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Original Investigation

Acute Kidney Injury and Prognosis After Cardiopulmonary Bypass: A Meta-analysis of Cohort Studies

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Background: Robust estimates and sources of variation in risks of clinical outcomes for cardiopulmonary bypass (CPB)-associated acute kidney injury (AKI) are needed to inform clinical practice and policy. We aimed to assess whether the methods for defining acute kidney disease modify the estimated association of AKI with CPB.

Study Design: Systematic review and meta-analysis.

Setting & Population: Adults undergoing CPB.

Selection Criteria for Studies: Cohort studies reporting adjusted associations between CPB-associated AKI and early mortality, later mortality, stroke, myocardial infarction, congestive heart failure, all-cause hospitalization, chronic kidney disease, end-stage kidney disease, bleeding complications, or perioperative infection.

Predictors: CPB-associated AKI and renal replacement therapy.

Outcomes: The primary outcome was early mortality (in-hospital or within 90 days of surgery) in studies reporting adjusted associations and secondary outcomes including total and cardiovascular mortality, major adverse cardiovascular events, rehospitalization, end-stage kidney disease, bleeding, and perioperative infection.

Results: 46 studies with 47 unique cohorts comprising 242,388 participants were included. The pooled rate of CPB-associated AKI was 18.2%, and of renal replacement therapy, 2.1%. CPB-associated AKI was associated with early mortality (risk ratio [RR], 4.0; 95% CI, 3.1-5.2; crude mortality with CPB-associated AKI, 4.6%; without CPB-AKI, 1.5%) with considerable heterogeneity between studies ($I^2 = 87\%$). The AKI definition did not modify prognostic estimates (P for subgroup analysis = 0.9). When heterogeneity was fully accounted for using credibility ceilings, risks of early mortality were attenuated (RR, 2.2; 95% CI, 1.8-2.8) but remained high. Renal replacement therapy also was associated with early mortality (RR, 5.3; 95% CI, 3.4-8.1). CPB-associated AKI also was associated with long-term mortality (RR, 2.0; 95% CI, 1.7-2.3) and stroke (RR, 2.2; 95% CI, 1.1-4.5). No other outcomes were reported in more than 3 studies.

Limitations: Unclear attrition from follow-up in most studies and variable adjustment for confounders across studies.

Conclusions: CPB-associated AKI is associated with a more than 2-fold increase in early mortality regardless of AKI definition.

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INDEX WORDS: Cardiopulmonary bypass (CBP); cardiac surgery; coronary artery bypass graft; valve surgery; meta-analysis; acute kidney injury (AKI); acute renal failure (ARF); mortality; stroke.

Ischemic-reperfusion injury is common following cardiopulmonary bypass (CPB) and causes acute kidney injury (AKI).[1] The importance of AKI as a risk factor for mortality following cardiac surgery is considered axiomatic; however, it has been argued that the previous absence of standardized definitions has made assessing the prognostic implications of CBP-associated AKI difficult. A robust understanding of prognosis associated with AKI is needed to enhance clinical decision making and provide a sound benchmark for epidemiologic and interventional research.

Despite many published reports describing the association of CBP-associated AKI with adverse outcomes, there have been few attempts to systematically summarize the prognostic implications of AKI in this clinical setting. In a subgroup analysis within a global incidence study of AKI, Susantitaphong et al[2] found that CBP-associated AKI was associated with an 8-fold increase in mortality based on results from 23 studies. However, this study was not designed to assess the impact of the different AKI definitions on estimated prognosis, evaluate the impact of adjustment for other AKI risk factors, or examine the associations between AKI and other outcomes.

Standardized AKI definitions, including first the RIFLE (risk, injury, failure, loss, end-stage renal

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disease) consensus definition in 2004[3] followed by the Acute Kidney Injury Network (AKIN)[4] and the KDIGO (Kidney Disease: Improving Global Outcomes)[5] definitions, facilitates prognostic analyses for AKI in various clinical settings, but it is unclear whether these definitions have different prognostic value.

To address these knowledge gaps, we conducted a systematic review and meta-analysis to examine the prognostic implications of CPB-associated AKI for mortality and other clinical outcomes, including adverse cardiovascular and renal events. We specifically aimed to determine whether the association between CPB-associated AKI and mortality differed according to AKI definition.

METHODS

Study Protocol

This systematic review and meta-analysis was conducted using a prespecified protocol and according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[6]

Search Strategy and Selection Criteria

We searched MEDLINE and EMBASE without language restriction for January 1, 2004, to June 2, 2014, using the following medical subject heading (MeSH) terms: acute kidney injury, renal failure, renal replacement therapy, dialysis, cardiac surgical procedure, cardiopulmonary bypass, coronary artery bypass, mortality, and death (see Item S1, available as online supplementary material, for search terms). We limited the search to studies published since the development of the first consensus AKI definition (RIFLE) in 2004.[3] We included cohort studies if they reported data for the association between AKI after surgery supported by CPB and one of the prespecified clinical outcomes. We excluded studies in children and studies in which >25% of participants underwent off-pump cardio-artery bypass grafting. For mortality outcomes, we considered only studies with adjusted risk estimates.

Definition of Exposure

We considered AKI as defined by KDIGO,[5] AKIN,[4] RIFLE,[3] or the study investigators. We assigned a primary definition to each study, according to the available consensus definitions in reverse chronological order: KDIGO, AKIN, RIFLE, or study investigators, where reported in each publication. The primary definition was used in all analyses unless otherwise stated. We also obtained risk estimates for the outcome of renal replacement therapy (RRT) separately from AKI, when reported.

Outcome Measures

The primary outcome was early mortality defined as in-hospital mortality or within 90 days. Secondary outcomes were total mortality, cardiovascular mortality, major adverse cardiovascular events (stroke, myocardial infarction, and congestive heart failure), all-cause hospitalization, chronic kidney disease (CKD), end-stage kidney disease requiring long-term RRT, bleeding complications, or perioperative infection.

Data Extraction

Two reviewers (J.W.P. and S.C.P.) independently reviewed titles and abstracts of a randomly selected 10% sample of citations to reach consensus on eligible studies. When consensus was achieved, a single reviewer (J.W.P.) screened all remaining citations. All potentially eligible citations then were examined in detail to identify studies that fulfilled the eligibility criteria.

We extracted prevalence of CPB-associated AKI and risk estimates for outcomes (as adjusted risk ratios [RRs], hazard ratios, or odds ratios together with their 95% confidence intervals [CIs]). When only crude outcome data were provided for nonmortality outcomes, we calculated unadjusted RRs. We treated multiple reports of results from the same study as a single risk evaluation and entered data for disaggregated cohorts within studies into the analyses separately. We extracted prespecified descriptive statistics for the key clinical characteristics and outcomes for each included cohort.

Statistical Analysis

We converted point estimates and their variances for each odds ratio to an RR when required using the techniques described in references.[7,8] We assumed that hazard ratios reasonably approximated relative risks. We summarized RRs using random-effects meta-analysis and reported results as RR together with 95% CI.[9] Heterogeneity was assessed by the I^2 statistic, which provides an estimate of the proportion of variation in risk estimates among studies that is beyond that expected by chance.[10] We considered I^2 thresholds of <25%, 25% to 75%, and >75% to represent low, moderate, and high heterogeneity, respectively.[10] When individual study–adjusted risk estimates had been provided separately for CPB-associated AKI severity stages, we calculated an overall CPB-associated AKI risk estimate using a fixed-effects model. In sensitivity analyses, we used credibility ceilings to account for possible spurious precision of pooled risk estimates[11] and additionally determined summary estimate risks for the primary outcome provided by the minimum credibility ceiling that generated $I^2 = 0\%$. We calculated the 95% prediction interval, which is the expected range of the effect in a new study.[12]

Potential sources of heterogeneity were explored using subgroup and univariate metaregression analyses and considered the following prespecified study-level demographic and clinical variables: age, sex, CKD, diabetes, ejection fraction, emergency surgery, radiocontrast use, intra-aortic pump use, operation type (coronary artery bypass grafting, valve surgery, or combination), CPB duration, cross-clamp time, preoperative creatinine level, off-pump proportion, the biomarker used to identify CPB-associated AKI (plasma or serum creatinine, estimated glomerular filtration rate [eGFR], urine output, or any combination of the 3 surrogates), and World Health Organization global region.[13]

We adjudicated study risks of bias according to domains described in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement,[14] including specific items concerning AKI definition, adjustment for potential confounding factors, and clarity of reporting of outcome assessments and statistical analyses. We conducted all analyses using packages meta and metafor from R statistical software version 3.1.0 (R Foundation for Statistical Computing) and used the ceiling.data function (www.dhe.med.uoi.gr/assets/software/ceiling.txt).

RESULTS

Description of Included Studies and Participants

The systematic search identified 3,618 citations, of which 320 were retrieved for full-text examination after review by title and abstract. Overall, 46 studies reporting on 47 cohorts comprising 242,388 patients (Fig 1; Table 1) were eligible and included in the review. Sample size varied from 68 to 28,220 (median, 1,610) participants (Table 1). There were 45 cohorts adjusted for covariates reporting at least one