Meta-analysis of AKI to CKD transition in perioperative patients

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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 risk 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].

| 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 |
| 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 x 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 = 2.9 x 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 x 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
1065 studies were identified

| Author(s) and Year | AKI (CKD+) | AKI (CKD-) | Control (CKD+) | Control (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; \( \hat{i}^2 = 97.9\% \))

3.32 [2.06, 5.34]

The effect size for each study included in the meta-analysis.
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Supplemental Table 1.docx