Pulmonary Hypertension, Mortality, and Cardiovascular Disease in CKD and ESRD Patients: A Systematic Review and Meta-analysis

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Background: Pulmonary hypertension is common in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) and may be associated with poor outcomes. The magnitude of the association between pulmonary hypertension and mortality is uncertain due to the small size and variable findings of observational studies.

Study Design: Systematic review and meta-analysis of observational studies using subgroup analyses and metaregression.

Setting & Population: Patients with ESRD or earlier stages of CKD.

Selection Criteria for Studies: Observational studies reporting clinical outcomes in patients with co-existing pulmonary hypertension and CKD or ESRD identified using a systematic search of PubMed and Embase.

Predictor: Pulmonary hypertension diagnosed by Doppler echocardiography.

Outcomes: All-cause mortality, cardiovascular mortality, and cardiovascular events.

Results: 16 studies, with 7,112 patients with an overall pulmonary hypertension prevalence of 23%, were included. Pulmonary hypertension was associated with increased risk for all-cause mortality among patients with CKD (relative risk [RR], 1.44; 95% CI, 1.17-1.76), with ESRD receiving maintenance dialysis (RR, 2.32; 95% CI, 1.91-2.83), and with a functioning kidney transplant (RR, 2.08; 95% CI, 1.35-3.20). Pulmonary hypertension was associated with increased risk for cardiovascular events in patients with CKD (RR, 1.67; 95% CI, 1.07-2.60) and ESRD receiving dialysis (RR, 2.33; 95% CI, 1.76-3.08). There was an association between pulmonary hypertension and increased risk for cardiovascular mortality in patients with CKD or ESRD (RR, 2.20; 95% CI, 1.53-3.15).

Limitations: Heterogeneity of included studies, possibility of residual confounding, unavailability of individual patient-level data, and possibility of outcome reporting bias.

Conclusions: Pulmonary hypertension is associated with a substantially increased risk for death and cardiovascular events in patients with CKD and ESRD. Risk is higher in patients with ESRD receiving dialysis compared with patients with CKD stages 1 to 5. Understanding the effect of interventions to lower pulmonary artery pressure on the survival of these patents awaits their evaluation in randomized controlled trials.

Complete author and article information provided before references.

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Pulmonary hypertension is relatively common in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), with prevalences ranging from 10% to 70% depending on the methods used to diagnose pulmonary hypertension and the stages of CKD evaluated.[1] Pulmonary hypertension may frequently coexist in such patients as a consequence of the pathophysiologic sequelae of CKD, which include volume overload, congestive heart failure, endothelial dysfunction, and arteriovenous fistulas.[2]

Pulmonary hypertension is typically defined as pulmonary artery mean pressure > 25 mm Hg at rest, measured by right-sided cardiac catheterization.[3] Due to the invasive nature of this diagnostic gold standard, noninvasive echocardiography is often used to calculate estimated pulmonary artery systolic pressure (PASP) to diagnose pulmonary hypertension. The World Health Organization categorizes pulmonary hypertension into 5 distinctive groups based on cause: pulmonary arterial hypertension, pulmonary hypertension due to left-sided cardiac disease, pulmonary hypertension due to lung disease or hypoxia, chronic thromboembolic pulmonary hypertension, and pulmonary hypertension due to unclear multifactorial mechanisms, respectively.[3]

Studies have suggested that the presence of pulmonary hypertension may be associated with greater risk for adverse outcomes in patients with CKD and ESRD. However, the magnitude of association between pulmonary hypertension and mortality remains unclear. Furthermore, the optimal management strategy for patients with pulmonary hypertension complicating CKD and ESRD requires further elucidation.

The goal of our meta-analysis was to systematically and quantitatively review the literature with regard to the impact of pulmonary hypertension on clinical outcomes in patients with CKD and ESRD.

Methods

Study Design

The present meta-analysis was designed and conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[4]

Data Sources and Search Strategy

PubMed and Embase were searched through February 2017 using key words related to CKD, ESRD, dialysis, and pulmonary hypertension, without restrictions on languages. The detailed search strategy was designed by a specialist information manager (Item S1). In addition, reference lists of included studies and pertinent review articles were manually screened. Unpublished studies and gray literature (including conference proceedings, dissertations, and theses) were identified using the ClinicalTrials.gov registry (www.ClinicalTrials.gov) in addition to the Conference Proceedings Citation Index and the OpenGrey website (http://www.opengrey.eu/).

Inclusion and Exclusion Criteria

Cohort studies that evaluated the impact of pulmonary hypertension or pulmonary artery pressure on all-cause mortality, cardiovascular mortality, and cardiovascular events in patients with CKD and ESRD were included. The definition and stages of CKD are consistent with criteria in the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) CKD guideline.[5] Studies had to report risk estimates (odds ratios [ORs], relative risks [RRs], or hazard ratios [HRs]) with corresponding 95% confidence intervals (CIs) or provide sufficient data for these to be calculated. We excluded animal studies, conference abstracts, case reports, reviews, and editorials. If duplicate publications were identified based on overlapping data, we included the one with the most informative report.

Data Extraction and Quality Assessment

Two independent reviewers (M.T. and C.L.) independently inspected articles for eligibility and extracted information for baseline characteristics and outcome using a standardized data collection form. Any discrepancy was resolved by discussion with a third reviewer (J.A.B.). The quality of included studies was appraised with the assessment tool of the Newcastle-Ottawa Scale for cohort studies ranging from 0 to 9.[6] We considered studies with scores ≤ 5 at high risk of bias.

Outcome Measures

The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular mortality and cardiovascular events. The definition of cardiovascular events varied by studies but generally included acute heart failure, myocardial infarction, stroke, and peripheral vascular disease. For studies that reported HRs from proportional hazards regression, HRs and 95% CIs were extracted, using participants with CKD/ESRD without pulmonary hypertension as the referent group. For risk estimates, a natural logarithm scale was used. If HRs were not reported directly, crude ORs and 95% CIs were calculated. Results from the final model that adjusted for the maximum covariates were used from each study.

Statistical Analyses

Meta-analysis was performed using the DerSimonian-Laird random-effects model. Between-study heterogeneity was evaluated by calculation of I^2 statistics. We considered heterogeneity low if I^2 was ≤50%, moderate if >50% to <75%, and high if ≥75%.

Subgroup analysis and metaregression were performed for the primary outcome to investigate possible sources of heterogeneity from a priori–defined factors that could influence estimates, including CKD stage (CKD stages 1-5 vs ESRD receiving dialysis), pulmonary hypertension measure (estimated PASP ≥ 35 mm Hg vs other criteria), age (average <60 vs ≥60 years), sex (male ≥ 60% vs <60%), adjustment for baseline cardiovascular disease in multivariable models (yes vs no), type of risk estimate (HR vs OR), country (United States vs non–US countries), duration of follow-up (≤1 vs >1 to ≤3 vs >3 years), and dialysis modality (hemodialysis vs peritoneal dialysis). Sensitivity analysis was conducted by performing the analysis with alternative models, including the restricted maximum likelihood (REML) random-effects model, Hartung-Knapp-Sidik-Jonkman adjustment (based on DerSimonian-Laird estimates), and Mantel-Haenszel fixed-effects model, and by excluding studies with fewer than 100 participants or high risk of bias. We considered statistical significance as 2-tailed $P < 0.05$. Stata, version 12.0 (StataCorp LP), was used to perform all statistical analyses.

Results

Characteristics and Quality of Included Studies

The preliminary search strategy identified 842 unique records, of which 30 were potentially eligible after screening titles and abstracts. Our final meta-analysis included 16 cohort studies,[7-22] with 7,112 patients with CKD and ESRD. The flow chart of selection and reasons for exclusion of studies is shown in Figure 1.

Baseline characteristics and quality scores of included studies are listed in Tables 1 and S1. The prevalence of pulmonary hypertension was 23% in our study population. Included studies had a median sample size of 247 (range, 36-2,959), and mean follow-up ranged from 1 to 7 years. Three studies recruited patients with CKD stages 1 to 5, two were of kidney transplant recipients, and the other 11 evaluated patients with ESRD undergoing dialysis. Of the 11 studies of dialysis populations, 7 were limited to hemodialysis, 2 were limited to peritoneal dialysis, and 2 included both.

Ascertainment of pulmonary hypertension was based on measurements using Doppler echocardiography in all 16 included studies. The most commonly used diagnostic standard was estimated PASP > 35 mm Hg, with 10 studies using this criterion and another 4 studies using alternative PASP cutoff values (30, 37, 45, and 50 mm Hg, respectively). One study adopted tricuspid regurgitant velocity > 2.5 m/s as the diagnostic method,[16] and another defined