Meta-analysis of AKI to CKD transition in perioperative patients

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Research

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Abstract

Background Recent research shows AKI increases the risk of incident CKD. We hypothesized that perioperative AKI may confer increased risk of subsequent CKD compared to nonperioperative AKI.

Methods A MEDLINE search was performed for “AKI, CKD, chronic renal insufficiency, surgery, and perioperative” and related terms yielded 5209 articles. 1065 relevant studies were reviewed. 1006 were excluded because they were review, animal, or pediatric studies. 59 studies underwent full manuscript review by two independent evaluators. 17 met all inclusion criteria and underwent analysis. Two-by-two tables were constructed from AKI +/- and CKD +/- data. The R package metafor was employed to determine odds ratio (OR) were calculated, and a random-effects model was used to calculate weighted ORs. Leave-1-out, funnel analysis, and structured analysis were used to estimate effects of study heterogeneity and bias.

Results Nonperioperative studies included studies of oncology, percutaneous coronary intervention, and myocardial infarction patients. Perioperative studies comprised patients from cardiac surgery, vascular surgery, and burns. There was significant heterogeneity, but ris of bias was overall assessed as low. The OR for AKI versus non-AKI patients developing CKD in all studies was 4.31 (95% CI 3.01-6.17; $p < 0.01$). Nonperioperative subjects demonstrated OR 3.32 for developing CKD compared to non-AKI patients (95% CI 2.06-5.34; $p < 0.01$) whilst perioperative patients demonstrated OR 5.20 (95% CI 3.12-8.66; $p < 0.01$) for the same event.

Conclusions We conclude that studies conducted in perioperative and nonperioperative patient populations suggest similar risk of development of CKD after AKI.

Introduction

Rationale

Clinical and translational studies suggest that incident acute kidney injury (AKI) leads to chronic kidney disease (CKD). A systematic review and meta-analysis by Coca et al [1] demonstrated patients with AKI had higher risk for developing CKD with a pooled adjusted hazard ratio of 8.8 compared to patients without AKI. Development of CKD after AKI is heterogeneous in that it occurs in a variety of patient populations and can be caused by plethora of disease processes, including sepsis, cardiovascular disease, nephrotoxin exposure, and surgically induced stressors. Surgery can affect long-term outcomes of nonsurgical disease; for example, surgical patients may have elevated risk of cognitive dysfunction [2] occurring remotely from surgery itself. Therefore, surgical patients may be at elevated risk of AKI-CKD transition. We hypothesized that perioperative status might confer differential risk of developing CKD after an AKI event.

Objectives

To perform subgroup analysis to determine whether risk of AKI-CKD transition varies according to perioperative or nonperioperative status.

Methods

Eligibility criteria

Studies published from 1975 to 2018 available in the English language were eligible for initial review. We excluded reviews, animal studies, and pediatric studies to select for studies involving adult human subjects.

Information sources and search

MEDLINE search terms included AKI, CKD, chronic renal insufficiency, nephrotoxins, surgery, and perioperative.

Study selection

We included studies in which:

1. Patients suffering AKI were included in the study
2. The study clearly defined AKI and CKD
3. The study excluded patients with prior CKD or separated patient data based on baseline kidney function (i.e. CKD stage, GFR) such that patients with CKD Stage $\geq$ 3 could be excluded from the analysis
4. The study allowed determination of perioperative status
5. The study stated CKD as an outcome
6. The study included data necessary for calculation of effect size

In studies in which patients with prior CKD were not excluded, but patient data was separated based on baseline kidney function, only patients with baseline (pre-AKI) GFR $\geq$ 60 or Stage 1-2 CKD were included in the data analysis. We defined incident CKD as CKD stage 3 or higher, according to the definition stated within each study.

Data collection process and data items

Studies selected for final review were analyzed for the number of subjects in each of the categories:

- Patients who suffered AKI and developed subsequent CKD

- Patients who suffered AKI but did not develop CKD
- Patients who did not suffer AKI but developed CKD
- Patients who did not suffer AKI and did not develop CKD

Using these data, we calculated the OR for development of CKD in patients who suffered AKI vs. those who did not suffer AKI.

Risk of bias in individual studies

We assessed risk of bias in individual studies using the Cochrane Collaboration's tool for assessing risk of bias [3]. We did not assess performance bias or detection bias because there was no intervention applied to the patient populations being analyzed. Supplemental Table 1 presents the results of this analysis.

Statistical analysis including summary measures, synthesis of results, risk of bias across studies, and additional analyses

Statistical analysis was conducted using R package metafor. The OR was calculated for each study using a random effects model to compute each weighted OR and subgroup ORs. Summary subgroup ORs were compared using a random effects model, meta-regression, and Wald analysis. Heterogeneity was assessed with the Cochrane Q test and I^2. Leave-1-out and funnel plots were also used to assess the effect of heterogeneity and publication bias.

Results

1065 studies were identified (Fig. 1). 1006 studies were excluded after abstract review because they were animal studies, pediatric studies, or review articles. 59 studies underwent full manuscript review by two independent reviewers (PA, EAS). 17 studies fulfilled all inclusion criteria and underwent analysis. The Kappa measure of agreement between independent reviewers was 0.84 ($p < 0.001$). Disagreements about inclusion of studies in the meta-analysis were resolved by discussion with the senior author (MPH), resulting in exclusion of four studies from the meta-analysis. Individual risk of bias for the studies included was low for sixteen of seventeen studies and high in one study, as demonstrated in Supplemental Table 1.

Characteristics of the included studies are shown in Table 1. Ten of seventeen studies involved AKI in populations that were primarily perioperative [4-13]. Of those, eight involved AKI in patients who underwent cardiac surgery [4, 5, 7-9, 11-13]. The two remaining studies were in patients with burns [6] and vascular surgery [10].

Table 1

Study Author	Sample Size	Definition of AKI	Definition of CKD	Population	Perioperative
Helgason, Dadi et al, 2018	10885	KDIGO criteria	KDIGO 2012 CKD guidelines	Coronary angiography	No
Brown, Solomon et al, 2016	24405	KDOQI guidelines	KDOQI guidelines	Cardiac catheterization	No
Chawla, Amdur et al, 2011	11589	ICD9 codes	CKD stage 4 or higher	Pneumonia or MI	No
James, Hemmelgarm et al, 2010	920985	ICD9 codes	ESRD or doubling of serum Cr	Mixed medical etiologies	No
Ando, Ohashi et al, 2010	158	≥ 2x increase in serum Cr	KDOQI guidelines	Myeloablative allogeneic hematopoietic cell transplantation	No
James, Ghali et al, 2010	11249	Percent increase in serum creatinine	MDRD	Coronary angiography	No
Weiss, Sandmaier et al, 2006	122	Percent decrease in GFR	Percent decrease in GFR ≥ 25%	Non-myeloablative hematopoietic cell transplantation	No
Wu, Buyun et al, 2017	1363	KDIGO criteria	KDIGO criteria	Cardiac surgery	Yes
Palomba, Henrique et al, 2017	350	AKIN criteria	eGFR < 60 mL/min	Cardiac surgery	Yes
Thalji, Kothari et al, 2017	18155	ICD9 codes	ICD9 codes	Burns	Yes
Legouis, Galichon et al, 2017	4791	KDIGO criteria	eGFR < 60 mL/min	Cardiac surgery	Yes
Chew, Ng et al, 2017	3008	AKIN criteria	CKD stage 5	Cardiac surgery	Yes
Helgadottir, Sigurdsson et al, 2016	1754	KDIGO criteria	KDOQI guidelines	CABG	Yes

Study Author	Sample Size	Definition of AKI	Definition of CKD	Population	Perioperative
Arora, Davari – Farid et al, 2015	717	AKIN criteria	KDOQI guidelines	Endovascular or open surgical revascularization of lower extremities	Yes
Xu, Zhu et al, 2015	3245	KDIGO criteria	KDIGO criteria	Cardiac surgery	Yes
Ryden, Sartipy et al, 2014	29330	AKIN criteria	Start of renal replacement therapy	CABG	Yes
Ishani, Nelson et al, 2011	29330	AKIN criteria	Start of renal replacement therapy	CABG	Yes

Seven studies described AKI to CKD transition in nonperioperative populations. These included patients undergoing coronary angiography/cardiac catheterization [14-16], non-myeloablative hematopoietic cell transplantation [17], myeloablative allogeneic hematopoietic cell transplantation [18], suffering from myocardial infarction or pneumonia [19], or with mixed medical etiologies [20].

Quality Assessment

Overall there was significant heterogeneity across all studies ($Q = 471.45$, $df = 16$, $p < 0.01$; $I2 = 98.3\%$). This was similar in perioperative studies ($Q = 188.97$, $df = 9$, $p < 0.01$; $I2 = 93.7\%$) and nonperioperative studies ($Q = 256.71$, $df = 6$, $p < 0.01$; $I2 = 97.9\%$).

Effect size

Figure 2 depicts the effect size for each study included in the meta-analysis. Overall, AKI was associated with increased risk of subsequent CKD (OR = 4.31; 95% CI 3.01-6.17; $p = 1.7 \times 10^{-15}$). In the subgroup of studies of perioperative patients, the risk of new onset CKD was 5.2 times greater in patients with AKI than in those without (OR = 5.20; 95% CI 3.12-8.66; p p $= 2.9 \times 10^{-10}$). In the subgroup of nonperioperative patients the effect size was similar to that in perioperative patients (nonperioperative OR = 3.32; 95% CI 2.06-5.34; $p = 8.0 \times 10^{-7}$). The difference in effect size between perioperative and nonperioperative studies was not statistically significant. Therefore, in the studies reviewed, the risk of new onset CKD is elevated in patients who suffer AKI. Perioperative status confers at least the same risk as nonperioperative status.

Discussion

The main finding of this meta-analysis is that studies conducted in perioperative populations demonstrate similar elevation of risk of AKI-CKD transition to those conducted in nonperioperative populations, with odds ratios of 5.20 and 3.32 respectively. Several groups have raised concerns that CKD could be a long-term outcome of perioperative AKI, and our data support this concern [7, 21]. Numerous strategies to reduce the incidence of perioperative AKI are investigational [22–24] and may therefore also potentially reduce postoperative development of CKD. Similarly, some have suggested patients with AKI receive surveillance for development of CKD [25]; our results suggest this may be worthy of study in perioperative patients, in whom AKI may have a well-defined onset during a hospital stay, making them more amenable to intervention.

A secondary finding is that there is now a considerable dataset documenting AKI-CKD transition in many patient subgroups, such that subgroup analysis may be performed. We tested the hypothesis that perioperative status might modify risk, but other subgroup analyses are possible, and might further elucidate high risk populations.

Finally, we acknowledge this study has limitations. The primary limitation is significant heterogeneity across studies. To some degree, this should be expected given the broad nature of the subgroups included in this analysis. The nonperioperative subgroup in particular constitutes a broad scope of studies including various disease types and concurrently a broad patient population. A second limitation of the nonperioperative group is that it is not possible to ensure that all patients in nonperioperative populations did not have surgical exposure, increasing the risk of type 2 error. In perioperative studies there was little diversity in the type of surgical procedures as nearly all studies of perioperative AKI-CKD have occurred in cardiac surgery patients who have high risk of AKI. This highlights an area for further investigation as risk seems likely to vary according to type of surgery. For example, same day/elective surgeries (e.g. cholecystectomy, appendectomy) may result in low-grade AKI (i.e. smaller changes in baseline creatinine) and thus may pose less risk of subsequent CKD compared to larger or emergent surgical procedures.

Conclusion

We conclude that studies conducted in perioperative and nonperioperative patient populations suggest similar risk of development of CKD after AKI.

Abbreviations

AKI, CKD, OR

Declarations

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Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PA performed the literature search. PA and ES were responsible for study selection, review, and collection of data. MH resolved disagreements in study selection and performed statistical analysis of the data. PA, ES, and MH contributed to manuscript writing. All authors read and approved the final manuscript.

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Figures

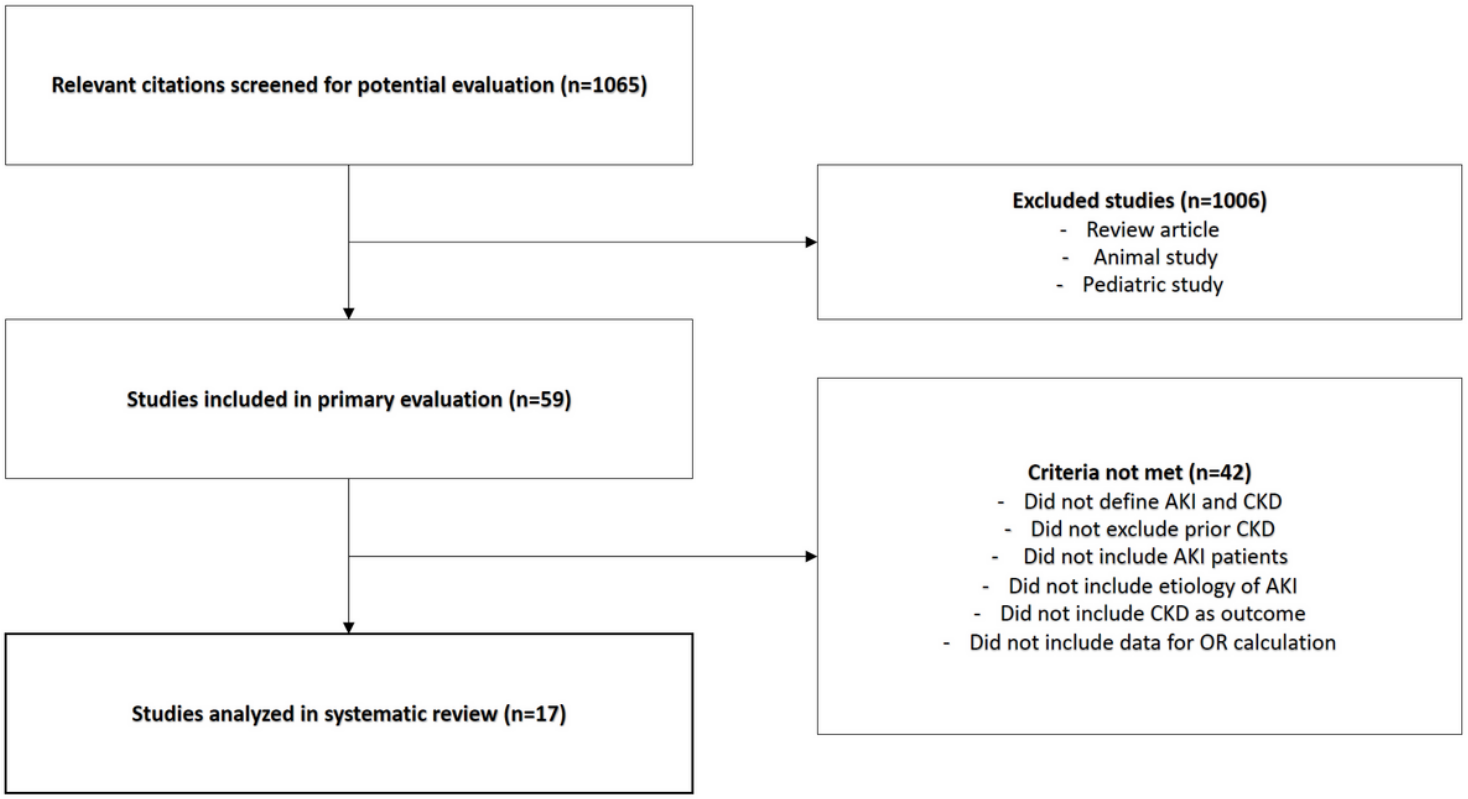

Figure 1

1065 studies were identified

	AKI		Control		
Author(s) and Year	*CKD+*	*CKD−*	*CKD+*	*CKD−*	*Odds Ratio [95% CI]*
Non perioperative patients					
Helgason, Dadi et al, 2018	42	40	75	158	2.21 [1.32, 3.69]
Brown, Solomon et al, 2016	1025	1728	3148	13501	2.54 [2.33, 2.77]
Chawla, Amdur et al, 2011	728	4623	1348	14569	1.70 [1.55, 1.87]
James, Hemmelgarm et al, 2010	179	1060	909	13894	2.58 [2.17, 3.07]
Ando, Ohashi et al, 2010	22	62	5	69	4.90 [1.75, 13.71]
James, Ghali et al, 2010	283	570	613	9783	7.92 [6.72, 9.34]
Weiss, Sandmaier et al, 2006	78	30	3	11	9.53 [2.49, 36.56]
RE Model for nonperioperative subgroup (Q = 256.71, df = 6, p = 0.00; I^2 = 97.9%)					***3.32 [2.06, 5.34]***

Figure 2

The effect size for each study included in the meta-analysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable1.docx