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Review Article

The Impact of Acute Kidney Injury on Chronic Kidney Disease After Cardiac Surgery: A Systematic Review and Meta-analysis

Rasmus Bo Lindhardt[*,†,1], Sebastian Buhl Rasmussen[*,†], Lars Peter Riber[†,‡], Jens Flensted Lassen[†,§], Hanne Berg Ravn[*,†]

[*]*Department of Anesthesiology and Intensive Care, Odense University Hospital, Odense, Denmark*
[†]*Department of Clinical Research, Health Faculty, University of Southern Denmark, Odense, Denmark*
[‡]*Department of Cardiac, Thoracic and Vascular Surgery, Odense University Hospital, Odense, Denmark*
[§]*Department of Cardiology, Odense University Hospital, Odense, Denmark*

Objectives: To evaluate the impact of acute kidney injury on transition to chronic kidney disease (CKD) after cardiac surgery and to determine frequency of incident CKD in these patients.

Design: A systematic review and meta-analysis of observational studies.

Setting: Electronic databases Medline and Embase were systematically searched from 1974 to February 6, 2023.

Participants: Eligible studies were original observational studies on adult cardiac surgery patients, written in the English language, and with clear kidney disease definitions. Exclusion criteria were studies with previously transplanted populations, populations with preoperative kidney impairment, ventricular assist device procedures, endovascular procedures, a kidney follow-up period of <90 days, and studies not presenting necessary data for effect size calculations.

Interventions: Patients developing postoperative acute kidney injury after cardiac surgery were compared with patients who did not develop acute kidney injury.

Measurements and Main Results: The search identified 4,329 unique studies, 87 underwent full-text review, and 12 were included for analysis. Mean acute kidney injury occurrence across studies was 16% (minimum-maximum: 8-50), while mean occurrence of CKD was 24% (minimum-maximum: 3-35), with high variability depending on definitions and follow-up time. Acute kidney injury was associated with increased odds of CKD in all individual studies. The pooled odds ratio across studies was 5.67 (95% confidence interval, 3.34-9.64; $p < 0.0001$).

Conclusions: Acute kidney injury after cardiac surgery was associated with a more than 5-fold increased odds of developing CKD. New-onset CKD occurred in almost 1 in 4 patients in the years after surgery.

Key Words: cardiac surgery; acute kidney injury; chronic kidney disease; perioperative management; organ protection

Acute kidney injury (AKI) is a common and serious complication after cardiac surgery, affecting approximately one-third of patients undergoing elective cardiac surgery.[1] Postoperative moderate to severe AKI has been associated with increased hospital length of stay, as well as increased short- and long-term mortality.[2] Likewise, a meta-analysis found a 4-fold increase in early mortality in patients undergoing cardiac surgery with postoperative AKI, compared with patients without AKI.[3] This result was even further pronounced in patients needing kidney replacement therapy.

AKI was previously considered a self-limiting and reversible condition, but recent studies suggest that even minor episodes of AKI are associated with progression to chronic

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[1]*Address correspondence to* Rasmus Bo Lindhardt, Odense University Hospital, J. B. Winsloews Vej 4, 5000 Odense, Denmark.
E-mail address: Rasmus.Bo.Lindhardt@rsyd.dk (R.B. Lindhardt).

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kidney disease (CKD).[4,5] The development of CKD is in itself associated with an increased risk of cardiovascular events and mortality,[6] and CKD may progress to an advanced state requiring dialysis and transplantation.[7] Whether the transition from AKI to CKD is directly caused by the AKI episode itself, or whether this is a surrogate for a more severe disease burden remains unknown, although recent studies have identified potential cellular mechanisms for the association, such as endothelial dysfunction and kidney fibrosis, resulting in maladaptive repair mechanisms.[8,9]

Patients undergoing cardiac surgery, in particular, face multiple risk factors for developing AKI, such as frequent use of radiocontrast, blood transfusions, and the use of cardiopulmonary bypass, in addition to the major surgery per se.[10,11] As a consequence, these patients are considered high risk for AKI development and potentially later progression to CKD. Previous studies have evaluated AKI to CKD transition in both surgical and nonsurgical populations,[5,12] but so far, the relationship between AKI and CKD has not been assessed in cardiac surgery patients exclusively. The aim of this systematic review of observational studies was to evaluate the impact of cardiac surgery-associated AKI on the development of incident CKD after hospital discharge and to determine the frequency of incident CKD in these patients in the years after surgery.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[13] The study protocol is published in PROSPERO with registration no. CRD42023391829. The study protocol was updated as the review unfolded.

Eligibility Criteria

Original observational studies on adult cardiac surgery patients, written in the English language and with clear definitions of AKI and CKD, were eligible for review. Studies with previously transplanted populations, ventricular assist device procedures, and isolated Maze, aneurysm, or dissection procedures were excluded. Studies that did not exclude or separate patients with preoperative CKD and studies with follow-up on kidney function <90 days were excluded. Furthermore, studies that did not present necessary data for effect size calculations were excluded.

Information Sources and Search Strategy

We performed a systematic literature search in the databases Medline and Embase from 1974 until conduct of the literature search February 6, 2023. The search string was developed in collaboration with a research librarian affiliated at University of Southern Denmark (Supplementary Table S1). The search string was constructed as a block search based on the PICO (Patient/Problem, Intervention, Comparison, Outcome) framework[14] and included both subject headings and free text search. No search restrictions were applied. Forward and backward citation searches were conducted after the primary study inclusion.

Study Selection and Data Collection

All references were imported into the collaboration software platform Covidence.[15] Duplicates were automatically removed by the software and confirmed by the reviewers. Two reviewers independently screened relevant articles based on eligibility criteria. The articles were first screened for title and abstract, and later full text reviewed. Data from relevant articles were independently extracted using a standardized extraction form. Disagreements in screening or extraction were settled in discussion or resolved by senior last author.

Data Items

Two reviewers independently extracted included studies for study author(s), year, location, sample size, definitions for AKI and CKD, surgery type, baseline population characteristics, and follow-up time. For effect size calculations, the studies were extracted for the number of participants in the following categories:

1. Patients who developed AKI and CKD
2. Patients who developed AKI but did not develop CKD
3. Patients who did not develop AKI but developed CKD
4. Patients who did not develop AKI nor CKD

Study Risk of Bias Assessment

Risk of bias was evaluated independently using the Newcastle-Ottawa Quality Assessment Scale for Cohort studies,[16] modified to only include items relevant for the current review (Supplementary Table S2). Any conflicts were settled in discussion or resolved by senior last author.

Effect Measures

Primary outcome measure was the odds ratio (OR) for incident CKD in the absence or presence of cardiac-surgery associated AKI. Secondary outcome measures were frequency of AKI and total number of incident CKD cases during follow-up.

Statistical Analysis

Numerical data are presented as means and categorical data as count or percentages. Missing data are expressed as not applicable. A restricted maximum likelihood random effects model was performed to calculate individual and pooled ORs including 95% confidence intervals (CI). The model is visualized by Forest Plot. Heterogeneity was assessed using Cochran's Q test and the I^2 statistic. Influence diagnostics was

conducted to identify potential influential studies and was verified by a postexclusion analysis.

Small study and reporting bias were evaluated using visual inspection of funnel plot asymmetry, and confirmed with Egger's regression test and rank correlation test. No assessment for certainty in the body of evidence was conducted in this descriptive systematic review. A 2-sided p value of <0.05 was considered statistically significant. All statistical analyses were conducted using the Metafor package for R and RStudio software.[17-19]

Results

Study Selection and Characteristics

The systematic literature search identified 4,329 unique studies. Of these, 4,242 studies were excluded after title and abstract review, while 86 studies were all retrieved for full-text review by 2 independent reviewers. Twelve studies fulfilled all inclusion criteria and underwent analysis.[20-31] From the included studies, 1 additional study was identified by citation search, but was excluded after full-text review. Full study selection process and reasons for exclusion are presented in the PRISMA flow chart (Fig 1).

Study characteristics for the 12 studies eligible for analysis are shown in Table 1. Seven of the 12 studies contained mixed populations with variable cardiac surgery procedures, and the remaining studies comprised patients with either isolated coronary artery bypass grafting or concomitant valve replacement or repair. The mean age in the complete study population was 61 years (minimum-maximum, 52-67 years). The most common comorbidities were hypertension (63%) and diabetes (32%). The mean follow-up time for CKD diagnosis across studies was 34 months (minimum-maximum, 3-73 months).

Study AKI and CKD Definitions

Studies classified AKI by The Kidney Disease Improving Global Outcomes (KDIGO) criteria[32] (creatinine increase of ≥26.5 μmol/L within 48 hours or ≥1.5 times baseline within 7 days or urine volume <0.5mL/kg/h for 6 hours) or The Acute Kidney Injury Network criteria[33] (creatinine increase of ≥26.4 μmol/L or ≥1.5 times baseline within 48 hours or urine volume of <0.5mL/kg/h for 6 hours). Only 4 studies (Husain-Syed et al 2019,[21] Xu et al 2019,[23] Wu et al 2017,[27] and Xu 2015[29]) assessed urine output when defining AKI.

CKD was predominantly classified by KDIGO criteria[34] (estimated glomerular filtration rate of <60 mL/min/1.73 m^2 or significant albuminuria or other kidney damage markers for >3 months) or The Kidney Disease Outcomes Quality Initiative (KDOQI) criteria[35] (estimated glomerular filtration rate of <60 mL/min/1.73 m^2 or significant albuminuria or other kidney damage markers for >3 months). Two studies classified CKD as the onset of kidney failure, defined as either incident dialysis requirement or kidney transplantation. None of the studies included albuminuria in the CKD definitions.

Kidney Outcomes

Kidney outcomes are displayed in Table 2. The mean AKI frequency across studies was 16% (minimum-maximum, 8-50%). The mean CKD frequency across studies using KDIGO or KDOQI definitions was 24% (minimum-maximum, 3-35%), with considerable variability depending on follow-up time and CKD definition. In the 2 studies using stage 5 kidney failure definitions, CKD frequency was 0.6% and 0.1%, respectively.

Results from the meta-analysis are depicted in the forest plot (Fig 2). Individually, AKI was associated with increased risk of CKD in all studies, with ORs ranging from 2.06 to 35.47. The pooled OR across studies was 5.67 (95% CI, 3.34-9.64; p < 0.0001), based on the random effects model. With a Q-test value of 110.29 (p < 0.001) and an I^2 value of 92.6% (95% CI, 83.1-97.7), considerable between-study heterogeneity was present.

Influence diagnostics identified the 2019 study by Xu et al[23] as a significant influencer of the pooled OR. Postexclusion reanalysis resulted in a pooled OR of 4.72 (95% CI, 2.99-7.48; p < 0.001), but still with considerable between-study heterogeneity (Supplementary Figs S1 and S2).

Risk of Bias

Risk of bias for individual studies was overall low to moderate with 5 of 12 studies assessed as having a low risk of bias in all domains, and 6 studies as having a high or uncertain risk of bias in a single domain (Fig 3).

Three studies determined their outcome measures partly based on self-reports, and 4 studies failed to account clearly for the population lost to follow-up (Fig 3). An extended risk of bias assessment chart is presented in Supplementary Table S2.

Small study and publication biases were assessed via funnel plot (Supplementary Fig S3) and reflected that mostly larger studies were included in the analysis. Egger's regression test found significant funnel plot asymmetry (p = 0.041); however, the Rank correlation test was not statistically significant (p = 0.55).

Discussion

This review is the first systematic meta-analysis evaluating the impact of AKI on CKD transition exclusively in patients undergoing cardiac surgery with normal preoperative kidney function. Twelve studies were included in the analysis. The mean frequency of postoperative AKI was 16% and CKD was 24%, with high variability between studies. A random-effects meta-analysis revealed a >5-fold increase in odds of acquiring CKD in patients with postoperative AKI. Considerable between-study heterogeneity was present, and risk of bias was low to moderate. Funnel plot analysis demonstrated that mainly larger studies were included in the analysis.

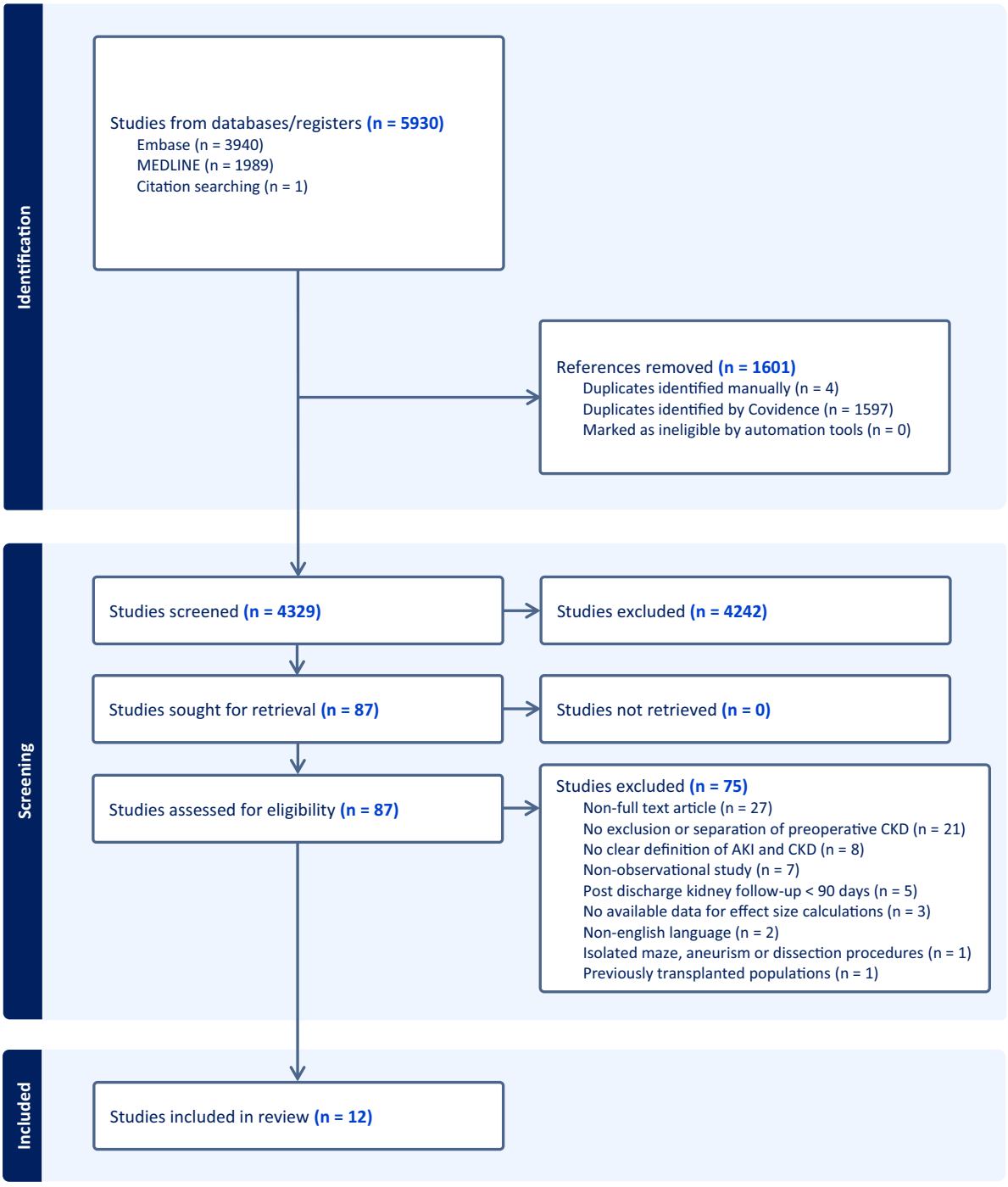

Fig 1. PRISMA diagram of study selection.

A previous systematic review has evaluated AKI to CKD transition and found a pooled OR of 4.31 for incident CKD in AKI patients compared with patients without AKI.[5] Similarly, 2 other systematic reviews found a hazard ratio of 2.67 and 8.82 in patients with AKI during hospital admission compared with patients without AKI, for a combined endpoint of incident or progressive CKD.[12, 36] However, all 3 reviews included heterogeneous patient populations with a mixture of medical admissions and surgical procedures, which impairs the translation of risk estimates to a specific clinical setting, like cardiac surgery in the present study. Of interest, preexisting kidney disease increases the risk of AKI development; simultaneously, an episode of AKI increases the risk of CKD progression.[37] Therefore, risk estimation in the latter 2 reviews may have been inflated by inclusion of acute-on-chronic kidney disease in the combined endpoint. In this systematic review, we excluded studies comprising patients with preexisting kidney impairment to assess specifically the impact of AKI on incident CKD as an outcome. For this reason, we excluded studies comprising patients undergoing ventricular assist device

Table 1
Characteristics of Included Studies

First Author, Year of Publication	Region	Design	Surgery	Definition of AKI	Definition of CKD	Sample Size (n)	Mean age (Years)	Male (%)	Hypertension (%)	Diabetes (%)	Mean Preoperative eGFR (mL/min/1.73 m^2)	Emergency Surgery (%)	Use of CPB (%)	KRT-AKI (%)	Mean Follow-up (Months)
Cho, 2021	Asia	Retrospective	Mixed	KDIGO	KDIGO	1519	63.5	52	45	17	91.6	NA	NA	10	12
Husain-Syed, 2019	Europe	Prospective	Mixed	KDIGO	KDIGO	110	60.7	73	64	6	93.5	0	100	NA	3
Lee, 2019	Asia	Retrospective	CABG	KDIGO	Kidney failure†	3089	65.5	74	58	44	70.1	NA	17	NA	73
Xu, 2019	Asia	Retrospective	Mixed	KDIGO	KDIGO	3869	54.0	59	29	9	94.5	NA	NA	NA	36
Legouis, 2018	Europe	Retrospective	Mixed	KDIGO	KDIGO	2398	63.0	73	54	28	81.0	NA	100	NA	12
Legouis, 2017	Europe	Retrospective	Mixed	KDIGO	KDIGO	4791	65.0	71	NA	24	80.5	0	100	NA	NA§
Palomba, 2017	South America	Prospective	CABG + valve	AKIN	KDIGO	819	60.0	60	84	35	68.5	0	77	NA	12
Wu, 2017	Asia	Retrospective	Mixed	KDIGO	KDIGO	1363	52.2	50	31	12	104.2	NA	NA	NA	39
Helgadottir, 2016	Europe	Retrospective	CABG	KDIGO	KDOQI	1754	66.0	82	65	16	NA	5	79	10	62
Xu, 2015	Asia	Prospective	Mixed	KDIGO	KDIGO	3245	53.5	65	27	9	NA	NA	84	4	24
Ryden, 2014	Europe	Retrospective	CABG	AKIN	Kidney failure†	29330	67.0	79	57	23	77.1	0	95	NA	52
Ishani, 2011	North America	Retrospective	CABG + valve	AKIN*	Modified KDOQI‡	30662	65.9	99	89	48	73.7	19	NA	NA	60

AKI, acute kidney injury; AKIN, acute kidney injury network; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease – Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; KRT-AKI, Kidney Replacement Therapy for Acute Kidney Injury; Mixed, all types of adult cardiac surgery; NA, not applicable; Valve, valvular surgery.

* AKIN categories in the study by Ishani et al. are calculated from available study data.

† Kidney failure defined by new renal replacement therapy or candidate for kidney transplantation.

‡ Incident CKD defined as eGFR < 60 over 3 months of follow-up in patients with preoperative eGFR > 60.

§ Minimum of 90 days.

Table 2
Study Kidney Outcomes

First Author, Year of Publication	AKI+		AKI−		Total AKI Rate (%)
	CKD+	CKD−	CKD+	CKD−	
Cho, 2021	31	217	36	830	22
Husain-Syed, 2019	2	8	1	75	12
Lee, 2019*	6	489	6	1,624	23
Xu, 2019	113	1,355	7	2,394	38
Legouis, 2018	52	90	42	338	27
Legouis, 2017	34	563	17	580	50
Palomba, 2017	54	34	19	108	41
Wu, 2017	42	415	19	887	34
Helgadottir, 2016	60	64	288	1,062	8
Xu, 2015	88	1,207	4	1,946	40
Ryden, 2014*	5	2,319	7	21,212	10
Ishani, 2011	1,200	1,120	5,874	12,067	11

AKI, acute kidney injury; CKD, chronic kidney disease.
* Defines CKD as kidney failure (dialysis requirement and/or transplantation requirement).

procedures, because patients undergoing ventricular assist device procedure often have a markedly different preoperative course, including prolonged hemodynamic instability or overt cardiogenic shock, as well as concomitant kidney dysfunction before surgery.[38]

Interestingly, we noted that in populations with low prevalence of comorbidities like hypertension and diabetes (i.e., Xu et al 2015,[29] Wu et al 2017,[27] and Xu et al 2019[23]), the frequency of postoperative AKI tended to be higher, compared with populations with higher prevalence of comorbidities (i.e., Ishani et al 2011,[31] Ryden et al 2014,[30] and Helgadottir et al 2016[28]) (Tables 1 and 2). This may be an incidental finding, because earlier studies have described both hypertension and diabetes as significant independent risk factors for developing AKI, both in the setting of cardiac surgery and other clinical situations.[39,40] This difference in AKI frequency may also be attributed to variable periprocedural risk of AKI, because the former studies included mixed cardiothoracic surgical procedures.[23,27,29]

Incident CKD occurred on average in 24% of the patients across studies, but with greater variation. This may partly relate to differences in follow-up time, which spanned between 3 and 73 months. Due to the progressive nature of CKD, as well as the age-related decline in kidney function, follow-up time has a significant influence on determining both the frequency of CKD as well as the stage of the disease. However, there is currently limited knowledge regarding onset of CKD after cardiac surgery. Thus, future studies examining the timing and progression of CKD development in a cardiac surgery setting are highly warranted. This work is paramount to better understand the course of the disease and to develop follow-up strategies, including identification of high-risk patients, for the timely initiation of kidney protective treatments (eg, sodium-glucose cotransporter-2 inhibitors).[41]

The variation in CKD occurrence can also partially be attributed to the lack of uniform outcome definitions. Although most researchers used KDIGO or KDOQI definitions for CKD diagnosis, 2 studies (Lee et al 2019[22] and Ryden et al 2014[30]) defined CKD as kidney failure, characterized by new dialysis or kidney transplantation requirement. Both studies were based on registry data with the identification of dialysis or kidney

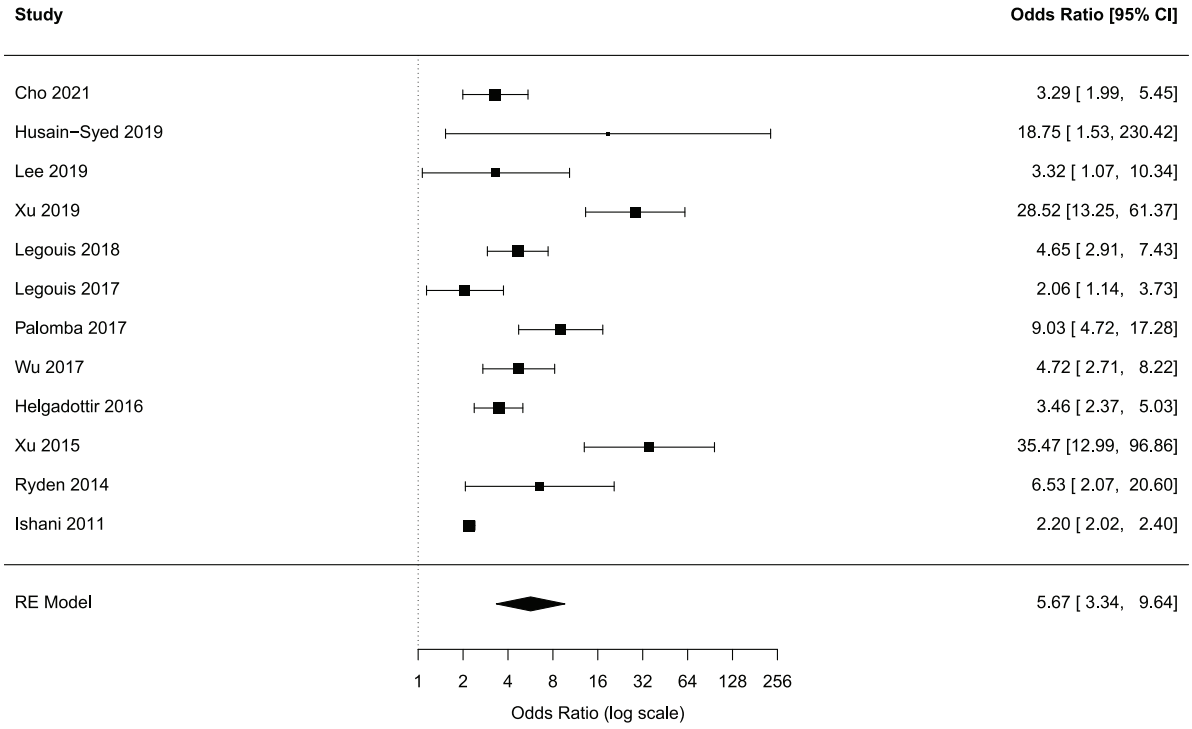

Fig 2. Meta-analysis on chronic kidney disease after cardiac surgery-associated acute kidney injury.
I2 = 92.6% (95% confidence interval, 83.1–97.7) . Q(11) = 110.3, $p < 0.0001$.

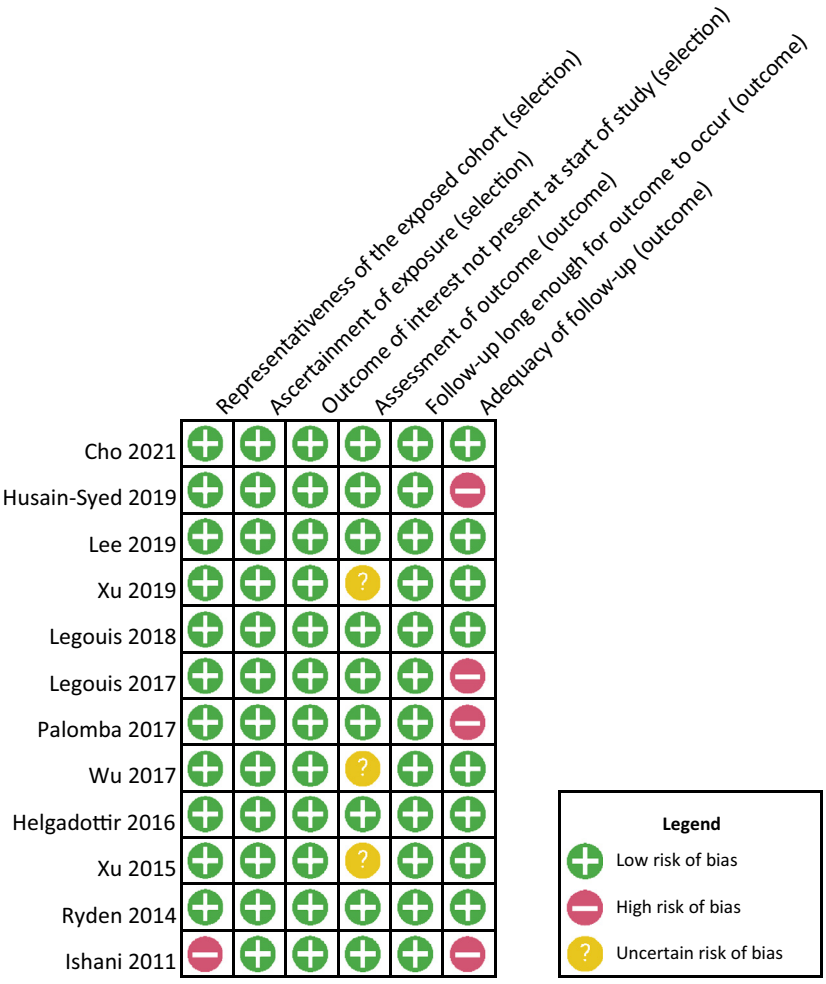

Fig 3. Risk of bias summary.

transplant procedures, which omits patients with less severe stages of CKD not yet requiring dialysis or kidney transplantation. This approach is valid for assessing the additional burden on the health care system. However, given the fact that only approximately 6% of patients with CKD reach stage 5 kidney failure,[6] this approach clearly underestimates the true frequency of CKD in the study populations. This factor is particularly important in the light of the increased risk of new cardiovascular events associated with CKD,[6] which in itself may be a much higher burden on the health care system compared with the costs of dialysis and kidney transplantation. Nevertheless, accounting for disease severity can also be advantageous when examining both AKI and CKD. A study from 2021, which did not meet the inclusion criteria for the present review, found that patients with dialysis-requiring postoperative AKI had higher risk of stage 5 CKD compared with patients with non–dialysis-requiring postoperative AKI.[42] Similarly, a recent meta-analysis found that the risk of incident or progressive CKD increases gradually according to higher KDIGO stages of AKI,[36] thereby emphasizing the importance of assessing disease severity in both AKI and CKD.

Even though not fully understood, several studies have identified potential pathophysiological pathways for the AKI to CKD transformation. During the initial AKI episode, core mechanisms of action are kidney hypoxia with subsequent ischemic injury.[8] These events are believed to cause multiple progressive and pathological changes in the kidneys, including progressive endothelial, interstitial, and glomerular dysfunction; leukocyte extravasation; and metabolic reprogramming and mitochondrial dysfunction; as well as progressive kidney fibrosis, all resulting in progressive kidney dysfunction.[9,43-45]

Notably, although cardiac surgery-associated AKI is a well-established postoperative complication, the short- and long-term consequences, including an increased risk of CKD, further emphasize the importance of AKI prevention. Although detailed strategies for AKI prevention are beyond the scope of this study, major modifiable risk factors include the avoidance of nephrotoxic agents, anemia, and red blood cell transfusion, as well as maintaining renal oxygen delivery above a safe threshold during cardiopulmonary bypass.[46]

Limitations of the present study include considerable between-study heterogeneity. This factor may limit the generalizability of calculated effect sizes. However, previous studies with similar outcomes, but different populations, have also

found AKI to be a significant risk factor for CKD development,[5,12] although whether this association reflects a causal relationship cannot be derived from observational data. Furthermore, despite the risk of bias being low to moderate across studies, differential misclassification bias could be present in some included studies, because most cardiac centers do not offer systematic kidney follow-up after discharge. Patients with postoperative AKI may have undergone closer postdischarge kidney surveillance compared with patients without postoperative AKI. However, because creatinine is included in many routine blood tests, CKD is often a random finding in other screening procedures. In addition, the wide range of follow-up times (3-73 months) is likely a contributing factor to the substantial variation in the occurrence of CKD between studies with short and long follow-up durations. Moreover, most studies solely used creatinine for diagnosing AKI and CKD, omitting the use of urine output or proteinuria, respectively. Although it is feasible to diagnose AKI and CKD without these parameters, the occurrence of both AKI and CKD may be underestimated. Last, this review only included English literature and no grey literature was searched. However, 4,329 potential studies were screened, and all individual studies reported AKI to be associated with CKD with no exceptions. As such, we believe the likelihood of omitting contradictory studies is limited.

A major strength of the present systematic review was that we were able to evaluate the impact of AKI on the development of CKD exclusively in cardiac surgery patients without preexisting kidney dysfunction, with data solely from studies with clear definitions of AKI and CKD. Additionally, all study screening, data extraction, and risk of bias assessment was done independently. Last, included studies had an overall low to moderate risk of bias, as well as no significant evidence of publication bias, which in total increases study validity.

In conclusion, this systematic review demonstrates that AKI after cardiac surgery is associated with a >5-fold increased odds of developing CKD. Additionally, new onset CKD occurred in almost 1 in 4 patients after cardiac surgery. Whether the CKD transition is accelerated by the AKI episode itself, or if this represents a subclinical susceptibility to kidney impairment, cannot be deduced from these observational data. The timing of CKD development after cardiac surgery remains to be elucidated, to develop cost-effective surveillance programs and improve patient outcomes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Rasmus Bo Lindhardt: Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sebastian Buhl Rasmussen:** Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – review & editing. **Lars Peter Riber:** Conceptualization, Writing – review & editing. **Jens Flensted Lassen:** Conceptualization, Writing – review & editing. **Hanne Berg Ravn:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Conceptualization, Funding acquisition, Investigation, Methodology.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2024.03.044.

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