin Lab Anal* 2013;**27**:253–60
Yeung	2018	Systematic review – retained as background material	Yeung ACY, Morozov A, Robertson FP, Fuller BJ, Davidson BR. Neutrophil Gelatinase-Associated Lipocalin (NGAL) in predicting acute kidney injury following orthotopic liver transplantation: a systematic review. *Int J Surg* 2018;**59**:48–54

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Yilmaz	2009	< 100 participants	Yilmaz A, Sevketoglu E, Gedikbasi A, Karyagar S, Kiyak A, Mulazimoglu M, *et al.* Early prediction of urinary tract infection with urinary neutrophil gelatinase associated lipocalin. *Pediatr Nephrol* 2009;**24**:2387–92
Ylinen	2014	< 100 participants	Ylinen E, Jahnukainen K, Saarinen-Pihkala UM, Jahnukainen T. Assessment of renal function during high-dose methotrexate treatment in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2014;**61**:2199–202
Yndestad	2009	Not a relevant biomarker assay or test	Yndestad A, Landrø L, Ueland T, Dahl CP, Flo TH, Vinge LE, *et al.* Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. *Eur Heart J* 2009;**30**:1229–36
Yoon	2018	< 100 participants	Yoon KC, Lee KW, Oh SC, Kim H, Kim HS, Hong SK, *et al.* Urinary neutrophil gelatinase-associated lipocalin as a biomarker for renal injury in liver transplant recipients using calcineurin inhibitors. *Transplant Proc* 2018;**50**:3667–72
Young-Min	2014	< 100 participants	Young-Min J, Cheul-Min HA, Ki-Cheul NOH, Chang-Hae PYO. The usefulness of plasma neutrophil gelatinase-associated lipocalin in acute pyelonephritis. *J Korean Soc Emerg Med* 2014;**25**:137–144
Youssef	2012	< 100 participants	Youssef DM, El-Shal AS. Urinary neutrophil gelatinase-associated lipocalin and kidney injury in children with focal segmental glomerulosclerosis. *Iran J Kidney Dis* 2012;**6**:355–60
Youssef	2013	< 100 participants	Youssef DM, Esh AM, Helmy Hassan E, Ahmed TM. Serum NGAL in critically ill children in ICU from a single center in Egypt. *ISRN Nephrol* 2013;**2013**:140905
Yuan	2014	Non-English-language publication	Yuan F, Liu H, Wang WX, Dai JJ, Dai LY, Yang XX, Fang WY. Study on early diagnosis of acute decompensated heart failure combined with acute renal injury. *J Shanghai Jiaotong Univ* 2014;**34**:1771–4
Zaleska-Kociecka	2017	< 100 participants	Zaleska-Kociecka M, Skrobisz A, Wojtkowska I, Grabowski M, Dabrowski M, Kusmierski K, *et al.* Serum beta-2 microglobulin levels for predicting acute kidney injury complicating aortic valve replacement. *Interact Cardiovasc Thorac Surg* 2017;**25**:533–40
Zaouter	2018	< 100 participants	Zaouter C, Priem F, Leroux L, Bonnet G, Bats ML, Beauvieux MC, *et al.* New markers for early detection of acute kidney injury after transcatheter aortic valve implantation. *Anaesth Crit Care Pain Med* 2018;**37**:319–26
Zaouter	2018	< 100 participants	Zaouter C, Potvin J, Bats ML, Beauvieux MC, Remy A, Ouattara A. A combined approach for the early recognition of acute kidney injury after adult cardiac surgery. *Anaesth Crit Care Pain Med* 2018;**37**:335–41

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TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Zappitelli	2007	Not a relevant biomarker assay or test	Zappitelli M, Washburn KK, Arikan AA, Loftis L, Ma Q, Devarajan P, Parikh CR, Goldstein SL. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Crit Care* 2007;**11**:R84
Zappitelli	2007	Duplicate of a study that had already been assessed	Zappitelli M, Washburn KK, Arikan AA, Loftis L, Ma Q, Devarajan P, *et al.* Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Crit Care* 2007;**11**:R84
Zappitelli	2012	No focus on DTA for AKI	Zappitelli M, Coca SG, Garg AX, Krawczeski CD, Thiessen Heather P, Sint K, *et al.* The association of albumin/creatinine ratio with postoperative AKI in children undergoing cardiac surgery. *Clin J Am Soc Nephrol* 2012;**7**:1761–9
Zarbock	2015	No focus on DTA for AKI	Zarbock A, Schmidt C, Van Aken H, Wempe C, Martens S, Zahn PK, *et al.* Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. *JAMA* 2015;**313**:2133–41
Zarbock	2016	Not a relevant type of population	Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, *et al.* Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA* 2016;**315**:2190–9
Zelt	2018	Duplicate of a study that had already been assessed	Zelt JGE, Mielniczuk LM, Liu PP, Dupuis JY, Chih S, Akbari A, Sun LY. Utility of novel cardiorenal biomarkers in the prediction and early detection of congestive kidney injury following cardiac surgery. *J Clin Med* 2018;**7**:540
Zeng	2014	Not a relevant biomarker assay or test	Zeng XF, Li JM, Tan Y, Wang ZF, He Y, Chang J, *et al.* Performance of urinary NGAL and L-FABP in predicting acute kidney injury and subsequent renal recovery: a cohort study based on major surgeries. *Clin Chem Lab Med* 2014;**52**:671–8
Zhang	2015	Not a relevant type of population	Zhang M, Zhao X, Deng Y, Tang B, Sun Q, Zhang Q, *et al.* Neutrophil gelatinase associated lipocalin is an independent predictor of poor prognosis in cases of papillary renal cell carcinoma. *J Urol* 2015;**194**:647–52
Zhang	2015	Not a primary study	Zhang Z. Biomarkers, diagnosis and management of sepsis-induced acute kidney injury: a narrative review. *Heart Lung Vessel* 2015;**7**:64–73
Zhang	2016	Meta-analysis – retained as background material	Zhang A, Cai Y, Wang PF, Qu JN, Luo ZC, Chen XD, *et al.* Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis. *Crit Care* 2016;**20**:41
Zhang	2017	No focus on DTA for AKI	Zhang Y, Yu Y, Jia J, Yu W, Xu R, Geng L, Wei Y. Administration of HES in elderly patients undergoing hip arthroplasty under spinal anesthesia is not associated with an increase in renal injury. *BMC Anesthesiol* 2017;**17**:29
Zhang	2017	< 100 participants	Zhang J, Han J, Liu J, Liang B, Wang X, Wang C. Clinical significance of novel biomarker NGAL in early diagnosis of acute renal injury. *Exp Ther Med* 2017;**14**:5017–21

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Zhang	2018	Not a relevant type of population	Zhang Y, Li J, Li F, Qi X, Zhang J. Neutrophil gelatinase-associated lipocalin accurately predicts renal tubular injury in patients with chronic hepatitis B treated with nucleos(t)ide analogs. *Hepatol Res* 2018;**48**:144–52
Zhang	2018	< 100 participants	Zhang D, Han QX, Wu MH, Shen WJ, Yang XL, Guo J, *et al.* Diagnostic value of sensitive biomarkers for early kidney damage in diabetic patients with normoalbuminuria. *Chin Med J* 2018;**131**:2891–2
Zhang	2018	Not a relevant type of population	Zhang J, Lin X, Tian B, Liu C. Evaluation of the efficacy of ischemic post-conditioning for the improvement of contrast induced nephropathy on patients with acute coronary syndrome. *Int J Clin Exp Med* 2018;**11**:4663–9
Zhang	2018	Not a relevant type of population	Zhang WR, Craven TE, Malhotra R, Cheung AK, Chonchol M, Drawz P, *et al.* Kidney damage biomarkers and incident chronic kidney disease during blood pressure reduction: a case-control study. *Ann Intern Med* 2018;**169**:610–18
Zheng	2013	< 100 participants	Zheng J, Xiao Y, Yao Y, Xu G, Li C, Zhang Q, *et al.* Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. *Pediatr Cardiol* 2013;**34**:880–6
Zhou	2016	Not a relevant biomarker assay or test	Zhou LZ, Yang XB, Guan Y, Xu X, Tan MT, Hou FF, Chen PY. Development and validation of a risk score for prediction of acute kidney injury in patients with acute decompensated heart failure: a prospective cohort study in China. *J Am Heart Assoc* 2016;**5**:e004035
Zhou	2016	Meta-analysis – retained as background material	Zhou F, Luo Q, Wang L, Han L. Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis. *Eur J Cardiothorac Surg* 2016;**49**:746–55
Zhou	2018	Not a relevant type of population	Zhou F, Song W, Wang Z, Yin L, Yang S, Yang F, *et al.* Effects of remote ischemic preconditioning on contrast induced nephropathy after percutaneous coronary intervention in patients with acute coronary syndrome. *Medicine* 2018;**97**:9579
Zhu	2014	< 100 participants	Zhu W, Liu M, Wang GC, Che JP, Xu YF, Peng B, Zheng JH. Urinary neutrophil gelatinase-associated lipocalin, a biomarker for systemic inflammatory response syndrome in patients with nephrolithiasis. *J Surg Res* 2014;**187**:237–43
Zhu	2016	Non-English-language publication	Zhu L, Shi D. [Early diagnostic value of neutrophil gelatinase-associated lipocalin and interleukin-18 in patients with sepsis-induced acute kidney injury.] *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2016;**28**:718–22
Zughaier	2013	< 100 participants	Zughaier SM, Tangpricha V, Leong T, Stecenko AA, McCarty NA. Peripheral monocytes derived from patients with cystic fibrosis and healthy donors secrete NGAL in response to *Pseudomonas aeruginosa* infection. *J Investig Med* 2013;**61**:1018–25

continued

TABLE 26 List of excluded studies (*continued*)

First author	Year of publication	Reason for exclusion	Reference
Zwaag	2019	No focus on DTA for AKI	Zwaag J, Beunders R, Warle MC, Kellum JA, Riksen NP, Pickkers P, Kox M. Remote ischaemic preconditioning does not modulate the systemic inflammatory response or renal tubular stress biomarkers after endotoxaemia in healthy human volunteers: a single-centre, mechanistic, randomised controlled trial. *Br J Anaesth* 2019;**123**:177–85
Zwiers	2015	< 100 participants	Zwiers AJ, Cransberg K, de Rijke YB, van Rosmalen J, Tibboel D, de Wildt SN. Urinary Neutrophil gelatinase-associated lipocalin predicts renal injury following extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2015;**16**:663–70

DTA, diagnostic test accuracy.

Appendix 6 Characteristics of included studies

TABLE 27 Characteristics of included studies

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Cummings *et al.*[26] 2019, USA	NephroCheck	Mean 67 (58–75)	400	14	KDIGO	67	NR	NR	NR	6	Patients who were originally enrolled in the AKI Cardiac Surgery RCT	Acute coronary syndrome, liver dysfunction, use of ciclosporin, current RRT, history of kidney transplant, pregnancy
Oezkur *et al.*[27] 2017, Germany	NephroCheck	• AKI: mean 65 (59–73) • No AKI: mean 71 (64–76)	150	35	KDIGO	72	Median 0.89 (IQR 0.75–1.02)	NR	NR	NR	Adult patients were eligible if they were undergoing elective cardiac surgery (CABG with or without mammary artery bypass, valve surgery with or without removal of the atrial auricle, combined CABG and valve surgery, or surgery of the thoracic aorta) involving CPB	Patients with advanced stages of CKD; signs of active infection; on medication with COMT inhibitors, MAO inhibitors or with immunosuppressive therapy, and women during pregnancy and lactation
Beitland *et al.*[28] 2016, Norway	NephroCheck	60 (13)	195	88	KDIGO	• AKI: 83.0 • No AKI: 86.0	NR	NR	NR	• AKI: 22 • No AKI: 9	Adult (≥ 18 years) comatose out-of-hospital cardiac arrest patients with return of spontaneous circulation	Patients with known CKD or who died within 24 hours of ICU stay, or who, for some reason, did not receive active treatment, were excluded
Kashani *et al.*[34] 2013, 21 sites in North America, 15 sites in Europe	NephroCheck	64 (53–73)	728	101	KDIGO	62	NR	NR	NR	NR	Critically ill patients who were at least aged 21 years, admitted to the ICU within 24 hours of enrolment, and expected to remain in the ICU with a urinary catheter for at least 48 hours	Patients with known existing moderate or severe AKI
Bihorac *et al.*[11] 2010, USA	NephroCheck	63 (17)	408	71	KDIGO	54	NR	NR	NR	NR	All enrolled patients were considered critically ill because of significant respiratory or cardiovascular dysfunction. The presence of an indwelling urinary catheter was also a prerequisite for inclusion	Patients with documented moderate to severe AKI (KDIGO stages 2–3) at the time of enrolment

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Hoste *et al.*[33] 2014, USA	NephroCheck	• AKI stage 2/3: 64 (54–75) • AKI stage 0/1: 65 (54–78)	153	27	KDIGO	• AKI stage 2/3: 44 • AKI stage 0/1: 60	NR	NR	NR	20	Patients at least aged 21 years, admitted to ICU within 24 hours of enrolment and expected to remain in the ICU with a urinary catheter for at least 48 hours after enrolment	NR
Di Leo *et al.*[30] 2018, Italy	NephroCheck	68 (51–78)	719	234	KDIGO	• NC(+): 63 • NC(–): 59	NR	NR	NR	AKI stage 2/3: 33	All patients aged ≥ 18 years were included in the study	Patients on chronic dialysis and with a life expectancy of < 24 hours were excluded
Kimmel *et al.*[36] 2016, Germany	NephroCheck, BioPorto urine and plasma NGAL tests	63 (14)	298	46	KDIGO (modified version)	72	NR	NR	NR	NR	Aged ≥ 18 years, willingness to sign an informed consent form, admission to the internal medicine service of the hospital, and haemoglobin level of ≥ 9.5 g/dl (women) or ≥ 10.5 g/dl (men)	Dialysis requirement, pregnancy, or failure to meet any of the inclusion criteria
Gayat *et al.*[32] 2018, France	NephroCheck	65 (54–75)	200	Unclear	KDIGO	78	NR	NR	NR	NR	NR	NR
Zelt *et al.*[80] 2018, USA	BioPorto plasma NGAL	67 (61–73)	178	35	AKIN	NR	NR	NR	NR	NR	All patients having elective cardiac surgery requiring CPB	ESRD; renal transplantation; solitary kidney, emergent operative status, off-pump procedures, procedures involving circulatory arrest, heart transplantation and left ventricular assist divide implantation
Lee *et al.*[82] 2018, the Republic of Korea	BioPorto plasma NGAL	59 (50–71)	279	111	KDIGO	66	NR	NR	NR	25	Non-traumatic cardiac arrest survivors aged > 18 years who were treated with therapeutic hypothermia and obtained plasma NGAL level results were enrolled	Transferred to another facility or died during therapeutic hypothermia, they had a pre-arrest cognitive impairment on the Cerebral Performance Categories scale of > 3, they had pre-arrest ESRD with RRT, they had cardiac arrest as a result of AKI, extracorporeal membrane oxygenation was applied during post-cardiac arrest care, or data were missing regarding their NGAL level

continued

TABLE 27 Characteristics of included studies (*continued*)

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Itenov *et al.*[81] 2017, Denmark	BioPorto plasma NGAL	67 (60–76)	454	87	KDIGO or Modification of Diets in Renal Disease study (in patients without serum creatinine samples before admission)	60	NR	NR	NR	21	Patients (aged ≥ 18 years) enrolled within 24 hours of ICU admission and expected to stay in ICU for at least 24 hours. For the present cohort study, the authors included patients without CKD who survived > 24 hours after admission and with plasma samples from admission available for biomarker analysis	Patients with high plasma concentrations of bilirubin (40 mg/dl) and/or triglycerides (1000 mg/dl) or patients at an increased risk from blood sampling were ineligible
Marino *et al.*[83] 2015, Italy	BioPorto plasma NGAL	77 (72–83)	101	49	RIFLE	60	NR	NR	NR	NR	Patients arriving in the ED with the diagnosis of sepsis, severe sepsis or septic shock between December 2011 and April 2012	Exclusion criteria were patients aged < 18 years and a patient's inability to give informed consent
Parikh *et al.*[37] 2011, North America	ARCHITECT urine NGAL	71 (10)	1200	60	Acute dialysis or doubling of serum creatinine at a median of 3 days after surgery (IQR 2–4)	68	Median 1.0 (IQR 0.9–1.20)	NR	NR	20	High risk for AKI was defined by the presence of one or more of the following: emergency surgery, preoperative serum creatinine level of > 2 mg/dl (> 177 µmol/l), ejection fraction of < 35% or grade 3 or 4 left ventricular dysfunction, aged > 70 years, diabetes mellitus, concomitant CABG and valve surgery, or repeat revascularisation surgery	Patients with evidence of AKI before surgery, prior kidney transplantation, preoperative serum creatinine level of > 4.5 mg/dl (> 398 µmol/l), or ESRD. Participants with multiple surgeries could be enrolled in the study only once
Albert *et al.*[45] 2018, Germany	ARCHITECT urine NGAL	70 (61–77)	101	15	RIFLE	72	NR	NR	NR	NR	Non-emergency open-heart surgery with CPB	Emergency operation or off-pump surgery, CKD or kidney transplant; patients aged < 18 years and patients on immunosuppression therapy

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Haase *et al.*[60] 2014, Germany	ARCHITECT urine NGAL, BioPorto plasma NGAL	72 (65–77)	100	23	RIFLE	75	NR	NR	NR	NR	Aged > 70 years, pre-existing renal impairment (preoperative creatinine level of > 120 µmol/l, left ventricular ejection fraction of < 35%, insulin-dependent type 2 diabetes, valvular surgery or valvular and coronary artery bypass surgery, redo cardiac surgery	Patients with chronic renal impairment (preoperative creatinine level of > 300 µmol/l), those undergoing an emergency cardiac surgery procedure, patients on immunosuppression therapy, and those enrolled in a conflicting research study
De Loor *et al.*[63] 2017, Belgium	BioPorto urine NGAL	69 (61–76)	203	95	KDIGO	66	NR	NR	NR	NR	Elective cardiac surgery	AKI stage ≥ 1, CKD stage 5; recent kidney transplant; surgery on Saturdays and Sundays
Garcia-Alvarez *et al.*[46] 2015, Spain	ARCHITECT urine NGAL	• AKI: 74 (68–80) • No AKI: 69 (59–76)	288	104	Serum creatinine of ≥ 200% or eGFR of < 50% from baseline	• AKI: 54 • No AKI: 46	NR	NR	NR	NR	All patients admitted to ICU after cardiac surgery and who provided informed consent	If patients required preoperative chronic or acute haemodialysis, had previously undergone renal transplant or had coronary angiography in the 7 days before surgery
Thanakitcharu and Jirajan[48] 2014, Thailand	ARCHITECT urine NGAL	51 (15.6)	130	46	Serum creatinine levels of ≥ 0.3 mg/dl within 48 hours	59	Mean 1.0 mg/dl (SD 0.3)	74.1 (25.9)	NR	NR	All patients who underwent cardiac surgery with CPB	Pre-existing renal dysfunction with baseline serum creatinine level of > 3mg/dl; kidney transplant patients; history of using nephrotoxic agents such as aminoglycoside, NSAIDs, radiocontrast agent in the 2 weeks before surgery; patients with sepsis; patients undergoing emergency operation < 24 hours after admission

continued

TABLE 27 Characteristics of included studies (*continued*)

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Tidbury *et al.*[64] 2019, UK	BioPorto urine NGAL	• AKI: 73 (54–87) • No AKI: 75 (59–85)	125	54	RIFLE	• AKI: 63 • No AKI: 47	NR	NR	NR	NR	High-risk patients undergoing elective surgery for on-pump such as valve replacement, CABG or combined valve and CABG. All had impaired renal function pre operation, established by an eGFR of < 60 ml/minute/ 1.73 m^2	Excluded if they were scheduled to undergo surgery with anticipated CPB time of < 60 minutes; undergoing surgery on great vessels such as aortic surgery; had impaired liver function; renal failure or were on dialysis; malignancy; being pregnant
Schley *et al.*[61] 2015, Germany	BioPorto urine and plasma NGAL tests	70 (10)	110	37	AKIN	76	Mean 1.2 mg/dl (SD 0.5)	NR	NR	NR	All patients undergoing cardiac surgery using CPB	Pre-existing haemodialysis-dependent ESRD, previous kidney transplantation, immunosuppressive medication and pregnancy
Collins *et al.*[51] 2012, USA	ARCHITECT urine NGAL	NR	399	20	Serum creatinine levels of ≥ 0.3 mg/dl or RIFLE	65	NR	NR	NR	NR	Modified Framingham criteria for acute heart failure; enrolled within 3 hours of first physician contact; received vasodilators or diuretics in the ED for treatment of acute heart failure	NR
Dupont *et al.*[52] 2012, USA	ARCHITECT urine NGAL	NR	141	35	Serum creatinine increase of ≥ 0.3 mg/dl	58	NR	NR	NR	NR	Aged > 18 years, clinical evidence of congestion, planned strategy for treatment with intravenous furosemide	Acute coronary syndrome, ESRD or RRT, exposure to nephrotoxic agents, planned surgery at the time of enrolment, haemoglobin level of < 9 mg/dl or active bleeding
Cullen *et al.*[49] 2014, UK	ARCHITECT urine NGAL	68 (11)	109	16	AKIN	NR	NR	NR	NR	NR	Patients admitted to critical care following major abdominal surgery	Refusal of consent, concurrent lithium therapy, acute myocardial ischaemia, acute arrhythmias, pregnancy, patients receiving palliative treatment only and weight of < 40 kg

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Nisula *et al.*[76] 2014, Finland	BioPorto urine NGAL	62 (50–73)	855	379	KDIGO	64	NR	NR	NR	NR	Emergency ICU admissions and post-operative patients admitted for > 24 hours	Patients aged < 18 years, re-admitted patients who received RRT during their previous admission, patients electively admitted with an ICU LOS of < 24 hours if discharged alive, patients on chronic dialysis, organ donors, patients without permanent residency in Finland or without sufficient language skills, patients transferred between study ICUs if included in the study for 5 days already, and patients receiving intermediate care
Doi *et al.*[71] 2011, Japan	BioPorto urine NGAL	• AKI: 65 (53–74) • No AKI: 66 (55–73)	339	131	RIFLE	• AKI: 70 • No AKI: 64	NR	NR	NR	NR	Patients aged > 20 years who had been admitted to the mixed ICU	Patients with ESRD or renal transplant were excluded
Cho *et al.*[69] 2013, the Republic of Korea	BioPorto urine NGAL	• AKI: 65.4 (14.8) • No AKI: 60.4 (17.4)	145	54	AKIN	• AKI: 61 • No AKI: 57	NR	NR	NR	NR	Adult patients aged > 18 years who were admitted to the medical or surgical ICU	ESRD or kidney transplantation and those with life expectancy of < 48 hours
Pipili *et al.*[58] 2014, Greece	ARCHITECT urine NGAL	64 (18)	106	44	RIFLE	64	1.0 mg/dl (SD 1.3)	NR	9 (3)	NR	All consecutive, mechanically ventilated patients admitted to the ICU were considered eligible for inclusion	Aged < 18 years, BMI of > 35 kg/m^2, ESRD on chronic haemodialysis, pregnancy, brain death, metastatic cancer and re-admission to ICU or missing baseline creatinine in the 6 months before admission
Mårtensson *et al.*[55] 2015, Australia	ARCHITECT urine NGAL	• Mild AKI: 69 (59–74) • Severe AKI: 68 (54–76) • No AKI: 62 (48–72)	102	28	RIFLE	• Mild AKI: 69 • Severe AKI: 64 • No AKI: 42	NR	NR	NR	NR	Aged > 18 years, the presence of two or more systemic inflammatory response criteria, the presence of oliguria for ≥ 2 consecutive hours and/or a 25-µmol/l increase in creatinine from baseline	NR

continued

TABLE 27 Characteristics of included studies (*continued*)

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Isshiki *et al.*[53] 2018, Japan	ARCHITECT urine NGAL	62 (51–73)	148	33	KDIGO	60	NR	NR	NR	NR	Aged > 18 years who were admitted to the ICU	Anuria patients at ICU admission, those deceased within 24 hours of ICU admission and those with ESRD
Tecson *et al.*[78] 2017, USA	BioPorto urine and plasma NGAL tests	• AKI stage 2/3: 68 (56–74) • AKI stage 0/1: 63 (54–73)	245	33	KDIGO	• AKI stage 2/3: 67 • AKI stage 0/1: 64	NR	NR	NR	NR	NR	NR
Matsa *et al.*[73] 2014, UK	BioPorto urine and plasma NGAL tests	60 (15)	194	59	RIFLE	66	80.8 mol/l (SD 29.1)	NR	NR	NR	Consecutive adult (aged > 18 years) patients admitted to the ICU were screened for inclusion	Refused consent, ESRD, previous renal transplant, patients already on RRT, patients referred to the ICU for RRT and patients with AKI as defined by RIFLE criteria for risk, injury or failure
Kokkoris *et al.*[54] 2012, Greece	ARCHITECT urine NGAL	• AKI: 63 (50–81) • No AKI: 49 (35–66)	100	36	RIFLE	57	NR	NR	NR	0	All consecutive patients admitted to the ICU were screened for eligibility	ESRD; CKD or nephrectomy or renal transplantation; expected ICU stay of or imminent death in < 48 hours; transfer from another ICU or high-dependency unit; brain death; aged < 18 years; inability to draw blood or urine (anuria)
Asada *et al.*[50] 2016, Japan	ARCHITECT urine NGAL	• AKI: 62 (48–74) • No AKI: 63 (51–73)	133	31	KDIGO	• AKI: 68 • No AKI: 58	NR	NR	NR	0	Patients aged ≥ 18 years who were admitted to the ICU	Presence of ESRD
Nickolas *et al.*[56] 2012, USA and Germany	ARCHITECT urine NGAL	64 (19)	1635	96	RIFLE	52	0.9 (0.4) mg/dl	70.5 (SD 33.2)	NR	0	Patients aged > 18 years, irrespective of their condition, who were in the process of admission to the hospital from the ED	Patients who had 24 hours of follow-up or were on long-term RRT

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Hjortrup *et al.*[72] 2015, Denmark	BioPorto urine and plasma NGAL tests	66 (57–75)	151	91	KDIGO	57	NR	NR	NR	0	Need of fluid resuscitation in the ICU, the fulfilment of severe sepsis criteria in the previous 24 hours and consent from patient or proxy	Aged < 18 years; allergy to hydroxyethyl starch or malic acid; any form of RRT; acute burn injury on > 10% of body surface area; severe hyperkalaemia within the previous 6 hours; liver or kidney transplantation or intracranial bleeding during current hospital admission; enrolment in another ICU trial of drugs with potential action on circulation, renal function or coagulation
Park *et al.*[57] 2017, USA	ARCHITECT urine NGAL	59 (11)	2466	NR	Serum creatinine (criteria not clearly defined)	54	NR	43 (18)	NR	0	Adults with an eGFR of 20–70 ml/minute/1.73 m^2 were enrolled	Polycystic kidney disease, multiple myeloma, or glomerulonephritis on active immunosuppression
Smith *et al.*[77] 2013, UK	BioPorto urine NGAL	69 (12)	158	40	KDIGO	75	NR	31 (11)	NR	0	NR	NR
Ariza *et al.*[67] 2016, Europe	BioPorto urine NGAL	• ACLF: 57 (11) • No ACLF: 57 (12)	716	NR	Serum creatinine levels of between ≥ 1.5 and < 2 mg/dl	• ACLF: 66 • No ACLF: 65	NR	NR	NR	0	NR	People with a urinary tract infection at the time of urine collection were excluded because the urine levels of NGAL may be increased as a result of high leucocyte concentration in urine
Treeprasertsuk *et al.*[59] 2015, Thailand	ARCHITECT urine NGAL	57 (15)	121	35	AKIN	62	NR	NR	NR	0	Cirrhotic patients who were admitted with AKI-prone conditions. All patients had normal baseline serum creatinine in the 3 months prior to admission with cirrhosis, aged > 18 years	Exclusion criteria were CKD, or previous liver or kidney transplantation. The diagnosis of cirrhosis was based on a combination of clinical, biochemical and imaging assessments or liver biopsy

continued

TABLE 27 Characteristics of included studies (*continued*)

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Barreto *et al.*[68] 2014, Spain	BioPorto urine NGAL	58 (12)	132	65	AKIN	70	1.5 (1.0) mg/dl	NR	NR	0	Cirrhotic patients with a bacterial infection	Chronic haemodialysis before admission, previous liver and/or kidney transplantation, hepatocellular carcinoma outside the Milan criteria or any other advanced malignancy, lack of informed consent, and patients with urinary tract infection (these patients were excluded because urine NGAL levels are increased in these patients and therefore may not reflect any impairment of kidney function)
Jaques *et al.*[62] 2019, Switzerland	BioPorto urine and plasma NGAL tests	58 (10)	105	55	AKIN	71	NR	NR	NR	0	Inclusion criteria were patients aged ≥ 18 years and known or suspected cirrhosis with ascites confirmed by ultrasonography	Exclusion criteria were proven multifocal hepatocellular carcinoma, known CKD stage 5 or dialysis before admission, prior kidney or liver transplantation, recent upper gastrointestinal bleeding, or a delay of > 24 hours between the admission and inclusion. Informed consent was sought from all eligible patients, or from a surrogate decision-maker if the patient was unable to provide consent
Cho *et al.*[66] 2014, the Republic of Korea	BioPorto urine NGAL	57 (12)	135	54	AKIN	63	NR	NR	NR	0	Patients who planned to undergo elective hepatobiliary surgery	Patients aged < 18 years, with baseline eGFR of < 60 ml/minute/1.73 m^2, on maintenance RRT, developed AKI preoperatively

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Nickolas *et al.*[74] 2008, USA	BioPorto urine NGAL	60 (18)	635	30	RIFLE	51	1.4 (1.8) mg/dl	NR	NR	0	Aged > 18 years, admitted to ED	Patients who were receiving haemodialysis and patients without subsequent creatinine measurements
Verna *et al.*[79] 2012, USA	BioPorto urine NGAL	56 (49–62)	118	52	Serum creatinine to > 1.5 and 0.3 mg/dl above baseline, not responding with 48 hours of volume resuscitation and not meeting the criteria for hepatorenal syndrome	61	NR	NR	NR	0	Adults with cirrhosis	Patients on chronic haemodialysis, anuria for the first 24 hours, urinary tract infection, proteinuria of > 500 mg per day, or urinary obstruction
Liebetrau *et al.*[47] 2013, Germany	ARCHITECT urine NGAL	• AKI: 74 (8) • No AKI: 68 (11)	141	47	KDIGO	• AKI: 60 • No AKI: 73	NR	NR	NR	0	Consecutive patients scheduled to undergo elective major cardiac surgery (CABG and/or valve replacement) with the use of extracorporeal circulation	Patients with a preoperative eGFR of < 30 ml/minute/1.73 m^2 body surface
Parikh *et al.*[84] 2011, North America	ARCHITECT urine NGAL	4 (5) years	311	53	Receipt of acute dialysis or doubling of serum creatinine levels at a median of 3 days after surgery (consistent with RIFLE stage 1 or AKIN stage 2)	55	NR	90 (26)	NR	0	All paediatric patients aged 1 month–18 years undergoing CPB	Prior renal transplantation or dialysis
Dong *et al.*[92] 2017, USA	BioPorto urine NGAL	• AKI: 1.4 (0.2–2.7) years • No AKI: 5 (4.1–5.9) years	150	50	KDIGO	• AKI: 40 • No AKI: 57	NR	NR	NR	0	All patients receiving CPB as long as the baseline serum creatinine level is normal for age	Pre-existing CKD
Bojan *et al.*[86] 2014, France	ARCHITECT urine NGAL	< 1 year	100	NR	AKIN	NR	NR	NR	NR	0	Surgery with CPB	NR
Bennett *et al.*[87] 2008, USA	ARCHITECT urine NGAL	4 years	196	99	Increase of ≥ 50% in serum creatinine level from baseline within 72 hours	54	NR	NR	NR	0	Elective CPB surgery	Pre-existing renal insufficiency, diabetes mellitus, peripheral vascular disease and use of nephrotoxic drugs before and during the study

continued

TABLE 27 Characteristics of included studies (*continued*)

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Cantinotti *et al.*[88] 2012, Italy	ARCHITECT urine NGAL	6 (1–49) months	135	52	RIFLE	58	NR	NR	NR	0	All patients undergoing cardiac surgery for correction/palliation of congenital heart defects	History of prior renal transplantation or dialysis requirements
Alcaraz *et al.*[89] 2014, Spain	ARCHITECT urine NGAL	25 (6.0–72.0) months	106	36	Paediatric RIFLE criteria	59	NR	NR	NR	0	Cardiac surgery for congenital lesions	Pre-existing renal dysfunction and heart transplantation
Lagos-Arevalo *et al.*[93] 2015, Canada	BioPorto urine NGAL	• Serum creatinine, AKI: 4.0 (5) years • No serum creatinine, AKI: 5.0 (6) years	160	70	KDIGO	NR	NR	NR	NR	0	Children aged between 1 month and 18 years who were not immediately admitted to PICU after cardiac surgery	Known ESRD, having received a renal transplant, a high likelihood of death in the subsequent 48 hours (determined by the PICU attending staff) and presence of < 25% of PICU days with both a cystatin C and a serum creatinine value available (determined by dividing number of available daily values by PICU admission days)
Zwiers *et al.*[91] 2015, the Netherlands	ARCHITECT urine NGAL	27 (1–85) days	100	35	RIFLE	66	N	NR	NR	0	Children (born at > 37 weeks of gestational age) between the ages of 1 day and 1 year admitted to the ICU and requiring endotracheal intubation and mechanical ventilation	Congenital abnormalities of the kidney or urinary tract, death anticipated within 24 hours or they received mechanical ventilation for other reasons. Patients were excluded when treatment with extracorporeal membrane oxygenation was required during the study period

Study, country	Test	Age (years) (range or SD)	Sample size (*n*)	AKI events (*n*)	AKI definition	Male sex (%)	Serum creatinine	eGFR	SOFA mean score	CKD (%)	Inclusion criteria	Exclusion criteria
Yang *et al.*[65] 2017, China	BioPorto urine NGAL	• Children: 22 (31) months • Adults: 46 (15) years	• Children: 323 • Adults: 398	• Children: 126 • Adults: 164	Acute dialysis or doubling of serum creatinine levels consistent with KDIGO stages 2 and 3 criteria	• Children: 62 • Adults: 43	• Children: 29.3 (SD 9.8) μmol/l • Adults: 76.6 (SD 24.2) μmol/l	• Children: 101.6 (35) • Adults: 93.5 (23.7)	NR	0	Patients receiving elective cardiac surgery (CPB)	Exposure to nephrotoxin in the 4 weeks before surgery, pre-existing advanced and urinary tract infection or obstruction
Seitz *et al.*[90] 2013, NR	ARCHITECT urine NGAL	0 (0–8) years	139	76	RIFLE	55	Mean 0.38 mg/dl (SD NR)	NR	NR	0	Patients undergoing CPB for surgical correction or palliation of congenital heart disease	Patients with pre-existing renal insufficiency, patients with history of nephrotoxin use during pre-operative days

ACLF, acute-on-chronic liver failure; CABG, coronary artery bypass graft; COMT, catechol-O-methyltransferase; CPB, cardiopulmonary bypass; IQR, interquartile range; MAO, monoamine oxidase; NC(+), NephroCheck positive; NC(–), NephroCheck negative; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; PICU, paediatric intensive care unit; SOFA, Sequential Organ Failure Assessment.

Appendix 7 The QUADAS-2 risk-of-bias and applicability assessment

TABLE 28 The QUADAS-2 risk-of-bias and applicability assessment

		Risk of bias				Applicability		
Study	Test	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Albert 2018[45]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Alcaraz 2014[89]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Ariza 2016[67]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Asada 2016[50]	ARCHITECT urine NGAL	Unclear	Unclear	Low	High	Unclear	Unclear	Low
Barreto 2014[68]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Beitland 2016[28]	NephroCheck	Low	Unclear	Low	Low	Low	Low	Low
Bennett 2008[87]	Urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Bihorac 2014[29]	NephroCheck	Low	Unclear	Low	Low	Low	Low	Low
Bojan 2014[86]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Cantinotti 2012[88]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Cho 2013[69]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Cho 2014[66]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Collins 2012[51]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Cullen 2014[49]	ARCHITECT urine NGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Cummings 2019[26]	NephroCheck	Low	Unclear	Low	Low	Low	Low	Low
De Loor 2017[63]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Di Leo 2018[30]	NephroCheck	Low	Unclear	Low	Low	Low	Low	Low
Doi 2014[70]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Dong 2017[92]	BioPorto urine NGAL	Low	Unclear	Low	Unclear	Low	Unclear	Low
Dupont 2012[52]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Garcia-Alvarez 2015[46]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Gayat 2018[32]	NephroCheck	Unclear	Unclear	Low	Low	Low	Low	Low

continued

TABLE 28 The QUADAS-2 risk-of-bias and applicability assessment (*continued*)

		Risk of bias				Applicability		
Study	Test	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Haase 2014[60]	ARCHITECT urine NGAL, plasma NGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Hjortrup 2015[72]	BioPorto urine NGAL, plasma NGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Hoste 2014[33]	NephroCheck	Unclear	Unclear	Low	Low	Low	Low	Low
Isshiki 2018[53]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Itenov 2017[81]	Plasma NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Jaques 2019[62]	BioPorto urine NGAL, plasma NGAL	Low	Unclear	Low	High	Unclear	Unclear	Low
Kashani 2013[34]	NephroCheck	Low	Unclear	Low	Low	Low	Low	Low
Kimmel 2016[36]	NephroCheck, BioPorto urine NGAL, plasma NGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Kokkoris 2012[54]	ARCHITECT urine NGAL, plasma NGAL	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Lagos-Arevalo 2015[93]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Lee 2018[82]	Plasma NGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Liebetrau 2013[47]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Marino 2015[83]	Plasma NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Mårtensson 2015[55]	ARCHITECT urine NGAL	Unclear	Unclear	Low	Low	Low	Unclear	Low
Matsa 2014[73]	BioPorto urine NGAL, plasma NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Nickolas 2008[74]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Nickolas 2012[56]	ARCHITECT urine NGAL	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
Nisula 2015[75]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Oezkur 2017[27]	NephroCheck	Low	Unclear	Low	Low	Low	Low	Low
Parikh 2011[37]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Parikh 2011[84]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Park 2017[57]	ARCHITECT urine NGAL	Unclear	Unclear	Low	Unclear	Low	Unclear	Low
Pipili 2014[58]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low

TABLE 28 The QUADAS-2 risk-of-bias and applicability assessment (*continued*)

Study	Test	Risk of bias				Applicability		
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Schley 2015[61]	BioPorto urine NGAL, plasma NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Seitz 2013[90]	ARCHITECT urine NGAL	Low	Low	Low	Low	Low	Unclear	Low
Smith 2013[77]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Tecson 2017[78]	BioPorto urine NGAL, plasma NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Thanakitcharu 2014[48]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Tidbury 2019[64]	BioPorto urine NGAL	Low	Unclear	Low	Unclear	Low	Unclear	Low
Treeprasertsuk 2015[59]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Verna 2012[79]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Yang 2017[65]	BioPorto urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Zelt 2018[80]	Plasma NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Zwiers 2015[91]	ARCHITECT urine NGAL	Low	Unclear	Low	Low	Low	Unclear	Low
Risk of bias/applicability*, n *(%)								
Low		45 (80)	1 (2)	54 (96)	50 (89)	54 (96)	8 (14)	54 (96)
Unclear		11 (20)	55 (98)	2 (4)	4 (7)	2 (4)	48 (86)	2 (4)
High		0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)

Appendix 8 The PROBAST risk-of-bias and applicability assessment

TABLE 29 The PROBAST risk-of-bias and applicability assessment

		Risk of bias					Applicability			
Study	Test	Participants	Predictors	Outcome	Analysis	Overall judgement	Participants	Predictors	Outcome	Overall judgement
Garcia-Alvarez 2015[46]	Urine NGAL	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Bennett 2008[87]	Urine NGAL	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Cullen 2014[49]	Urine NGAL	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Doi 2014[70]	Urine NGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Nisula 2015[75]	Urine NGAL	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Marino 2015[83]	Plasma NGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Hjortrup 2015[72]	Urine NGAL, plasma NGAL	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Treeprasertsuk 2015[59]	Urine NGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Gayat 2018[32]	NephroCheck	Unclear	Unclear	Unclear	High	High	Unclear	Low	Low	Unclear
Mårtensson 2015[55]	Urine NGAL	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Isshiki 2018[53]	Urine NGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Lee 2018[82]	Plasma NGAL	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low

Appendix 9 Forest plots of sensitivity and specificity estimates and summary receiver operating characteristic plots

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hoste 2014[33]	24	59	3	67	0.89 (0.71 to 0.98)	0.53 (0.44 to 0.62)
Bihorac 2014[29]	65	182	6	155	0.92 (0.83 to 0.97)	0.46 (0.41 to 0.51)
Kimmel 2016[36]	35	118	11	134	0.76 (0.61 to 0.87)	0.53 (0.47 to 0.59)
Di Leo 2018[30]	150	202	84	256	0.64 (0.58 to 0.70)	0.56 (0.51 to 0.61)
Kashani 2013[34]	90	313	11	314	0.89 (0.81 to 0.94)	0.50 (0.46 to 0.54)

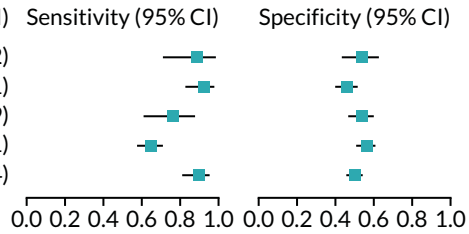

FIGURE 26 Forest plots of sensitivity and specificity for NephroCheck for detection of AKI in adults: critical care setting. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

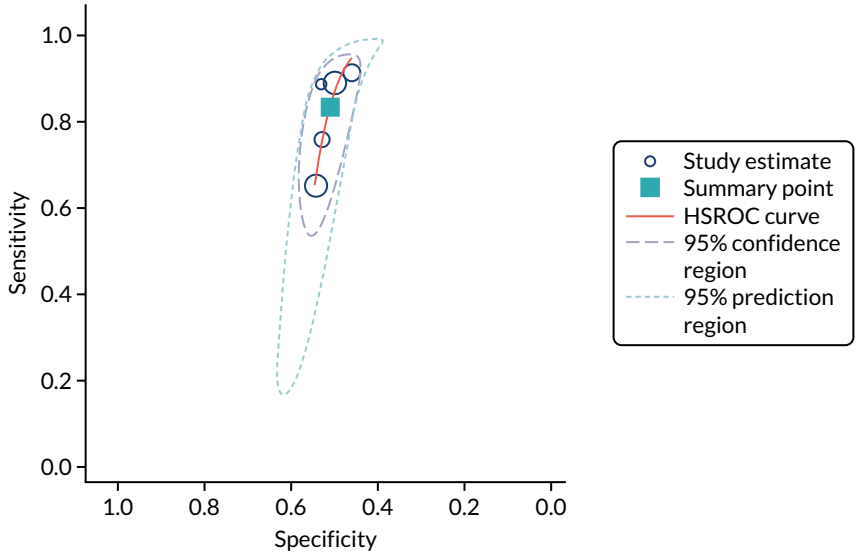

FIGURE 27 The SROC plot for NephroCheck studies: critical care setting. HSROC, hierarchical summary receiver operating characteristic.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dupont 2012[52]	22	45	13	61	0.63 (0.45 to 0.79)	0.58 (0.48 to 0.67)
Kokkoris 2012[54]	28	18	8	46	0.78 (0.61 to 0.90)	0.72 (0.59 to 0.82)
Nickolas 2012[56]	65	293	31	1247	0.68 (0.57 to 0.77)	0.81 (0.79 to 0.83)
Treeprasertsuk 2015[59]	27	23	8	63	0.77 (0.60 to 0.90)	0.73 (0.63 to 0.82)

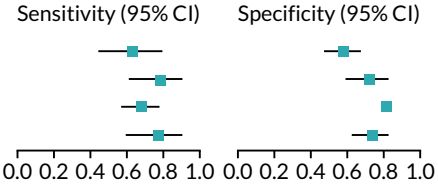

FIGURE 28 Forest plots of sensitivity and specificity for ARCHITECT urine NGAL for detection of AKI in adults: critical care setting. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

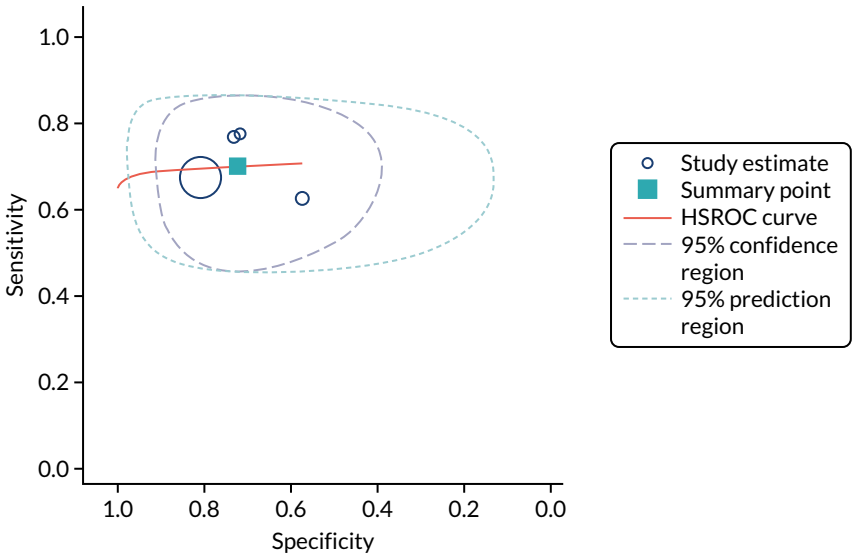

FIGURE 29 The SROC plot for ARCHITECT urine NGAL studies: clinical care setting (adult population). HSROC, hierarchical summary receiver operating characteristic.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nickolas 2008[74]	27	3	3	602	0.90 (0.73 to 0.98)	1.00 (0.99 to 1.00)
Cho 2013[69]	40	27	14	64	0.74 (0.60 to 0.85)	0.70 (0.60 to 0.79)
Matsa 2014[73]	34	15	25	80	0.58 (0.44 to 0.70)	0.84 (0.75 to 0.91)
Barreto 2014[68]	43	20	22	47	0.66 (0.53 to 0.77)	0.70 (0.58 to 0.81)
Hjortrup 2015[72]	24	23	8	77	0.75 (0.57 to 0.89)	0.77 (0.68 to 0.85)
Tecson 2017[78]	21	40	12	172	0.64 (0.45 to 0.80)	0.81 (0.75 to 0.86)

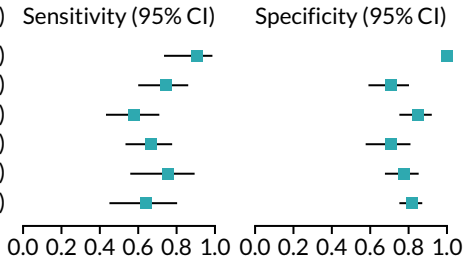

FIGURE 30 Forest plots of sensitivity and specificity for BioPorto urine NGAL for detection of AKI in adults: critical care setting. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

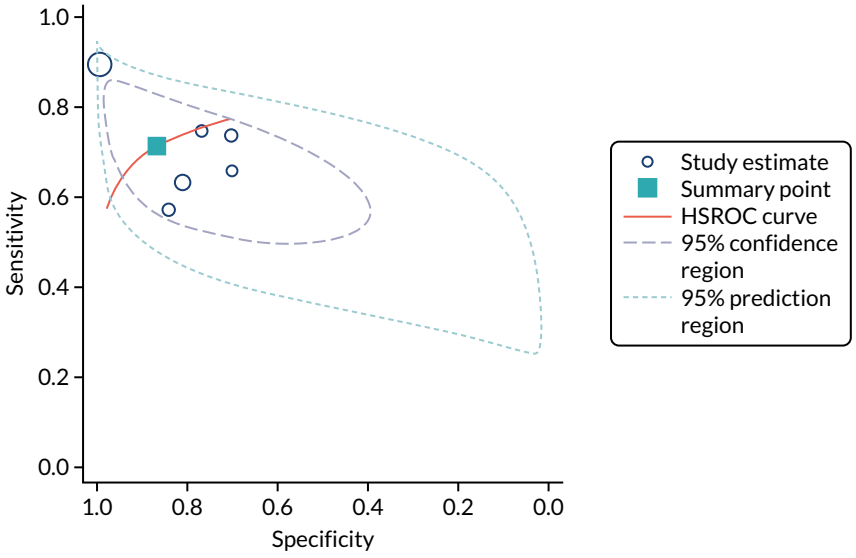

FIGURE 31 The SROC plot for BioPorto urine NGAL studies: critical care setting. HSROC, hierarchical summary receiver operating characteristic.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barreto 2014[68]	43	20	22	47	0.66 (0.53 to 0.77)	0.70 (0.58 to 0.81)
Cho 2013[69]	40	27	14	64	0.74 (0.60 to 0.85)	0.70 (0.60 to 0.79)
Dupont 2012[52]	22	45	13	61	0.63 (0.45 to 0.79)	0.58 (0.48 to 0.67)
Hjortrup 2015[72]	24	23	8	77	0.75 (0.57 to 0.89)	0.77 (0.68 to 0.85)
Kokkoris 2012[54]	28	18	8	46	0.78 (0.61 to 0.90)	0.72 (0.59 to 0.82)
Matsa 2014[73]	34	15	25	80	0.58 (0.44 to 0.70)	0.84 (0.75 to 0.91)
Nickolas 2008[74]	27	3	3	602	0.90 (0.73 to 0.98)	1.00 (0.99 to 1.00)
Nickolas 2012[56]	65	293	31	1247	0.68 (0.57 to 0.77)	0.81 (0.79 to 0.83)
Tecson 2017[78]	21	40	12	172	0.64 (0.45 to 0.80)	0.81 (0.75 to 0.86)
Treeprasertsuk 2015[59]	27	23	8	63	0.77 (0.60 to 0.90)	0.73 (0.63 to 0.82)

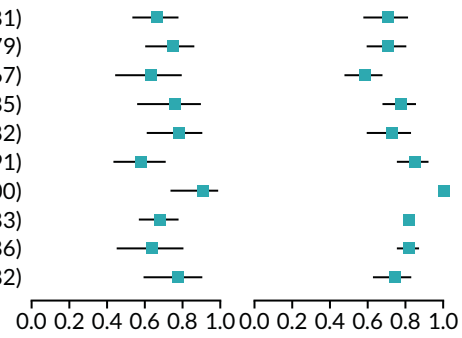

FIGURE 32 Forest plots of sensitivity and specificity for all urine NGAL assays (ARCHITECT and BioPorto) for detection of AKI in adults admitted to critical care. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

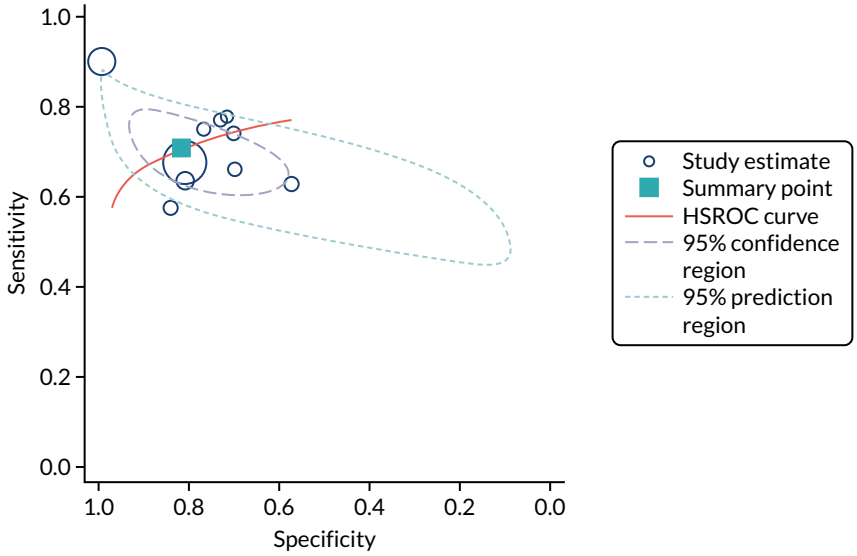

FIGURE 33 The SROC plot for all urine NGAL assays (ARCHITECT and BioPorto) for detection of AKI in adults: critical care setting. HSROC, hierarchical summary receiver operating characteristic.

Appendix 10 Forest plots of area under the curve meta-analyses for detection of acute kidney injury

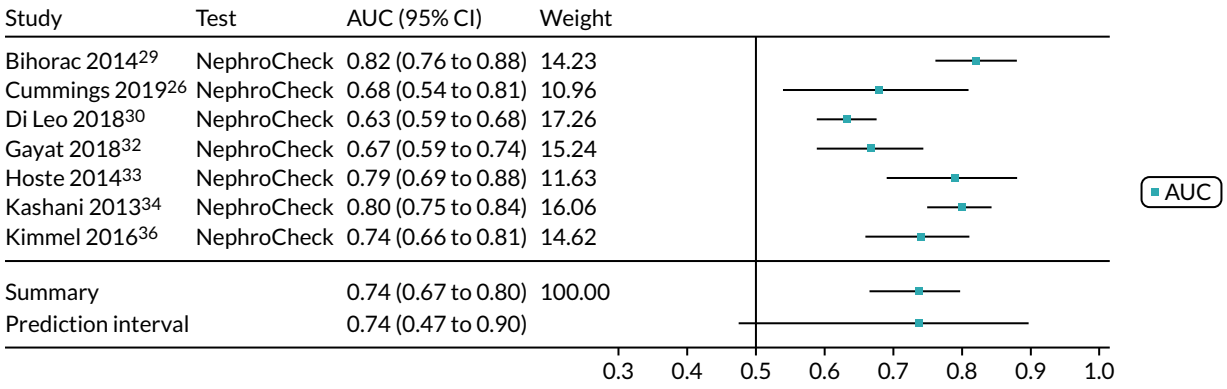

FIGURE 34 NephroCheck: all settings (adult population).

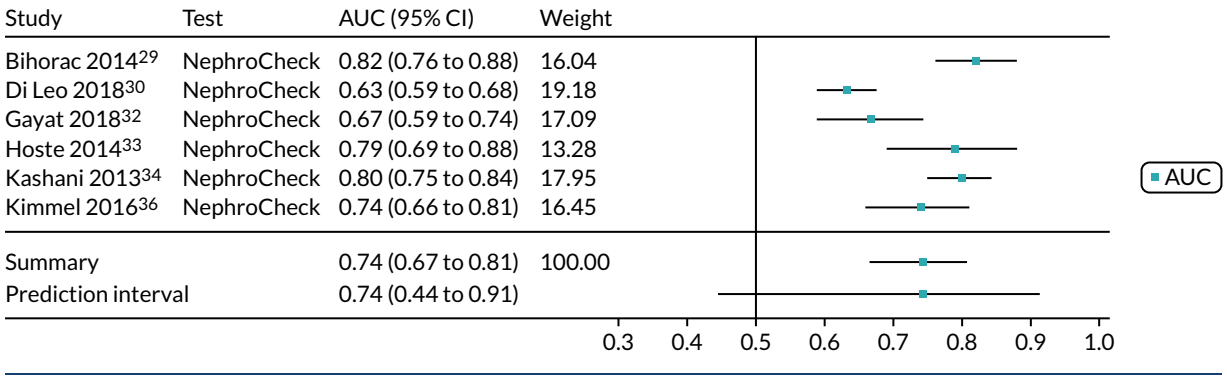

FIGURE 35 NephroCheck: critical care (adult population).

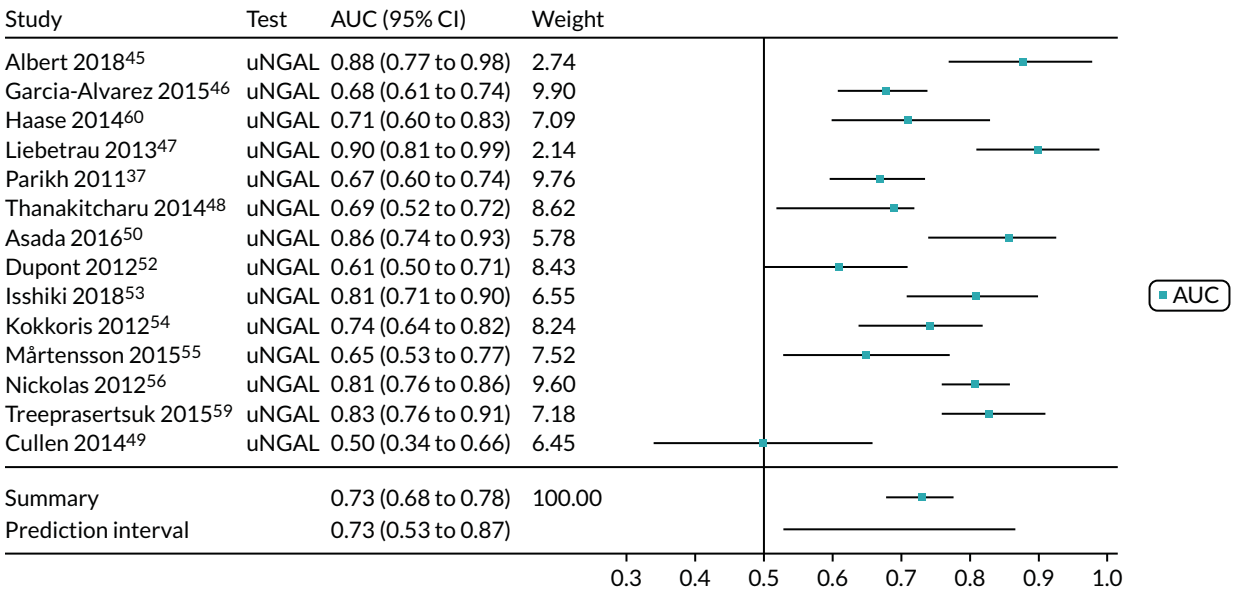

FIGURE 36 ARCHITECT urine NGAL: all settings (adult population). uNGAL, urine NGAL.

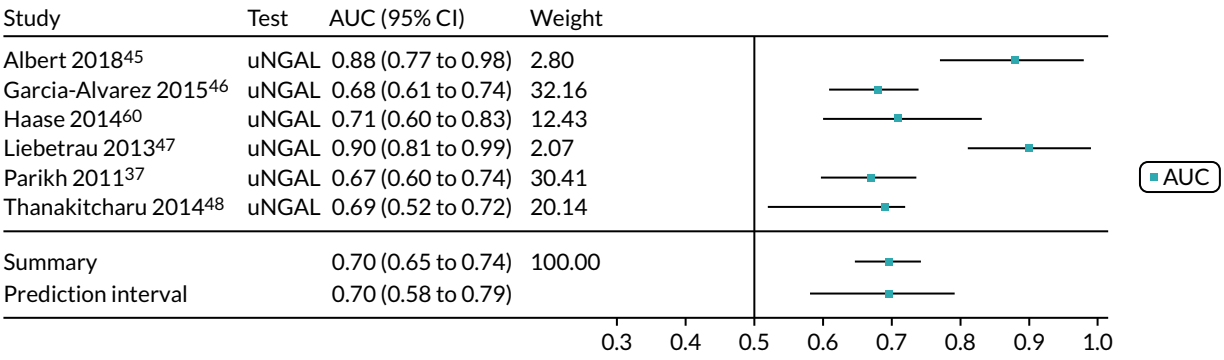

FIGURE 37 ARCHITECT urine NGAL: cardiac surgery (adult population). uNGAL, urine NGAL.

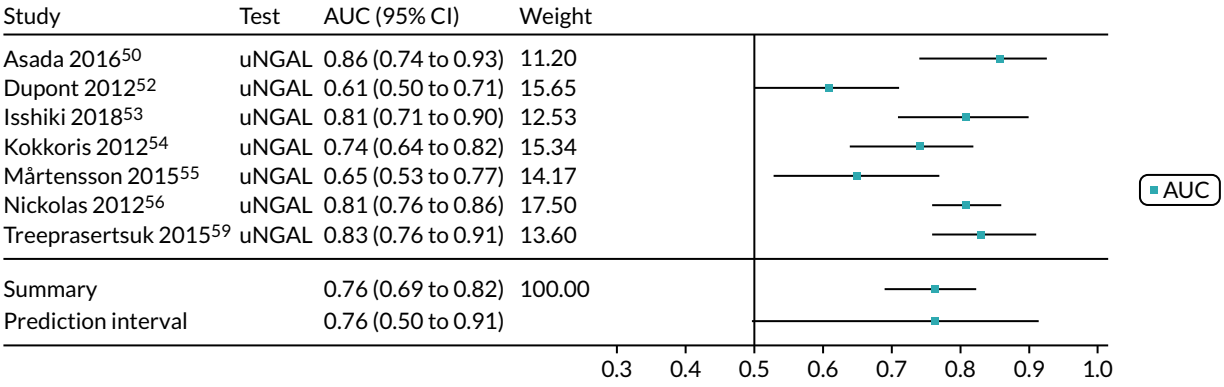

FIGURE 38 ARCHITECT urine NGAL: critical care (adult population). uNGAL, urine NGAL.

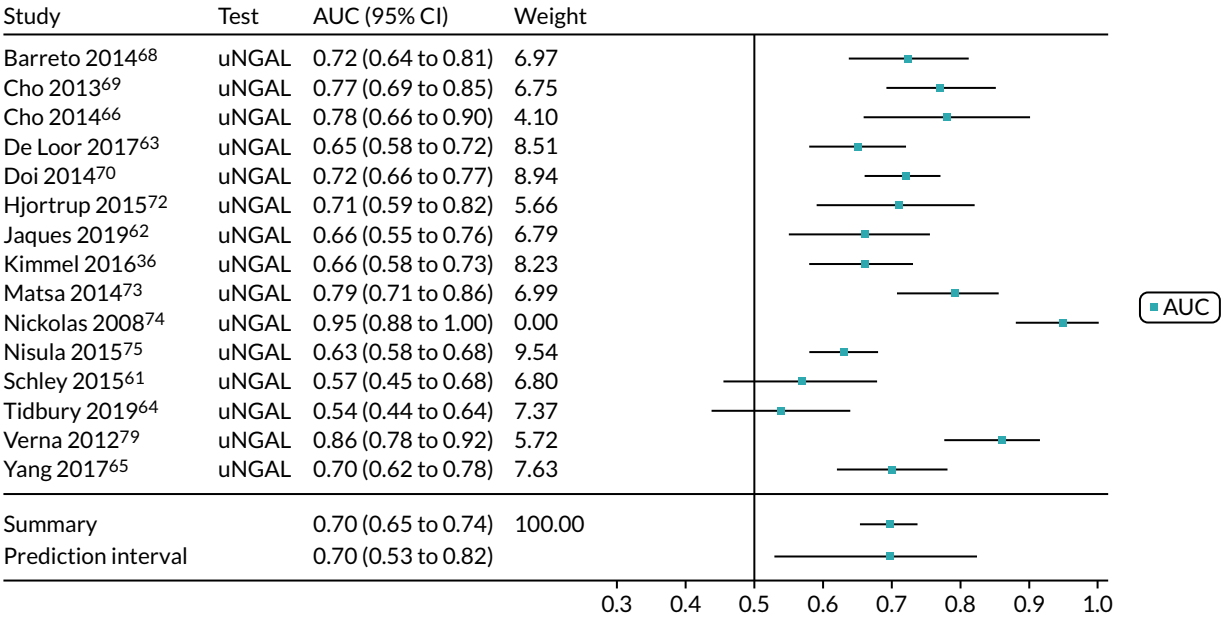

FIGURE 39 BioPorto urine NGAL: all settings (adult population). uNGAL, urine NGAL.

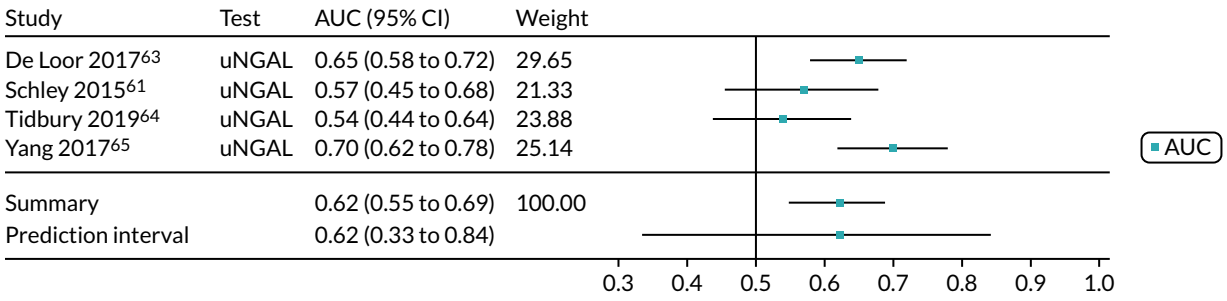

FIGURE 40 BioPorto urine NGAL: cardiac surgery (adult population). uNGAL, urine NGAL.

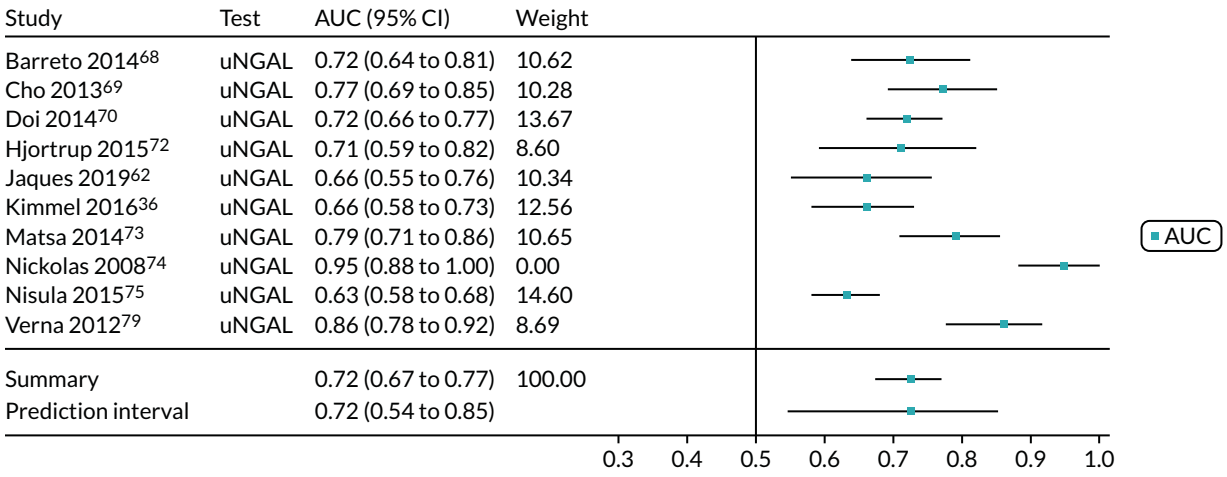

FIGURE 41 BioPorto urine NGAL: critical care (adult population). uNGAL, urine NGAL.

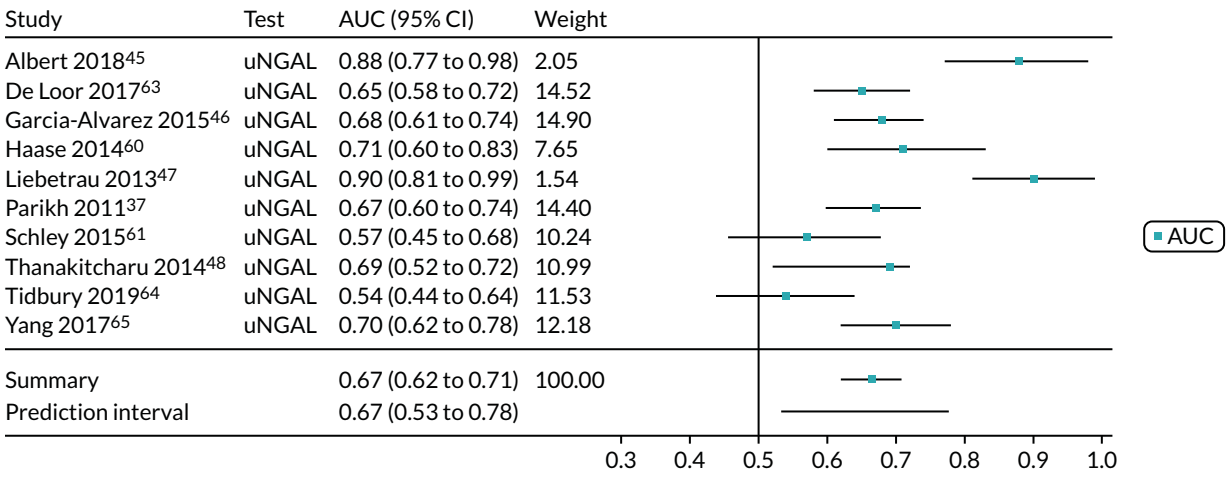

FIGURE 42 Urine NGAL (ARCHITECT and BioPorto): cardiac surgery (adult population). uNGAL, urine NGAL.

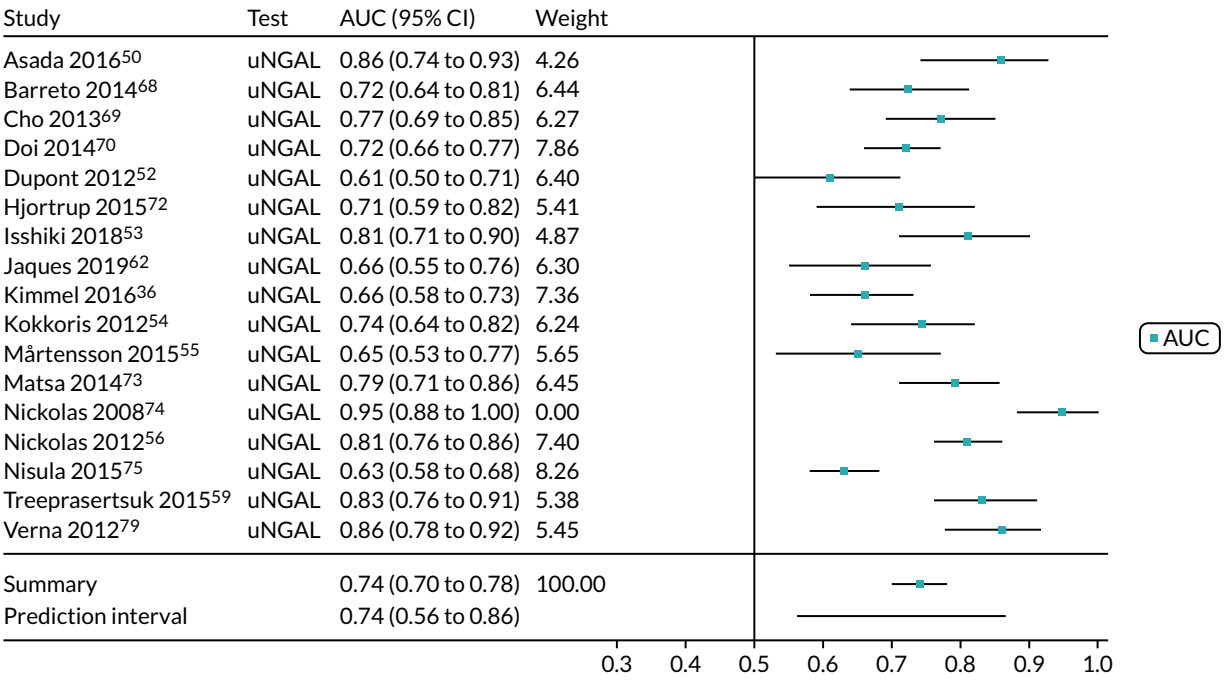

FIGURE 43 Urine NGAL (ARCHITECT and BioPorto): critical care (adult population). uNGAL, urine NGAL.

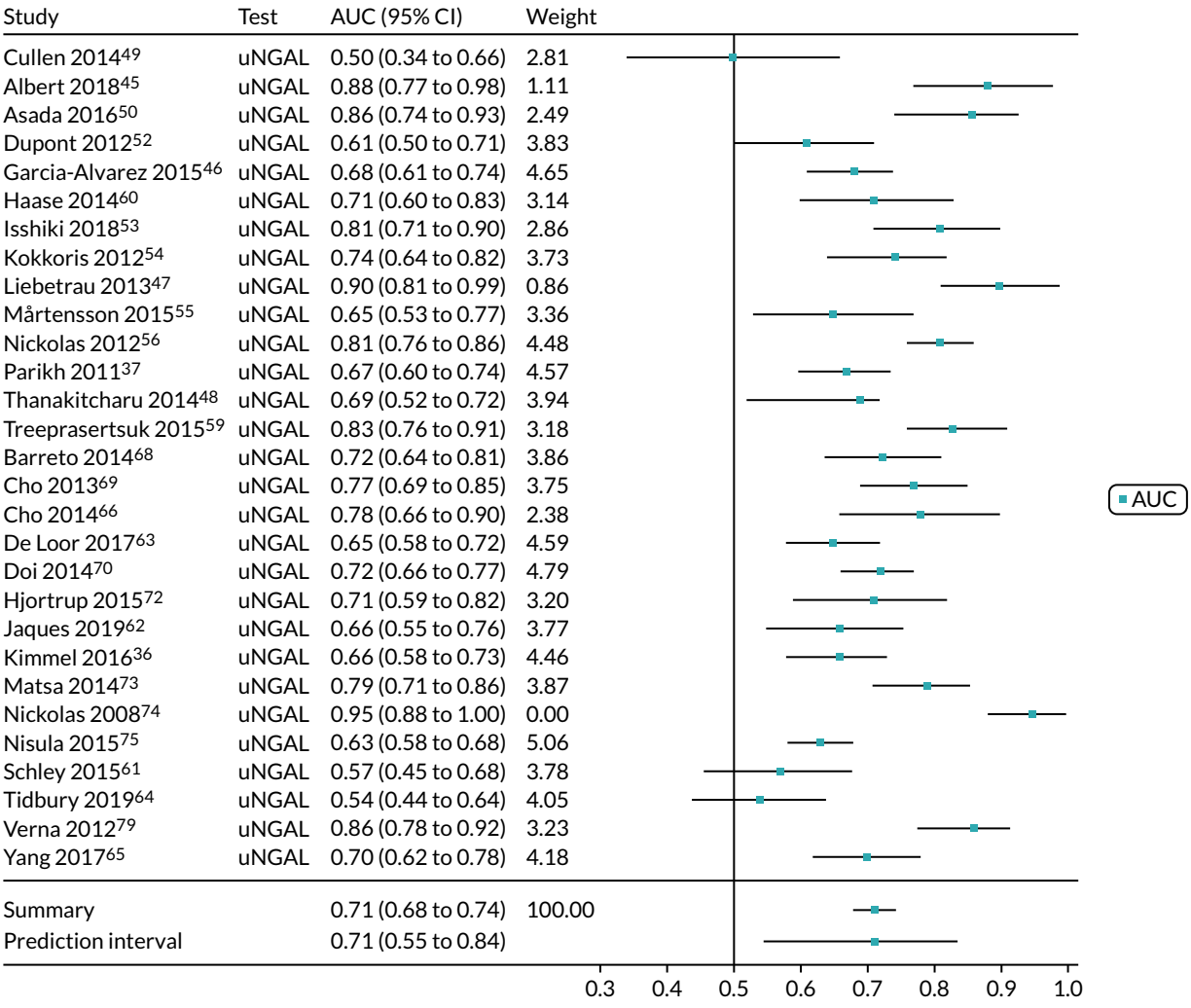

FIGURE 44 Urine NGAL (ARCHITECT and BioPorto): all settings (adult population). uNGAL, urine NGAL.

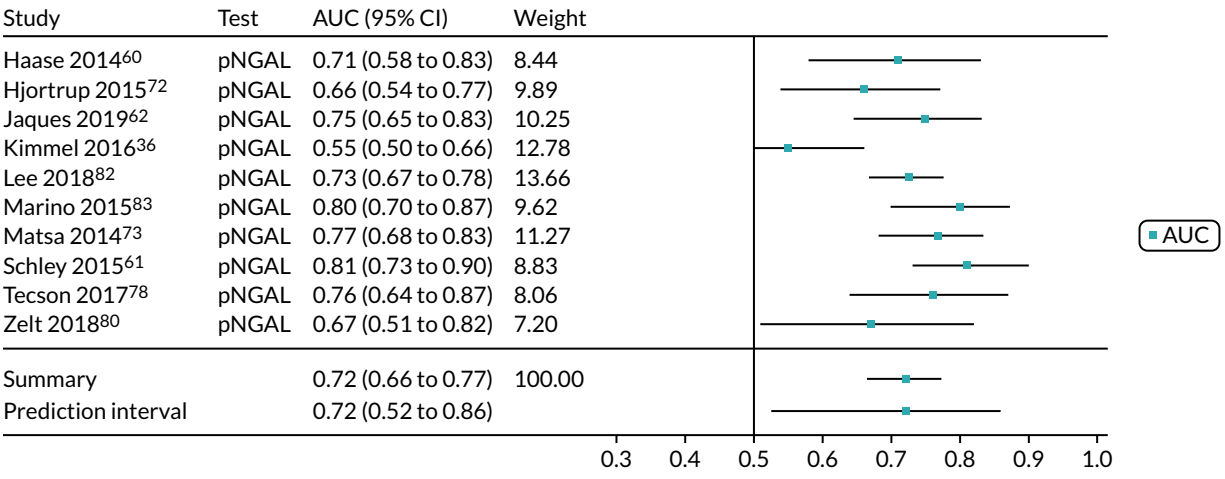

FIGURE 45 BioPorto plasma NGAL: all settings (adult population). pNGAL, plasma NGAL.

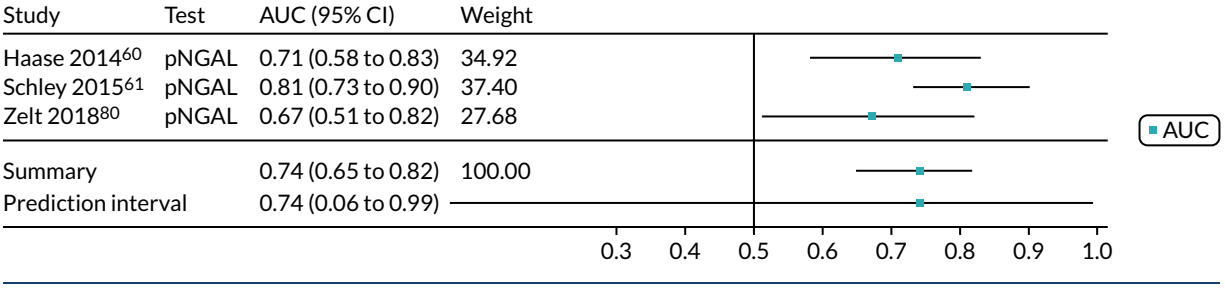

FIGURE 46 BioPorto plasma NGAL: cardiac surgery (adult population). pNGAL, plasma NGAL.

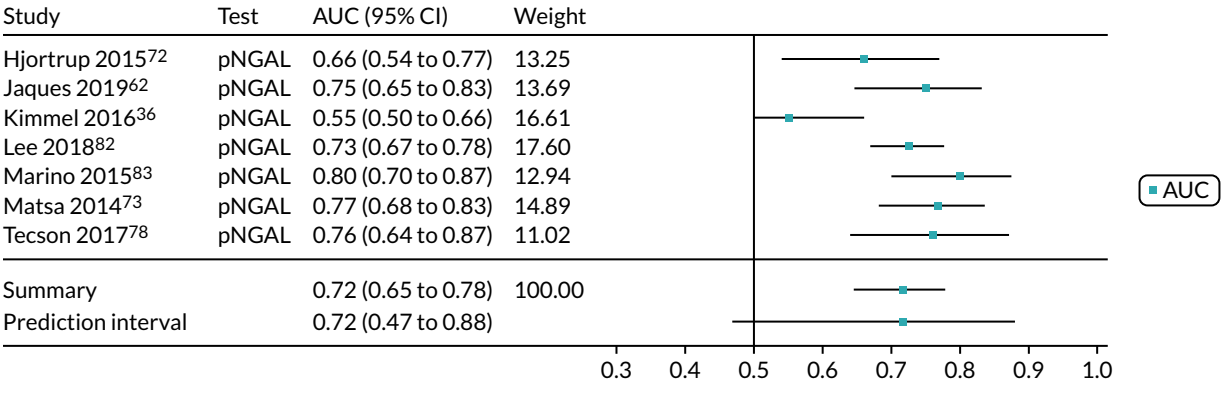

FIGURE 47 BioPorto plasma NGAL: critical care (adult population). pNGAL, plasma NGAL.

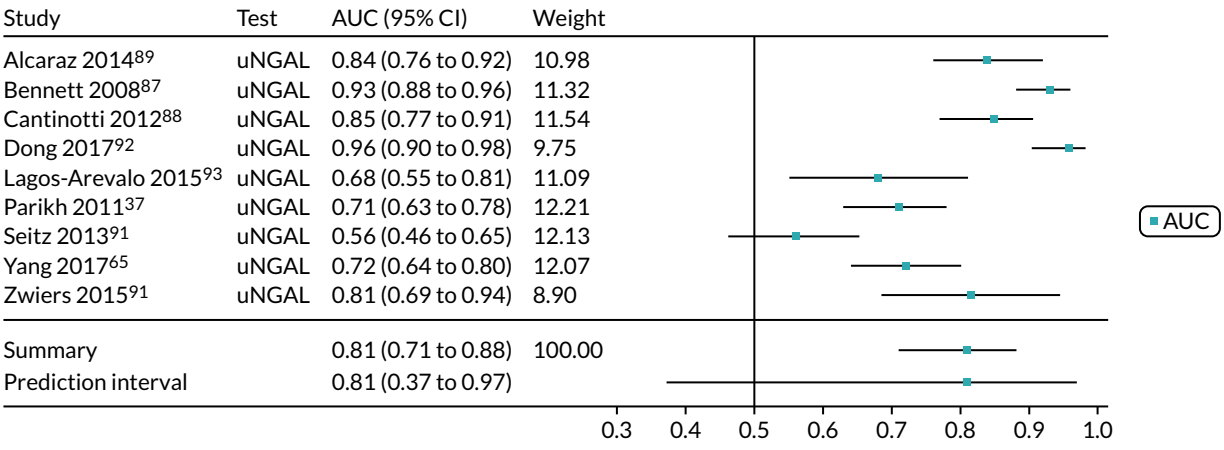

FIGURE 48 Urine NGAL (ARCHITECT and BioPorto): all settings (child population). uNGAL, urine NGAL.

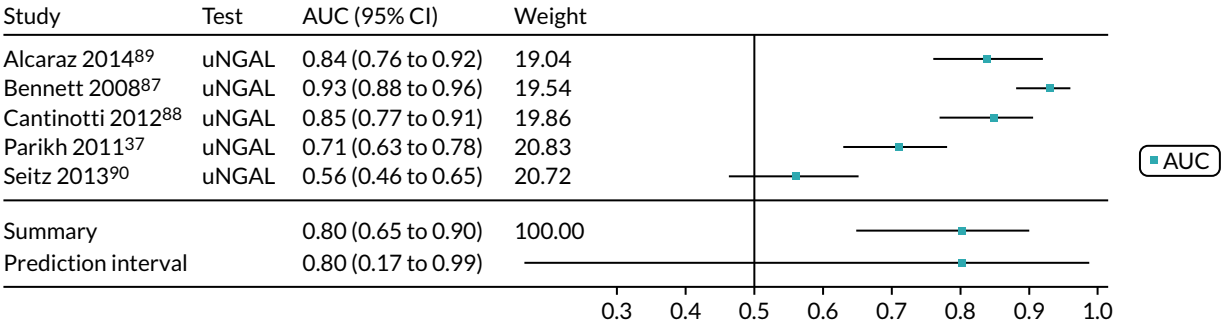

FIGURE 49 ARCHITECT urine NGAL: cardiac surgery (child population). uNGAL, urine NGAL.

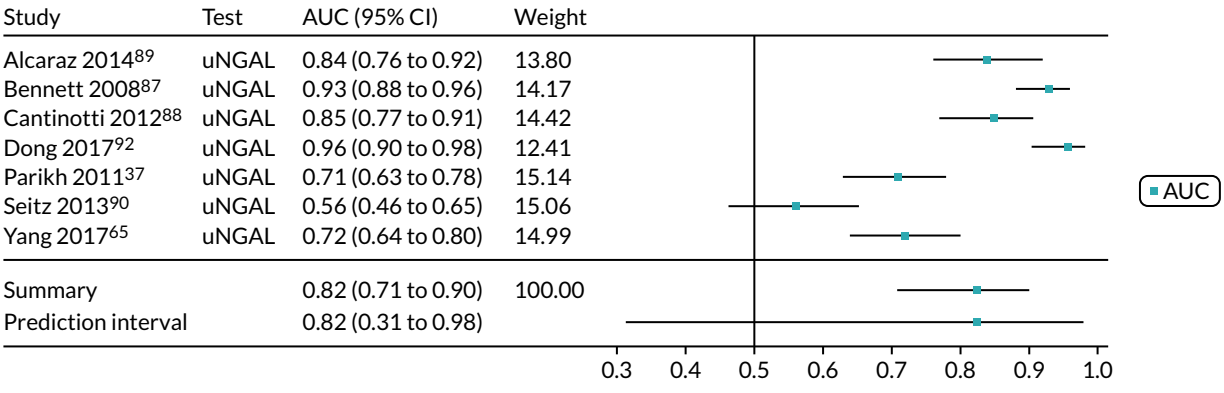

FIGURE 50 Urine NGAL (ARCHITECT and BioPorto): all cardiac surgery (child population). uNGAL, urine NGAL.

Appendix 11 Forest plots of area under the curve meta-analyses for prediction of worsening of acute kidney injury, mortality and need for renal replacement therapy

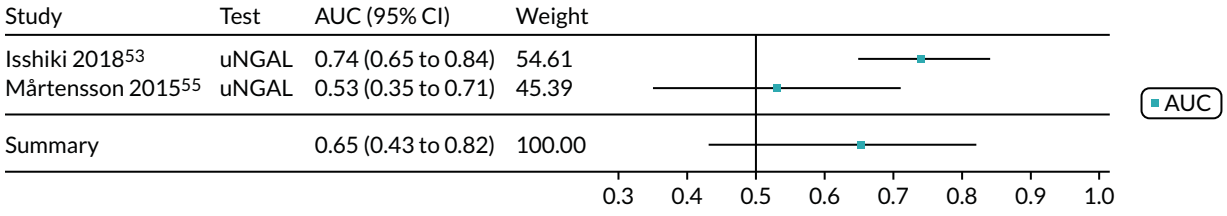

FIGURE 51 Prediction of AKI among adults: ARCHITECT urine NGAL – critical care setting. uNGAL, urine NGAL.

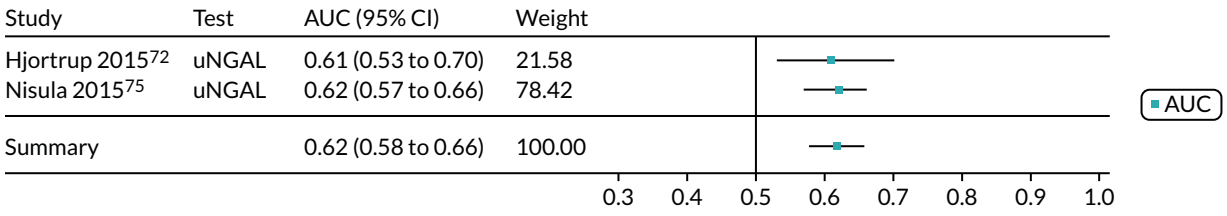

FIGURE 52 Prediction of mortality among adults: BioPorto urine NGAL – critical care setting. uNGAL, urine NGAL.

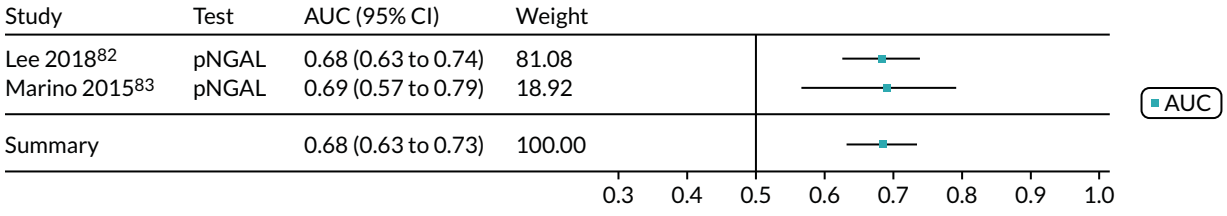

FIGURE 53 Prediction of mortality among adults: BioPorto plasma NGAL – critical care setting. pNGAL, plasma NGAL.

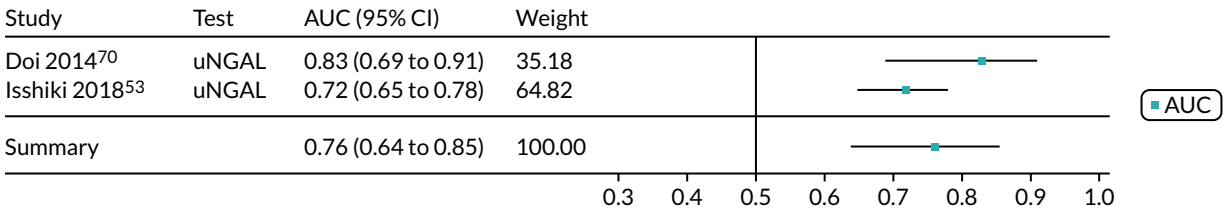

FIGURE 54 Prediction of mortality among adults: urine NGAL (ARCHITECT and BioPorto) – critical care setting. uNGAL, urine NGAL.

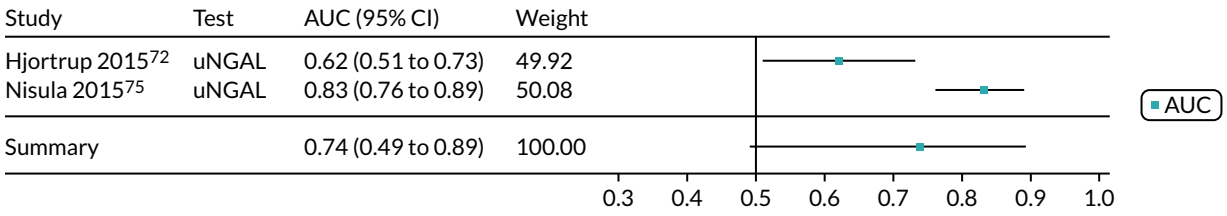

FIGURE 55 Prediction of RRT among adults: BioPorto urine NGAL – critical care setting. uNGAL, urine NGAL.

Appendix 12 Addition of biomarkers to existing clinical models

TABLE 30 Addition of biomarkers to existing clinical models for prediction of development or worsening of AKI, mortality and need for RRT

Study, geographical location, biomarker, setting	Diagnosis or prediction	AUC (95% CI or SEM)			OR (95% CI)			Adjustment of the model
		Clinical model	Biomarker	Biomarker plus clinical model	Clinical model	Biomarker	Biomarker plus clinical model	
AKI								
Kashani 2013,[34] North America and Europe, NephroCheck, critical care – mixed population	Diagnosis of AKI within 12 hours Events: 101	0.81 (0.76 to 0.85)[a]	0.80 (0.75–0.84)[a]	0.87 (0.84 to 0.90)[a]	NR	NR	NR	Age, serum creatinine level, APACHE III score, hypertension, nephrotoxic diagnosis, liver disease, diabetes mellitus and CKD
Bihorac 2014,[29] USA, NephroCheck, critical care – mixed population	Diagnosis of AKI within 12 hours Events: 71	0.70 (0.63 to 0.76); $p < 0.001$	NR	0.86 (0.80 to 0.90); $p < 0.001$	NR	NR	NR	Included clinical variables for which a univariate association with AKI at $p < 0.1$ was found. Also included serum creatinine and the KDIGO criteria. They used a univariate significance level of < 0.1. Final model seems to include enrolment serum creatinine level, APACHE III score (non-renal), BMI
Parikh 2011,[37] North America, ARCHITECT urine NGAL, cardiac surgery	Diagnosis of AKI within 72 hours Events: 60	0.69 (0.04)	0.67 (0.04)	0.73 (0.04); $p = 0.12$	NR	NR	NR	Variables included in the clinical model were age, sex, white ethnicity, CPB time of > 120 minutes, non-elective surgery, pre-operative eGFR, diabetes, and hypertension. The improvement of risk prediction with the addition of biomarkers to the clinical model was determined using the NRI index and the IDI
Schley 2015,[61] Germany, BioPorto urine and plasma NGAL, cardiac surgery	Diagnosis of AKI within 72 hours of surgery Events: 37	0.76; $p < 0.001$	• Plasma NGAL: 0.81 (0.73 to 0.90); $p < 0.001$) • Urine NGAL: 0.63 (0.51 to 0.74); $p < 0.001$	• Plasma NGAL: 0.80; $p < 0.001$ • Urine NGAL 0.76; $p < 0.001$	NR	NR	NR	The clinical model was based on the European System for Cardiac Operative Risk Evaluation (EuroSCORE). A multivariable analysis was conducted to analyse the combination of biomarkers and clinical scores

Study, geographical location, biomarker, setting	Diagnosis or prediction	AUC (95% CI or SEM)			OR (95% CI)			Adjustment of the model
		Clinical model	Biomarker	Biomarker plus clinical model	Clinical model	Biomarker	Biomarker plus clinical model	
Kokkoris 2012,[54] Greece, ARCHITECT urine NGAL, critical care – mixed population	AKI detection within 7 days Events: 36	0.76 (0.66 to 0.83)	0.78 (0.68 to 0.85)	0.85 (NR); $p = 0.03$	NR	NR	NR	The most efficient reference clinical model for AKI prediction included the SAPS III and INR. Addition of plasma NGAL to the clinical model improved the AUC. However, the combination of plasma NGAL and serum creatinine showed the best AUC (0.86; $p = 0.04$)
Isshiki 2017,[53] Japan, ARCHITECT urine NGAL, critical care – mixed population	Worsening kidney function within 7 days Events: 58	0.85 (0.77 to 0.92)	0.74 (0.65 to 0.84)	0.85 (0.77 to 0.92)	NR	NR	NR	Variables included in the clinical model for the prediction of newly developed AKI were age, sex, APACHE II score, sepsis, baseline eGFR, serum creatinine level at ICU admission
Lee 2018,[82] the Republic of Korea, BioPorto plasma NGAL, critical care – mixed population	Development of AKI Events: 111	NR	NR	NR	5.31 (0.67 to 11)	0.6 (0.2 to 1.7); $p = 0.314$	1.004 (1.002 to 1.006); $p = 0.001$	Adjusting for potential confounders as determined by the univariate analyses. The adjusted model includes age, CHF, diabetes mellitus, adrenaline dosage, time to ROSC, Glasgow Coma Scale score, lactate, PaO_2 and $PaCO_2$ after ROSC, initial creatinine level, SOFA score, CVI and NGAL level. Of these, only SOFA renal, NGAL and CVI were significant, but a final model was not selected
Alcaraz 2014,[89] Spain, ARCHITECT urine NGAL, cardiac surgery – child population	Prediction of AKI Events: 36	0.85 (0.78 to 0.93)	0.84 (0.76 to 0.92)	0.91 (0.84 to 0.97); $p = 0.057$	NR	NR	NR	A multivariable logistic regression analysis was used to assess the predictors of AKI and the performance of the model. The clinical model (age, CPB time, total circulatory arrest use, and RACHS-1 score) was determined using backward elimination

continued

TABLE 30 Addition of biomarkers to existing clinical models for prediction of development or worsening of AKI, mortality and need for RRT (*continued*)

Study, geographical location, biomarker, setting	Diagnosis or prediction	AUC (95% CI or SEM)			OR (95% CI)			Adjustment of the model
		Clinical model	Biomarker	Biomarker plus clinical model	Clinical model	Biomarker	Biomarker plus clinical model	
Mortality								
Isshiki 2017,[53] Japan, ARCHITECT urine NGAL, critical care – mixed population	In-hospital mortality (38 patients died)	0.79 (0.71 to 0.86)	0.72 (0.65 to 0.78)	0.79 (0.71 to 0.86)	NR	NR	NR	Variables included in the clinical model for the prediction of mortality were age, sex, APACHE II score, sepsis. Variables were derived from univariate logistic regression analysis
Verna 2012,[79] USA, BioPorto urine NGAL, critical care – mixed population (cirrhosis)	In-hospital mortality (15 patients died)	NR	NR	NR	2.95 (1.68 to 5.61)	2.00 (1.36 to 2.94)	6.05 (1.35 to 27.2)	Adjusted for age, serum creatinine level, MELD score of > 17, hepatorenal syndrome

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CHF, congestive heart failure; CPB, cardiopulmonary bypass; CVI, cumulative vasopressor index; IDI, Integrated Discrimination Index; INR, international normalised ratio; MELD, Model for End-Stage Liver Disease; NR, not reported; NRI, net reclassification improvement; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; RACHS-1, Risk Adjustment for Congenital Heart Surgery; ROSC, return of spontaneous circulation; SAPS III, Simplified Acute Physiology Score III; SEM, standard error of the mean; SOFA, Sequential Organ Failure Assessment.
a C-statistics.

Appendix 13 Assessment of cost-effectiveness: additional tables

TABLE 31 Test costs

Cost element	NephroCheck	BioPorto urine and plasma NGAL	ARCHITECT urine NGAL	Alinity i[a] urine NGAL
Platform				
Astute140 Meter (NephroCheck only)				
Cost (£)	3000.00	–	–	–
Expected service life (years)	5.00	–	–	–
Equivalent annual cost (£)	664.44[b]	–	–	–
Subtotal: platform (cost per test) (£)	0.53[c]	–	–	–
Subtotal: equipment (cost per test) (£)	49.80[d]	20.00[e]	25.71[f]	28.29[g]
Subtotal: maintenance/ consumables (cost per test)[h] (£)	4.23	1.90	3.51	3.51
Staff resource use				
Time to conduct test (sample preparation plus time to get result) (minutes)	20	20	20	20
Time to interpret test (minutes)	5	5	5	5
Prepare urine sample: band 5 nurse (minutes)	15	15	15	15
Bring urine sample to laboratory: porter (minutes)	15	15	15	15
Cost of staff time for testing (per test) (£)	14.67	14.67	14.67	14.67
Cost of staff time for interpreting (per test) (£)	6.89	6.89	6.89	6.89
Cost of staff time to prepare urine sample (per test) (£)	9.25	9.25	9.25	9.25
Cost of delivery to laboratory (per test) (£)	6.82	6.82	6.82	6.82
Subtotal: staff costs (per test) (£)	37.62	37.62	37.62	37.62
Staff training[i]				
Assumed average turnover (years)	5	5	5	5
Time for training (minutes)	90	30	30	30
Total training costs (£)	438.00	146.00	146.00	146.00
Equivalent annual cost of total training (£)	97.01	32.34	32.34	32.34
Equivalent annual cost of total training per test (£)	0.08	0.03	0.03	0.03

continued

TABLE 31 Test costs (*continued*)

Cost element	NephroCheck	BioPorto urine and plasma NGAL	ARCHITECT urine NGAL	Alinity i[a] urine NGAL
Total cost (£)	92.26	59.55	66.87	69.44

a The cost of Alinity i is not included in the model because none of the studies in the clinical effectiveness review evaluated the Alinity i urine NGAL.
b £644.44 = £3000/{[1 – (1.035)$^{-5}$]/0.035}, where 3.5% is the discount rate applied to the platform cost.
c Assuming that the number of tests performed annually is 1253 (Hall *et al.*[97]), based on throughput at the ICU department of St James's University Hospital, Leeds. This is likely to be a conservative estimate of throughput that might be observed outside the ICU department and probably reflects the maximum bound of the allocated platform cost per test.
d NephroCheck single-use test cartridge.
e BioPorto NGAL test.
f ARCHITECT urine NGAL Test Reagent 100-test kit (produces 80 tests) (source: company submitted request for information to NICE).
g Alinity i urine NGAL Test Reagent 100-test kit (produces 80 tests) (source: company submitted request for information to NICE).
h The detailed calculations on the maintenance and consumables costs are provided in *Appendix 13*, *Table 34*.
i Staff training time for all tests was based on information provided by the manufacturers when possible. For NephroCheck, training takes 1–2 hours; therefore, we assumed that, on average, training would take 1.5 hours (NICE's request for information document). Training was assumed to take 30 minutes for all NGAL tests because the manufacturers stated that only 'limited training' (BioPorto) or time 'to read the instructions for use' (ARCHITECT) would be required. The total training cost was based on the total cost of training staff who would be conducting and interpreting the test results.

TABLE 32 Care bundle costs

Resource use	Assumptions	Care bundle cost (£)	Source
Intravenous fluids			
Intravenous sodium chloride, 0.9% infusion, 2-l bags (Terumo BCT Ltd, Larne, UK)	1 l per hour for 3 hours, thereafter 2 l per day for 3 days (five 2-l bags total)	22.14	Clinical expert opinion,[a] BNF 2019[126]
Band 6 nurse	Initial fluid: 10 minutes	5.33	Clinical expert opinion,[a] PSSRU 2018[124]
Band 6 nurse	Fluid replacement: 5 minutes	10.67	Clinical expert opinion,[a] PSSRU 2018[124]
Nephrologist review			
Hospital-based doctor, medical consultant	30 minutes	54.00	Clinical expert opinion,[a] PSSRU 2018[124]
Pharmacist review			
Pharmacist, band 6 (AfC)	20 minutes	15.00	Clinical expert opinion,[a] PSSRU 2018[124]
Stop blood pressure medication			
N/A	Stop blood pressure medication for 3 days	–0.78	Clinical expert opinion,[a] BNF 2019.[126] Based on the annual cost of blood pressure medication (see *Table 36*), and calculated over 3 days
Total cost for 3 additional days of the KDIGO care bundle		106.36	

AfC, Agenda for Change; BNF, *British National Formulary*; N/A, not applicable.
a Simon Sawhney and Callum Kaye, personal communication.

TABLE 33 Summary of studies identified from supplementary searches of the literature post Hall *et al.*[97]

First author	Year	Population	Country	Utility measure	Valuation set	Sample size (*n*)	Age (years)[a]	Male (%)	Utility values reported	Mean	Median	SE	SD	95% CI	IQR
Afiatin[151]	2017	ESRD with PD and HD	Indonesia	EQ-5D-3L	Thailand	68	≥ 18	55.9	PD (no comp)	0.82		0.03			
									HD (no comp)	0.70		0.04			
									PD (+comp)	0.31		0.09			
									HD (+comp)	0.37		0.11			
Chang[152]	2016	ESRD with PD and HD	Taiwan	EQ-5D-3L	UK	Total: 1687	Total: NR								
						HD: 1403	HD: mean 57.1 (SD 13.6)	HD: 49.9	HD	0.83		0.19			
						PD: 284	PD: mean 46.7 (SD 13.2)	PD: 51.1	PD	0.90		0.16			
Cho[153]	2018	CKD requiring dialysis	The Republic of Korea	EQ-5D-3L	The Republic of Korea	50	NR	NR	CKD, undergoing dialysis	0.63		0.04			
Eriksson[154]	2016	CKD patients (anaemic and non-anaemic) with/without dialysis	France, Germany, Italy, Spain, UK	EQ-5D-3L	Unclear, presume UK	Total: 1177 • Non-anaemic: 313 (27%) • Anaemic: 864 (73%)	Mean 63.7 (SD 15.1)	60	Non-anaemic: (27%)	Non-anaemic: (27%)			Non-anaemic: (27%)		
									CKD stage 3	0.85			0.21		
									CKD stage 4	0.81			0.22		
									Dialysis	0.74			0.29		
									Total	0.83			0.23		
									Anaemic: (73%)	Anaemic: (73%)			Anaemic: (73%)		
									CKD stage 3	0.78			0.29		
									CKD stage 4	0.71			0.28		
									Dialysis	0.70			0.32		
									Total	0.72			0.31		
El Filali[155]	2017	Chronic HD patients	Morocco	EQ-5D-3L	Unclear	103	Mean 49.7 (SD 14.7)	45.60	HD	0.41			0.36		
Hishii[156]	2018	Chronic HD patients	Japan	EQ-5D-3L	Unclear	60	Mean 71.1 (SD 12)	51.67	HD	0.688			0.233		
Jardine[157]	2017	Maintenance HD	Australia (28%), Canada (6%), China (62%), New Zealand (4%)	EQ-5D-3L	Unclear	200	Mean 51.8 (SD 12.1)	69.50	HD	0.78			0.24		

continued

TABLE 33 Summary of studies identified from supplementary searches of the literature post Hall *et al.*[97] (*continued*)

First author	Year	Population	Country	Utility measure	Valuation set	Sample size (*n*)	Age (years)[a]	Male (%)	Utility values reported	Mean	Median	SE	SD	95% CI	IQR
Jesky[158]	2016	Pre-dialysis CKD (as per NICE guidance[159])	UK	EQ-5D-3L	UK	• All CKD: 745 • G1/2: 29 • G3a: 45 • G3b: 173 • G4: 423 • G5: 75	[Median (IQR) values] • All CKD: 64 (50–76) • G1/2: 41 (34.5–55.5) • G3a: 55 (45–66.5) • G3b: 61.5 (48.3–73.8) • G4: 69 (54–75.5) • G5: 64 (53.5–75.5)	• All CKD: 60.80 • G1/2: 65.52 • G3a: 71.11 • G3b: 66.86 • G4: 59.00 • G5: 49.35	All CKD		0.74				0.66–0.88
									G1/2		0.85				0.70–1
									G3a		0.80				0.69–1
									G3b		0.80				0.68–1
									G4		0.74				0.62–0.85
									G5		0.73				0.62–1
Katayama[160]	2016	Chronic HD patients	Japan	EQ-5D-3L	Unclear	Baseline: 71	Mean 70.9 (SD 10.6)	58	HD (baseline)	0.720			0.224		
						1-year follow-up: 43	Mean 69.1 (SD 10.8)	60	HD (1 year)	0.790			0.181		
Kilshaw[161]	2016	ESRD (CM)	UK	EQ-5D-5L	None	41	Mean 82.7 (SD 5.7)	56	NR	NR	NR	NR	NR	NR	NR
Kularatna[162]	2019	CKD	Sri Lanka	EQ-5D-3L	UK	Early stage: 254	Median: ≈ 41	56.10	Early	0.588			0.30		
						Stage 4: 614			Stage 4	0.566			0.42		
						Stage 5: 151			Stage 5	0.467			0.42		
						Dialysis: 38			Dialysis	0.126			0.39		
Lee[163]	2016	Early- to mid-stage CKD	The Republic of Korea	EQ-5D-3L	The Republic of Korea	CKD stage 3/4: 75	Mean 61.4 (SD 9.9)	41	CKD stage 3/4	0.87			0.19		
						CAPD: 75	Mean 59.1 (SD 12.9)	41	CAPD	0.90			0.15		
Li[164]	2017	Kidney transplant recipients and waiting list	UK	EQ-5D-5L	UK value set	Transplant recipients: 512	Median: ≈ 50	60	Waiting list	0.773		0.005			
						Waiting list: 1704	Median: ≈ 50	58	Transplant (inc)	0.054		0.011			
McNoe[165]	2019	ESRD with or without dialysis	New Zealand	EQ-5D-3L	VAS only	No dialysis: 56	≥ 65	66.1	No dialysis		70				50–80
						HD: 109		57.8	HD		70				60–80
						PD: 60		73.3	PD		67.5				70–80
Nagasawa[166]	2018	Patients receiving dialysis	Japan	EQ-5D-3L	Japan	51	Mean 67.7 (SD 12.1)	70.60	Dialysis patients with CKD or ESRD	0.779			0.193		

First author	Year	Population	Country	Utility measure	Valuation set	Sample size (*n*)	Age (years)[a]	Male (%)	Utility values reported	Mean	Median	SE	SD	95% CI	IQR
Nguyen[136]	2018	CKD and ESRD	UK	EQ-5D-3L	UK	CKD stage 1: 56	Mean 44.6 (SD 18.2)	33.9	CKD stage 1	Base NR				Base NR	
						CKD stage 2: 106	Mean 60 (SD 17.4)	50.0	CKD stage 2	−0.112				−0.189 to −0.034	
						CKD stage 3a: 155	Mean 65.3 (SD 14.8)	46.5	CKD stage 3a	−0.062				−0.128 to 0.005	
						CKD stage 3b: 35	Mean 74.1 (SD 13.4)	60.0	CKD stage 3b	−0.185				−0.299 to −0.071	
						CKD stage 4/5: 5	Mean 72.2 (SD 10.3)	40.0	CKD stage 4/5	−0.284				−0.408 to −0.160	
Schlackow[167]	2017	Moderate to advanced CKD	UK	EQ-5D-3L	UK	6356	Mean 62 (SD 12)	63	Regression						
									Mean (intercept)	0.86				0.84 to 0.88	
									Male	0.06				0.05 to 0.07	
									Age + 10 years	−0.05				−0.05 to −0.04	
									PFKT	−0.07				−0.11 to −0.03	
									Dialysis	−0.06				−0.07 to −0.04	
Sekercioglu[168]	2017	CKD	Canada	SF-6D	Canada	All: 303	Mean 62.7 (SD 14.5)	58.8	All CKD	0.720			0.110		
						Dialysis: 101	Mean 60.6 (SD 14.4)	57.0	Dialysis	0.670			0.110		
						Non-dialysis: 202	Mean 63.8 (SD 14.4)	61.0	No dialysis	0.740			0.100		
Senanayake[169]	2019	Pre-dialysis patients	Sri Lanka	EQ-5D-3L	Sri Lanka	1036	Median: ≈ 60	62.40	Pre-dialysis CKD	0.52			0.33		
Shah[170]	2019	ESRD (dialysis or CM)	UK and Australia	SF-6D	UK	Total: 129	≥ 75	69	Total	0.62			0.14		
						Dialysis: 83		59	Dialysis	0.61			0.13		
						CM: 46		65	CM	0.65			0.15		
Shimizu[171]	2018	HD patients	Japan	EQ-5D-5L	Japan	All: 717	Mean 72.9 (SD 6.5)	62.50	All HD	0.738			0.207		
						Aged 60–69 years: 278			Aged 60–69 years	0.784			0.179		
						Aged 70–79 years: 311			Aged 70–79 years	0.744			0.202		
						Aged ≥ 80 years: 118			Aged ≥ 80 years	0.616			0.231		

continued

TABLE 33 Summary of studies identified from supplementary searches of the literature post Hall *et al.*[97] (*continued*)

First author	Year	Population	Country	Utility measure	Valuation set	Sample size (*n*)	Age (years)[a]	Male (%)	Utility values reported	Mean	Median	SE	SD	95% CI	IQR
Snowsill[172]	2017	Kidney transplant recipients	UK	EQ-5D-3L	UK	N/A	N/A	N/A	Regression			NR			
									Mean (intercept)	0.968					
									Age	−0.002					
									Age sq	−0.000					
									Male	0.023					
									FG	−0.053					
									HD	−0.277					
									PD	−0.264					
									PTDM	−0.060					
Tang[173]	2017	ESRD	Taiwan	EQ-5D-5L	Japan	APD: 117	NR	NR	APD	0.82			0.19		
						CAPD: 129			CAPD	0.82			0.21		
Thaweethamcharoen[174]	2019	Patients receiving PD	Thailand	EQ-5D-5L	Thailand	64	Mean 63.44 (SD 16.57)	68.75	PD	0.801			0.228		
Van Loon[175]	2019	ESRD	The Netherlands	EQ-5D-3L	Dutch	CM: 89	Mean 82 (SD 6)	NR	CM	0.77			0.21		
						Dialysis (23% PD): 192	Mean 75 (SD 7)		Dialysis	0.82			0.18		
Wee[176]	2016	Pre dialysis, CKD stages 3–5	Singapore	EQ-5D-3L	USA	309	Mean 62.6 (SD 11.06)	58.20	CKD stages 3–5, pre dialysis	0.8			0.24		
Wolfgram[177]	2017	Hypertensive CKD and non-CKD patients	USA	EQ-5D-3L	USA	All: 2620	Mean 79.85 (SD 3.99)	62.1	All	0.85		0.00	0.13		
						Non-CKD: 1459	Mean 79.39 (SD 3.73)	62	Non-CKD	0.85		0.01	0.13		
						CKD: 1161	Mean 80.42 (SD 4.23)	62.3	CKD	0.84		0.01	0.13		
						eGFR of ≥ 60 ml/minute/1.73 m^2 (CKD stage 2 or better): 372	NR	NR	eGFR of ≥ 60 ml/minute/1.73 m^2	0.85					
						eGFR of 44–60 ml/minute/1.73 m^2 (CKD stage 3a): 781	NR	NR	eGFR of 44–60 ml/minute/1.73 m^2	0.85					
						eGFR of < 44 ml/minute/1.73 m^2 (CKD stage 3b or worse): 1449	NR	NR	eGFR of < 44 ml/minute/1.73 m^2	0.82					

First author	Year	Population	Country	Utility measure	Valuation set	Sample size (*n*)	Age (years)[a]	Male (%)	Utility values reported	Mean	Median	SE	SD	95% CI	IQR
Wong[178]	2019	ESRD on dialysis	China	SF-6D	China/ Hong Kong	All: 397	Mean 57.3 (SD 12.7)	61.9	All dialysis	0.766			0.111		
						PD: 103	Mean 63.1 (SD 12.7)	61.2	PD	0.778			0.110		
						Hospital HD: 135	Mean 56.4 (SD 12.6)	57.0	Hospital HD	0.731			0.114		
						Home HD: 41	Mean 47.9 (SD 8.5)	67.4	Home HD	0.778			0.091		
						Community HD: 118	Mean 56.8 (SD 11.6)	66.1	Community HD	0.790			0.107		
Yang[179]	2019	ESRD on dialysis	Singapore	SF-12 mapped to EQ-5D-3L	Unclear	Total: 266	Mean 59.3 (SD 12.5)	45.5	Total	0.59			0.21		
						CAPD: 145	Mean 60.8 (SD 11.4)	45.5	CAPD	0.58			0.21		
						APD: 121	Mean 57.4 (SD 13.6)	45.5	APD	0.60			0.22		
Yang[180]	2018	Dialysis	France, Germany, Italy, Spain Singapore	EQ-5D-3L, EQ-5D-5L	Country-specific value sets	France: 299	Mean 66.6 (SD 14.1)	62.5	France	0.622			0.383		
						Germany: 413	Mean 61.8 (SD 14.4)	57.1	Germany	0.796			0.224		
						Italy: 278	Mean 60.8 (SD 13.4)	54.7	Italy	0.864			0.185		
						Spain: 225	Mean 60.6 (SD 16.4)	60.0	Spain	0.746			0.292		
						Singapore (EQ-5D-5L): 163	Mean 60.5 (SD 11.5)	52.2	Singapore	0.621			0.447		
Zyoud[181]	2016	ESRD on HD	Palestine	EQ-5D-5L	Unclear	Aged ≥ 60: 97	Mean NR	52.1	ESRD	0.17			0.4		
Park[182]	2016	CKD	The Republic of Korea	EQ-5D-3L	The Republic of Korea	All: 46,676	45.4 (SE 0.1)	49.5	All	0.943		0.001			
						No CKD: 44,108	44.6 (SE 0.2)	49.9	No CKD	0.946		0.001			
						CKD stage 1: 793	38.7 (SE 2.8)	42.8	Stage 1	0.955		0.011			
						CKD stage 2: 444	54.9 (SE 3.3)	56.6	Stage 2	0.901		0.017			
						CKD stage 3a: 1030	72.8 (SE 0.5)	42.6	Stage 3a	0.826		0.005			
						CKD stage 3b: 211	73.2 (SE 1.1)	44.9	Stage 3b	0.787		0.011			
						CKD stage 4/5 (ESRD): 90	64.0 (SE 1.8)	44	Stage 4/5	0.793		0.018			

Age sq, age squared; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CM, conservative management; comp, complication; EQ-5D-3L, EuroQol-5 Dimensions, three-level version; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; FG, functioning graft; HD, haemodialysis; inc, increment; IQR, interquartile range; N/A, not applicable; NR, not reported; PD, peritoneal dialysis; PFKT, previous failed kidney transplant; PTDM, post-transplantation diabetes mellitus; SE, standard error; SF-6D, Short Form questionnaire-6 Dimensions; SF-12, Short Form questionnaire-12 items; VAS, visual analogue scale.

Note
G1–G5 are CKD classifications based on eGFR.

TABLE 34 Maintenance cost and consumables for the different tests

Maintenance/consumables	Price (£)	Cost per test (£)	Formula
NephroCheck			
Paper roll	2.50	0.10	£2.50/number of tests in kit (= 25 tests)
Liquid quality control (one per kit)	100.00	4.00	£100/number of tests in kit (= 25 tests)
Electronic quality control (every 6 months)	80.00	0.13	£80 × 2/number of tests performed per year in hospital laboratory (= 1253, in St. James's University Hospital, Leeds (source: Hall *et al.*[97])
BioPorto			
NGAL calibrator	385.00	1.28	£385/number of tests in kit (= 300)
NGAL control kit	185.00	0.62	£185/number of tests in kit (= 300)
ARCHITECT			
ARCHITECT urine calibrator kit	165.00	2.06	£165/number of tests a kit can produce (= 80)
ARCHITECT urine control kit	115.00	1.44	£115/number of tests a kit can produce (= 80)
Reaction vessels and bulk solutions		0.01	Manufacturer estimation (sourced from NICE's request for information document)
Alinity i			
Alinity i urine calibrator kit	165.00	2.06	£165/number of tests a kit can produce (= 80)
Alinity i urine control kit	115.00	1.44	£115/number of tests a kit can produce (= 80)
Reaction vessels and bulk solutions		0.01	Manufacturer estimation (sourced from NICE's request for information document)

TABLE 35 Erythropoiesis-stimulating agent medication

Cost element	NeoRecormon® (epoetin beta; F. Hoffman-La Roche Ltd, Basel, Switzerland)	Aranesp® (darbepoetin alba; Amgen Inc., Thousand Oaks, CA, USA)	Source
Price per IU	£0.007	£0.007	BNF 2019[126]
	Haemodialysis	***Peritoneal dialysis***	
Proportion taking erythropoiesis-stimulating agents	92.6%	78.6%	UK Renal Registry (2019)[115]
Dose per week	8000 IU	4000 IU	UK Renal Registry (2019)[115]
Cost per year	£2765	£1174	
Proportion on haemodialysis	87.5%	12.5%	
Total cost per year (based on the proportion on haemodialysis and peritoneal dialysis)	£2566		

BNF, *British National Formulary*; IU, international units.

TABLE 36 Blood pressure medication

Medication	Unit cost per year (£)	Proportion of patients on each type of medication	Total average cost (£)	Source
ACEIs	35.74	0.211	7.54	Tan *et al.* 2016,[183] BNF 2019[126]
ARBs	43.04	0.156	6.70	Tan *et al.* 2016,[183] BNF 2019[126]
Calcium-channel blockers	28.80	0.219	6.31	Tan *et al.* 2016,[183] BNF 2019[126]
Diuretics	21.92	0.487	10.66	Tan *et al.* 2016,[183] BNF 2019[126]
Beta blockers	15.52	0.248	3.85	Tan *et al.* 2016,[183] BNF 2019[126]
Alpha blockers	7.83	0.172	1.35	Tan *et al.* 2016,[183] BNF 2019[126]
Total average cost per year			36.41	Tan *et al.* 2016,[183] BNF 2019[126]

BNF, *British National Formulary*.

TABLE 37 Utility studies for AKI that were considered for economic modelling

First author	Year	Population	Country	Utility measure	Valuation set	Sample size (*n*)	Age (years)	Male (%)	Utility values reported	Mean	Median	SD	IQR
Ethgen[184]	2015	AKI, intensive care	USA	Decision-analytic modelling: unclear (sourced from literature)	Unclear	NR	NR	NR	CRRT (ICU)	0.13		NR	
									CRRT (DI)	0.84			
									CRRT (DD)	0.62			
									IRRT (ICU)	0.13			
									IRRT (DI)	0.84			
									IRRT (DD)	0.62			
Hall[97]	2018	AKI, intensive care	UK	Mix	Various	Mix			ICU	−0.402		0.20	
									Ward (post ICU)	0.44		0.31	
									Discharged (post ICU)	0.62		0.32	
									DD decrement	0.11		0.02	
Kaier[185]	2016	Surgical aortic valve replacement	Germany	EQ-5D-3L	German	• Baseline: 169 • Follow-up: 2294	82.15 (5.16)	NR	Baseline	0.78		0.23	
									Follow-up	0.77		0.25	
									AKIN 1	0.0659		NR	
									AKIN 2	−0.158		NR	
									AKIN 3	−0.177		NR	
Oeyen[186]	2015	Critically ill after AKI, need RRT	Belgium	EQ-5D-3L	None	141	57	66	None	NR		NR	

First author	Year	Population	Country	Utility measure	Valuation set	Sample size (*n*)	Age (years)	Male (%)	Utility values reported	Mean	Median	SD	IQR
Soliman[187]	2016	AKI patients in a mixed ICU population	The Netherlands	EQ-5D-3L	Dutch		[Median (IQR) values]						
						All: 2420	59 (47–69)	58.7	All		0.806		0.590–0.940
						No AKI: 1588	59 (47–69)	58.3	No AKI		0.810		0.640–1.000
						Risk: 456	59 (47–69)	57.0	Risk		0.778		0.570–0.890
						Injury: 253	59 (47–69)	61.7	Injury		0.772		0.470–0.870
						Failure: 123	59 (47–69)	63.4	Failure		0.666		0.370–0.850

CCRT, continuous renal replacement therapy; DD, dialysis dependence; DI, dialysis independence; EQ-5D-3L, EuroQol-5 Dimensions, three-level version; IQR, interquartile range; IRRT, intermittent renal replacement therapy; NR, not reported.

TABLE 38 Summary of post-Hall *et al.*[97] utility studies considered for the economic modelling

First author	Year	Population	Country	Utility measure	Valuation set	*n*	Age (years)	Proportion male (%)	Utility values reported	Mean	Median	SE	SD	95% CI	IQR
Chang[152]	2016	ESRD with PD and HD	Taiwan	EQ-5D-3L	UK	Total: 1687	Total: NR								
						HD: 1403	HD: mean 57.1 (SD 13.6)	HD: 49.9	HD	0.83			0.19		
						PD: 284	PD: mean 46.7 (SD 13.2)	PD: 51.1	PD	0.90			0.16		
Jesky[158]	2016	Pre-dialysis CKD (as per NICE guidance)[159]	UK	EQ-5D-3L	UK	All CKD: 745	All CKD: median 64 (IQR 50–76)	All CKD: 60.80	All CKD		0.74				0.66–0.88
						G1/2: 29	G1/2: median 41 (IQR 34.5–55.5)	G1/2: 65.52	G1/2		0.85				0.70–1
						G3a: 45	G3a: median 55 (IQR 45–66.5)	G3a: 71.11	G3a		0.80				0.69–1
						G3b: 173	G3b: median 61.5 (IQR 48.3–73.8)	G3b: 66.86	G3b		0.80				0.68–1
						G4: 423	G4: median 69 (IQR 54–75.5)	G4: 59.00	G4		0.74				0.62–0.85
						G5: 75	G5: median 64 (IQR 53.5–75.5)	G5: 49.35	G5		0.73				0.62–1
Kularatna[162]	2019	CKD	Sri Lanka	EQ-5D-3L	UK	Early stage: 254	Median approximate age 41	56.10	Early stage	0.588			0.30		
						Stage 4: 614			Stage 4	0.566			0.42		
						Stage 5: 151			Stage 5	0.467			0.42		
						Dialysis: 38			Dialysis	0.126			0.39		
Li[164]	2017	Kidney transplant recipients and waiting list	UK	EQ-5D-5L	UK	Waiting list: 1704	Median ≈ 50	58	Waiting list	0.773		0.005			
						Transplant recipients: 512	Median ≈ 50	60	Transplant (inc)	0.054		0.011			

First author	Year	Population	Country	Utility measure	Valuation set	*n*	Age (years)	Proportion male (%)	Utility values reported	Mean	Median	SE	SD	95% CI	IQR
Nguyen[136]	2018	CKD and ESRD	UK	EQ-5D-3L	UK	CKD stage 1: 56	Mean 44.6 (SD 18.2)	33.9	CKD stage 1	Base NR				Base NR	
						CKD stage 2: 106	Mean 60 (SD 17.4)	50.0	CKD stage 2	−0.112				−0.189 to −0.034	
						CKD stage 3a: 155	Mean 65.3 (SD 14.8)	46.5	CKD stage 3a	−0.062				−0.128 to 0.005	
						CKD stage 3b: 35	Mean 74.1 (SD 13.4)	60.0	CKD stage 3b	−0.185				−0.299 to −0.071	
						CKD stage 4/5: 5	Mean 72.2 (SD 10.3)	40.0	CKD stage 4/5	−0.284				−0.408 to −0.160	
Schlackow[167]	2017	Moderate to advanced CKD	UK	EQ-5D-3L	UK	6356	Mean 62 (SD 12)	63	Regression						
									Mean (intercept)	0.86				0.84 to 0.88	
									Male	0.06				0.05 to 0.07	
									Age + 10 years	−0.05				−0.05 to −0.04	
									PFKT	−0.07				−0.11 to −0.03	
									Dialysis	−0.06				−0.07 to −0.04	
Snowsill[172]	2017	Kidney transplant recipients	UK	EQ-5D-3L	UK	N/A	N/A	N/A	Regression			NR			
									Mean (intercept)	0.968					
									Age	−0.002					
									Age sq	−0.000					
									Male	0.023					
									FG	−0.053					
									HD	−0.277					
									PD	−0.264					
									PTDM	−0.060					

Age sq, age squared; EQ-5D-3L, EuroQol-5 Dimensions, three-level version; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; FG, functioning graft; HD, haemodialysis; inc, increment; IQR, interquartile range; N/A, not applicable; NR, not reported; PD, peritoneal dialysis; PFKT, previous failed kidney transplant; PTDM, post-transplantation diabetes mellitus; SE, standard error.

Note
G1–G5 are CKD classifications based on eGFR.

Appendix 14 Addendum to the External Assessment Group report

This addendum was prepared by the EAG in response to the consultation comments for the assessment, whereby several comments were made in relation to the test costs applied for NephroCheck and NGAL (BioPorto), the cost applied for fluids in the KDIGO preventative care bundle, and the RR parameters applied in the model for averting and reducing the severity of AKI. With respect to this last issue, the economic model used RR estimates derived from Meersch *et al.*,[110] when another study by Göcze *et al.*[116] was also available. Therefore, in this addendum we present three further scenario analyses that explore (1) alternative test costs for NephroCheck and NGAL (BioPorto), (2) alternative costs of fluids in those with a positive test who receive the care bundle and (3) alternative RRs for the aversion and redistribution of AKI in the cohort that receives the care bundle.

Additional cost-effectiveness results

The three additional scenario analyses are conducted on base case 1 (*Table 39*) and base case 2 (*Table 40*). The scenarios are labelled as 1R to 1T, and 2R to 2T.

In the first scenario analysis (1R and 2R), the alternative testing costs for NephroCheck and NGAL (BioPorto) were explored to address the company's (bioMérieux SA, Marcy-l'Étoile, France) concerns about the costing assumptions. The following assumptions were made in this alternative scenario, as suggested by bioMérieux:

- Excluding all capital cost (on the basis that the company provide the capital equipment without charge).
- Assuming the liquid quality control for NephroCheck is conducted monthly. The monthly test throughput is assumed to be ≈ 104 (= 1253/12), in which the test throughput of 1253 is based on throughput at an ICU department in a hospital in Leeds (St James's University Hospital) (Hall *et al.*[97]). The liquid quality control cost is therefore slightly cheaper at £1.91 {= [£100 + (2 × £49.8)]/(1253/12)}.
- Assuming wastage may occur for NGAL (BioPorto) owing to the 4-week shelf-life of the calibrator and test control kit once opened. This results in a slightly more expensive test maintenance cost of £5.46 [= (385 + 185)/(1253/12)] for NGAL (BioPorto).

The impact on the cost-effectiveness results is very limited and does not change the cost-effectiveness conclusions.

In the second scenario (1S and 2S), we apply a more expensive buffered solution for fluids given as part of the KDIGO care bundle. The more expensive solution was assumed to be Hartmann's solution, at a list price of £3.25 per litre [Baxter International Inc. (Deerfield, IL, USA), 2019, personal communication]. This resulted in a slightly greater care bundle cost (£7.11 greater care bundle cost overall) applied to those with a positive biomarker test result. However, the slightly greater care bundle cost had very little impact on the cost-effectiveness results.

In the third scenario (1T and 2T), the RR applied to the averted and redistributed cohort was equal to that reported in Göcze *et al.*[116] The RRs of having AKI versus no AKI, having AKI 1 given AKI, and having AKI 2/3 given AKI were 0.666, 1.347 and 0.509, respectively. Therefore, the effect sizes are larger than those reported in the Meersch *et al.* study,[110] which was used in the base case. Consequently, all the tests accrued greater QALYs and greater ICU cost savings in these scenarios, with all tests being dominant compared with standard care in base case 1. In base case 2, NephroCheck was the only dominant strategy.

TABLE 39 Additional scenario analyses on base case 1 (assuming that the NGAL tests can avert AKI)

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Base case 1								
Test 3 (BioPorto urine NGAL)	22,887	–	6.07332	–	–	Dominant	43.5	54.6
Test 2 (BioPorto plasma NGAL)	22,900	£14	6.07332	0.00001	£2,694,918	Dominant	11.1	47.6
Standard care (serum creatinine)	22,901	Dominated	6.07296	Dominated	Dominated	–	45.1	–
Test 4 (ARCHITECT urine NGAL)	22,912	Dominated	6.07328	Dominated	Dominated	£32,131	0.1	41.4
Test 1 (NephroCheck)	22,938	Dominated	6.07332	Dominated	Dominated	£101,456	0.2	31.9
1R: Alternative test costs for NephroCheck and NGAL (BioPorto)								
Test 3 (BioPorto urine NGAL)	22,746	–	6.074431	–	–	Dominant	39.6	52.5
Test 2 (BioPorto plasma NGAL)	22,758	£12	6.074439	0.000008	£1,621,578	Dominant	12.2	45.7
Standard care (serum creatinine)	22,760	Dominated	6.074090	Dominated	Dominated	–	46.8	–
Test 4 (ARCHITECT urine NGAL)	22,766	Dominated	6.074404	Dominated	Dominated	£16,592	0.9	42.6
Test 1 (NephroCheck)	22,789	Dominated	6.074438	Dominated	Dominated	£80,747	0.4	34.3
1S: Alternative solution for fluid assistance (Hartmann's solution)								
Test 3 (BioPorto urine NGAL)	23,121	–	6.071715	–	–	Dominant	39.3	51.5
Standard care (serum creatinine)	23,132	Dominated	6.071353	Dominated	Dominated	–	47.8	–
Test 2 (BioPorto plasma NGAL)	23,135	£14	6.071729	0.00001	£1,015,368	£9202	12.3	46.7
Test 4 (ARCHITECT urine NGAL)	23,146	Dominated	6.071686	Dominated	Dominated	£41,624	0.3	40.7
Test 1 (NephroCheck)	23,173	Dominated	6.071724	Dominated	Dominated	£112,505	0.3	31.4
1T: Alternative RR parameters (Gözce et al.[116])								
Test 3 (BioPorto urine NGAL)	23,079	–	6.082680	–	–	Dominant	49.3	67.1
Test 2 (BioPorto plasma NGAL)	23,091	£12	6.082690	0.000010	£1,158,117	Dominant	16.8	62.2
Test 4 (ARCHITECT urine NGAL)	23,107	Dominated	6.082632	Dominated	Dominated	Dominant	0.3	57.5
Test 1 (NephroCheck)	23,129	Dominated	6.082688	Dominated	Dominated	Dominant	0.9	47.9
Standard care (serum creatinine)	23,135	Dominated	6.082137	Dominated	Dominated	–	32.7	–

TABLE 40 Additional scenario analyses on base case 2 (assuming that the NGAL tests cannot avert AKI)

Scenario	Cost (£)	Incremental cost	QALY	Incremental QALY	ICER (incremental)	ICER vs. standard care	Probability (%) of being cost-effective at	
							£20,000	£20,000 vs. standard care
Base case 2								
Standard care (serum creatinine)	22,978	–	6.07277	–	–	–	64.5	–
Test 1 (NephroCheck)	23,016	£38	6.07313	0.00036	£105,965	£105,965	29.7	32.0
Test 3 (BioPorto urine NGAL)	23,049	Dominated	6.07290	Dominated	Dominated	£539,041	5.3	11.0
Test 2 (BioPorto plasma NGAL)	23,064	Dominated	6.07290	Dominated	Dominated	£633,846	0.3	7.3
Test 4 (ARCHITECT urine NGAL)	23,065	Dominated	6.07289	Dominated	Dominated	£725,061	0.0	6.3
2R: Alternative test costs for NephroCheck and NGAL (BioPorto)								
Standard care (serum creatinine)	22,865	–	6.07020	–	–	–	65.0	–
Test 1 (NephroCheck)	22,899	£34	6.07055	0.00035	£97,745	£97,771	31.2	33.0
Test 3 (BioPorto urine NGAL)	22,937	Dominated	6.07033	Dominated	Dominated	£581,613	3.1	9.6
Test 4 (ARCHITECT urine NGAL)	22,951	Dominated	6.07032	Dominated	Dominated	£751,404	0.0	6.1
Test 2 (BioPorto plasma NGAL)	22,952	Dominated	6.07033	Dominated	Dominated	£686,614	0.7	7.2
2S: Alternative solution for fluid assistance (Hartmann's solution)								
Standard care (serum creatinine)	22,934	–	6.07636	–	–	–	65.5	–
Test 1 (NephroCheck)	22,977	£42	6.07671	0.00035	£119,969	£119,969	29.1	31.1
Test 3 (BioPorto urine NGAL)	23,002	Dominated	6.07648	Dominated	Dominated	£545,923	4.6	11.3
Test 2 (BioPorto plasma NGAL)	23,017	Dominated	6.07648	Dominated	Dominated	£650,943	0.8	8.3
Test 4 (ARCHITECT urine NGAL)	23,019	Dominated	6.07647	Dominated	Dominated	£751,697	0.0	6.3
2T: Alternative RR parameters (Gözce et al.[116])								
Test 1 (NephroCheck)	23,048	–	6.06367	–	–	Dominant	38.9	46.9
Standard care (serum creatinine)	23,051	Dominated	6.06314	Dominated	Dominated	–	45.6	–
Test 3 (BioPorto urine NGAL)	23,099	Dominated	6.06341	Dominated	Dominated	£175,838	12.6	29.5
Test 2 (BioPorto plasma NGAL)	23,115	Dominated	6.06342	Dominated	Dominated	£227,728	2.9	25.1
Test 4 (ARCHITECT urine NGAL)	23,118	Dominated	6.06339	Dominated	Dominated	£268,527	0.0	20.9

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