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Meta-Analysis of Prophylactic Renal Replacement Therapy after Cardiac Catheterization in Patients with Chronic Kidney Disease

ABSTRACT

Background: The benefits of prophylactic renal replacement therapy after cardiac catheterization in patients with chronic kidney disease remain unclear. The aim of this study is to confirm the benefit of prophylactic renal replacement therapy after cardiac catheterization.

Methods: We systematically searched for studies published from inception to December 2022 examining the benefits of prophylactic renal replacement therapy after cardiac catheterization in MEDLINE and EMBASE. Data analysis was performed according to the PRISMA statement using the Mantel–Haenszel method.

Results: Five studies met the inclusion criteria, which comprised of 532 chronic kidney disease patients who underwent coronary angiography (268 had prophylactic renal replacement therapy and 264 did not have prophylactic renal replacement therapy). The pooled analysis revealed a non-significant decreased risk of 1-year mortality in chronic kidney disease patients who underwent coronary angiography and prophylactic renal replacement therapy compared to those who did not have prophylactic renal replacement therapy (RR = 0.59; $P = .18$; CI: 0.28-1.2795, $I^2 = 60.4\%$). The risk of hemodialysis during hospitalization and renal replacement therapy requirement in 1 year in chronic kidney disease patients who underwent coronary angiography and prophylactic renal replacement therapy were lower than in those who did not have prophylactic renal replacement therapy (RR = 0.13; $P = .001$; CI: 0.04-0.43, $I^2 = 9.1\%$ and RR = 0.29; $P = .015$; CI: 0.11-0.78, $I^2 = 49.9\%$, respectively). The sensitivity analysis demonstrated that the overall findings remained consistent and did not significantly alter.

Conclusions: Prophylactic renal replacement therapy did not seem to lower 1-year mortality among chronic kidney disease patients who underwent coronary angiography. However, prophylactic renal replacement therapy appeared to reduce the risk of hemodialysis during hospitalization and renal replacement therapy requirement in 1 year.

Keywords: Cardiac catheterization, chronic kidney disease, meta-analysis, prophylactic renal replacement therapy

META-ANALYSIS

INTRODUCTION

Contrast-associated acute kidney injury (CA-AKI), one of the major complications following coronary angiography, is the third leading etiology of hospital-acquired renal failure.[1] Contrast-associated acute kidney injury following cardiac catheterization is associated with increased in-hospital mortality and long-term complications.[2,3] Moreover, baseline advanced chronic kidney disease (CKD) is a crucial risk factor for CA-AKI.[2,4]

Several interventions have shown benefits in preventing CA-AKI, including fluid supplements, a double dose of *N*-acetylcysteine, low-osmolarity contrast, and reducing the contrast media.[5-12] However, there are challenges for CKD patients who do not tolerate fluid supplements, particularly when they have advanced CKD (stages 4 and 5) or poor cardiac function. Therefore, prophylaxis of acute kidney injury in patients with baseline advanced CKD remains unclear.

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As the contrast media is excreted in the kidney, its elimination is decreased in advanced CKD patients. The half-life of iodinated contrast media in patients with normal renal function is approximately 2 hours. In comparison, in patients with advanced CKD, the elimination can be delayed to over 30 hours depending on the severity of renal dysfunction.[13] In this situation, hemodialysis (HD) effectively removes contrast media in CKD patients.[14] Moreover, HD has other benefits, such as fluid removal and correction of metabolic acidosis and electrolyte abnormalities.[15-17] There were studies evaluating the role of prophylactic renal replacement therapy (RRT) after coronary angiography. However, the results were controversial. Therefore, we performed a meta-analysis to confirm the benefits of prophylactic RRT in CKD patients after cardiac catheterization.

METHODS

Search Strategy

Two investigators (Y.T. and W.V.) independently searched for published studies indexed in MEDLINE and EMBASE databases and written in the English language from inception to December 2022 using the same search strategy (Figure 1) using the terms: "hemodialysis," "hemofiltration," "contrast-induced nephropathy," "chronic kidney disease," "coronary angiography," and "cardiac catheterization." A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

Inclusion Criteria

The eligibility criteria included the following:

1. Cohort (prospective or retrospective) or case–control studies of prophylactic RRT in CKD patients who underwent coronary angiography reporting incidence of 1-year mortality, dialysis during hospitalization, or RRT requirement in 1 year.
2. Studies that provided the relative risk, hazard ratio, odd ratio, incidence ratio, or standardized incidence ratio with 95% CIs or sufficient raw data for the calculations.
3. Studies where CKD patients who underwent coronary angiography and not getting prophylactic RRT were used as controls.

Two investigators independently determined the study eligibility (Y.T. and W.V.), and the differences were resolved by mutual consensus. Newcastle–Ottawa quality assessment scale was used to evaluate each study in 3 domains: recruitment of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies.[18]

Data Extraction

A standardized data collection form was used to obtain the following information from each study: title of study, name of the first author, year of study, year of publication, number of participants, demographic data of participants, the method used to identify cases and controls, the method used to diagnose the outcomes of interest (1-year mortality, dialysis during hospitalization, and RRT requirement in 1 year), average duration of follow-up with adjusted confounders, and adjusted effect estimate with 95% CI and adjusted covariates in the multivariable analysis. To ensure accuracy, each investigator independently performed this data extraction process. Any data discrepancy was resolved by referring to the original articles.

Statistical Analysis

We performed a meta-analysis on included cohort studies using a random-effect model. The studies were excluded from the analysis if they did not present an outcome in each intervention group or did not provide enough information required for comparison. We pooled the point estimates from each study using the generic inverse-variance method of Der Simonian and Laird.[19] The effect size heterogeneity was estimated using the I^2 statistic and Q statistic. For the Q statistic, substantial heterogeneity was defined as $P < .10$. The I^2 statistic ranges in value from 0% to 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25\%$-50%, moderate heterogeneity; and $I^2 > 50\%$, substantial heterogeneity).[20] A sensitivity analysis was performed to assess each study's influence on the overall results by omitting one study at a time. We evaluated the publication bias using a funnel plot and Egger's regression test as appropriate given the known limitations of these methods,[21] in which $P < .05$ was considered significant. All data analyses were performed using the Stata SE 15.1 software from StataCorp LP.

RESULTS

Description of Included Studies

Our search strategy yielded 800 potentially relevant articles (645 articles from EMBASE and 155 from MEDLINE). After excluding 127 duplicated articles, 673 articles proceeded to title and abstract review. Six hundred four articles were excluded at this stage since they were not cohort studies, did not report the outcome of interest, or were not conducted in CKD patients who underwent coronary angiography, resulting in 69 articles for full-length article review. Among them, 64 studies were excluded, as they were descriptive studies without comparison and unclear outcome definitions. Therefore, 5 retrospective cohort studies were included in this meta-analysis. Figure 1 outlines the search and literature review process. Summaries of clinical characteristics and outcomes of the included studies are shown in Table 1.

Quality Assessment of Included Studies

Newcastle–Ottawa scales of the included studies are described in Supplementary Table 1. The scale uses a star system (0-9) to evaluate included studies on 3 domains:

HIGHLIGHTS

- Prophylactic renal replacement therapy (RRT) failed to demonstrate a 1-year mortality benefit in patients with chronic kidney disease undergoing cardiac catheterization.
- Prophylactic RRT prevented hemodialysis required during hospitalization by 87%.
- The incidence of RRT required in 1 year was 71% less in the prophylactic RRT group.

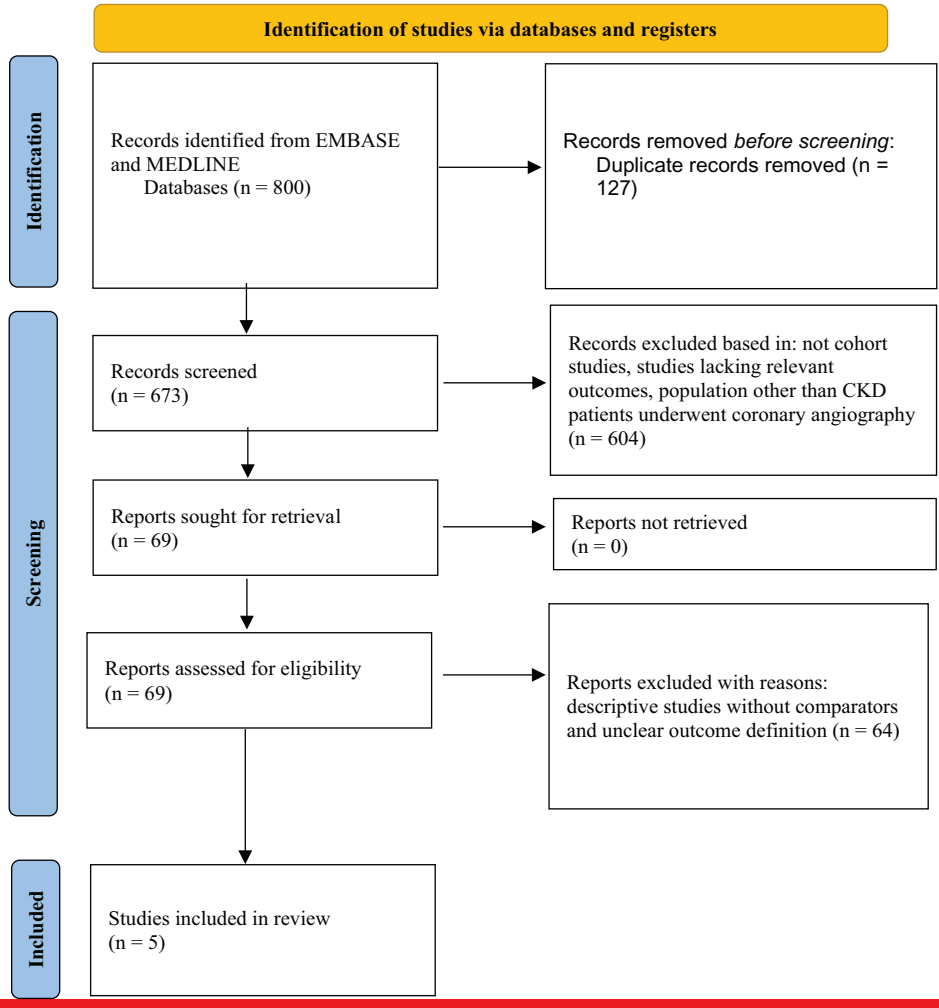

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram of study selection.

selection, comparability, and outcomes. Higher scores represent higher study quality. Intra-study risk of bias of included studies is also described in Supplementary Figure 1 and 2.

Meta-Analysis Results

Five studies were included in this meta-analysis, involving 532 CKD patients who underwent coronary angiography (268 had prophylactic RRT, and 264 did not have prophylactic RRT). Prophylactic RRT in 3 out of 5 studies was HD,[22-24] and the other 2 studies were hemofiltration.[25,26] Only 3 studies showed the association between decreasing 1-year mortality rate and prophylactic RRT.[24-26] While the study by Hsieh et al[23] showed no significant benefit of prophylactic RRT in 1-year mortality. The pooled analysis revealed a non-significant decreased risk of 1-year mortality in CKD patients who underwent coronary angiography and prophylactic RRT compared to those who did not have prophylactic RRT (RR = 0.59; P = .18; CI: 0.28-1.2795, I^2 = 60.4%) (Figure 2).

Among the 5 included studies, 3 reported the incidence of dialysis during hospitalization, and 2 reported the RRT requirement in 1 year. The pooled analysis revealed a significantly decreased risk of hemodialysis during hospitalization and RRT requirement in 1 year among the CKD patients who underwent coronary angiography and prophylactic HD compared to those who did not have prophylactic HD (RR = 0.13; P = .001; CI: 0.04-0.43, I^2 = 9.1% and RR = 0.29; P = .015; CI: 0.11-0.78, I^2 = 49.9%, respectively) (Figures 3 and 4).

Sensitivity Analysis

We conducted a sensitivity analysis by excluding one study at a time and finally performed the pooled analysis. In the overall analysis, no result was significantly altered. Similarly, no result was changed considerably in the subgroup analysis.

Publication Bias Assessment

The publication bias among the studies was visualized and estimated from the funnel plot (Figures 5, 6 and 7). However, Egger's test was not performed due to the low number of studies.

DISCUSSION

The incidence of atherosclerotic cardiovascular disease in CKD patients is high,[27] and coronary angiography in this population increases the risk of developing CA-AKI. Subsequently, CA-AKI is associated with increased length of hospital stay, cost, and mortality.[28] Patients with CA-AKI who required dialysis had up to 30% in-hospital mortality,

Table 1. Characteristic of Included Trials

Author (year)	Design	Country	Number of Patients	Age (years)	Baseline Renal Function; Creatinine (mg/dL)		Contrast Agent	Volume of Contrast (mL)		Standard Treatment
					Control	RRT Group		Control	RRT Group	
Hsieh Y et al, 2004	Retrospective	Taiwan	40 (20/group)	40	3.5	3.9	Ultravist	NA	NA	NA
Chen H et al, 2021	Retrospective, propensity score matching	Taiwan	236 (118/group)	73	3.2	3.1	Omnipaque	NA	NA	IV NSS at 1 mL/kg/h for 6 hours before and 12 hours after exposure to the contrast medium
Marenzi G et al, 2015	Interventional study with historical control	Italy	60 (30/group)	79	2.5	2.4	Non-ionic, low- or iso-osmolar contrast agents	211 ± 105	236 ± 167	IV NSS at a rate of 1 mL/kg/h for 12 hours before and after coronary angiography
Marenzi G et al, 2003	RCT	Italy	114 (intervention = 58, control = 56)	69	3.1	3	Iopentol	258 ± 132	247 ± 125	IV NSS at a rate of 1 mL/kg/h given 6-8 hours before and 24 hours after the coronary procedure
Lee P et al, 2007	RCT	Taiwan	82 (intervention = 42, control = 40)	65	4.9	4.9	Omnipaque	108.1 ± 32.6	106.8 ± 44	IV NSS at 1 mL/kg/h for 6 hours before and 12 hours after contrast medium exposure

NSS, normal saline solution; RCT, randomized controlled trial; RRT, renal replacement therapy.

54.5% 1-year mortality, and 80% mortality in 2 years.[28,29] Therefore, the prevention of CA-AKI is important in patients with preexisting advanced renal failure.

The pathophysiology of CA-AKI is complex and remains unclear. Multiple factors, including vasoconstriction, oxidative stress, and direct tubular toxicity, could be contributing to the pathogenesis of CA-AKI.[30] In patients with advanced kidney disease, excretion of contrast media is delayed,[31] and HD can facilitate rapid removal of contrast media.[14,31-33] However, the benefits of prophylactic HD after coronary angiography in previous studies were controversial due to small sample sizes, different types and doses of contrast media, and variations in baseline renal function.

Our meta-analysis demonstrated that prophylactic RRT did not seem to improve 1-year survival compared to standard treatment (RR = 0.59; $P = .18$; CI: 0.28-1.2795, $I^2 = 60.4\%$). However, the risk of HD during hospitalization and RRT requirement in 1 year appeared to be lower with prophylactic RRT. Moreover, heterogeneity across included trials was found. There are multiple considering factors to determine the high-risk population and potential benefits of prophylactic RRT as follows:

Preexisting CKD is a strong risk factor for CA-AKI, with lower baseline kidney function associated with higher risk. A high-risk population with very low baseline creatinine clearance is vulnerable to further kidney injury after exposure to contrast media. According to the meta-analysis by Song et al,[34] prophylactic HD was not beneficial in patients with baseline CKD state 3. However, a significant benefit (RR = 0.19, $P < .001$) was found in patients with CKD stages 4-5 compared to standard treatment. In one of the included studies in our meta-analysis, patients with advanced CKD (baseline creatinine of 4.9 mg/dL) had immense improvement in renal outcome (lower serum creatinine concentration, in-hospital RRT, and requirement of long-term dialysis) from prophylactic HD compared to the control group.[22] Therefore, prophylactic RRT could be considered in this high-risk population.

Patients with acute myocardial infarction (AMI) require primary percutaneous coronary intervention (PCI) to restore coronary blood flow, preserve ventricular function, and improve survival.[35,36] Nevertheless, patients with AMI treated with primary PCI are at higher risk for developing CA-AKI than those undergoing elective PCI.[37] Several contributing factors, such as hypotension or shock from left ventricular dysfunction, a large volume of contrast media, and impracticability to initiate a renal prophylactic therapy due to the urgency of coronary intervention, are associated with AKI in this setting.[37] Some studies demonstrated that AMI and CKD are a high-risk combination with up to 30% in-hospital mortality in patients with end-stage renal disease.[38]

Moreover, low-osmolarity contrast medium (LOCM) and iso-osmolarity contrast medium (IOCM) are associated with less kidney injury compared to high-osmolarity contrast media.[39] Therefore, LOCM and IOCM are recommended for coronary

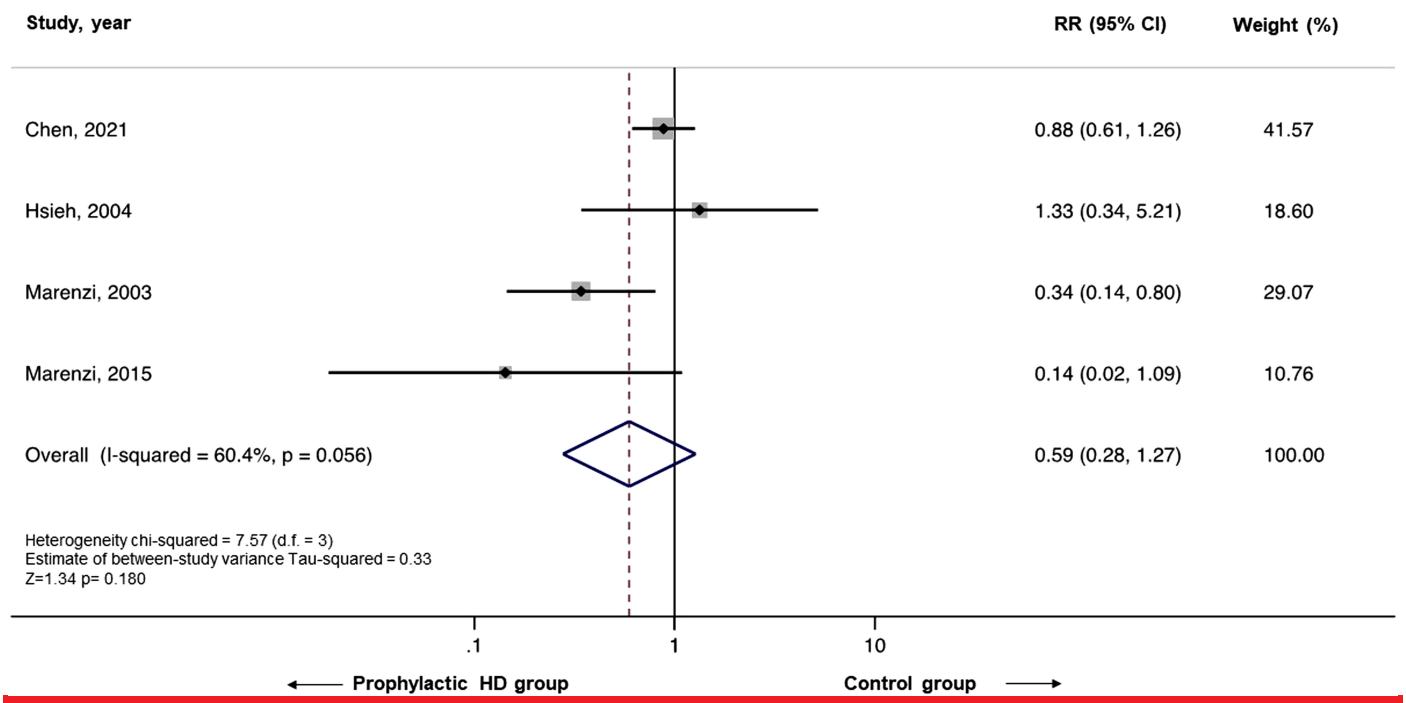

Figure 2. Forest plot of the included studies assessing the association between prophylactic HD and 1-year mortality among patients with CKD who underwent coronary angiography. CKD, chronic kidney disease; HD, hemodialysis.

angiography and intervention as class I recommendations from the European Society of Cardiology and the American Heart Association/American College of Cardiology.[40,41] Benefits of LOCM in decreasing CA-AKI compared to IOCM were controversial. Jovin et al[42] performed a study using the Veterans Affairs database and showed no difference in major adverse renal and cardiovascular events between LOCM and IOCM use.

The volume of contrast media is one of the most important contributing factors for CA-AKI in patients with CKD. Marenzi et al[25,26] demonstrated significant renal outcomes and 1-year mortality benefits of prophylactic periprocedural hemofiltration in 2003 and 2015. The studies were conducted in advanced CKD patients (creatinine level >2 mg/dL[26] and estimated glomerular filtration rate ≤30 mL/min/1.73 m^2)[25] who were exposed to a high volume of contrast agent (mean

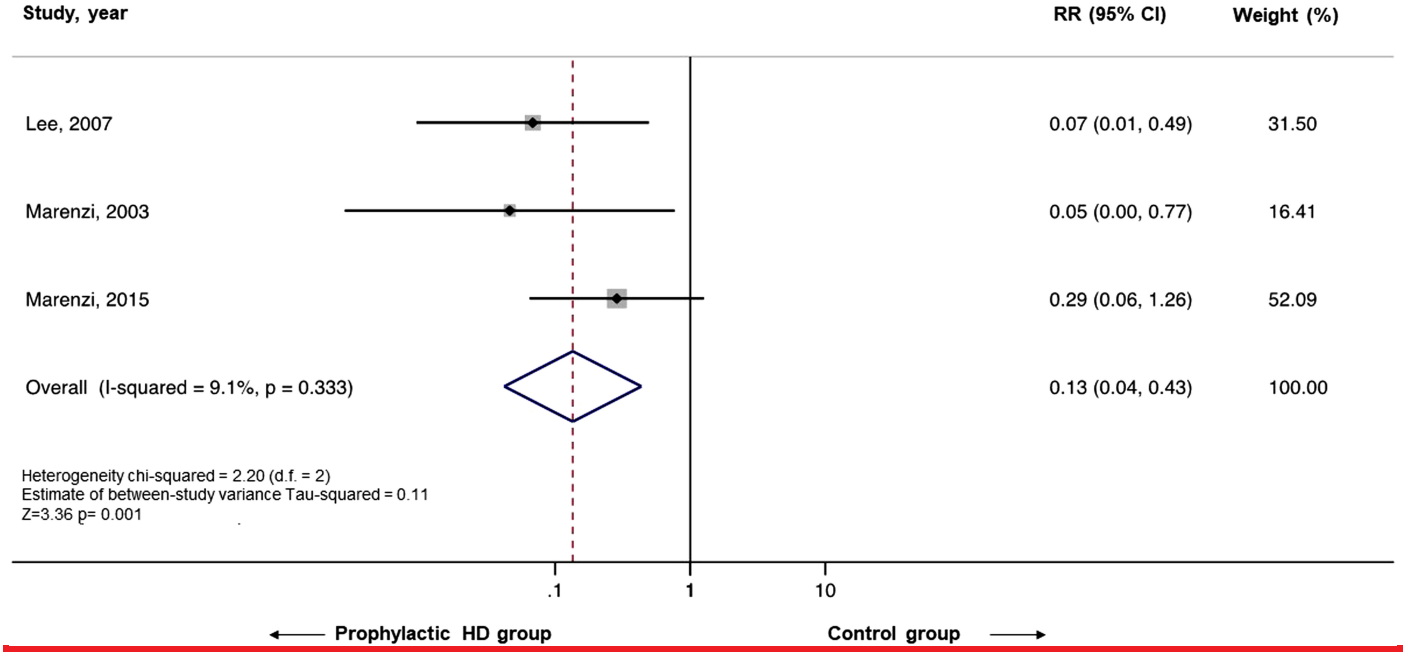

Figure 3. Forest plot of the included studies assessing the association between prophylactic HD and dialysis during hospitalization among patients with CKD who underwent coronary angiography. CKD, chronic kidney disease; HD, hemodialysis.

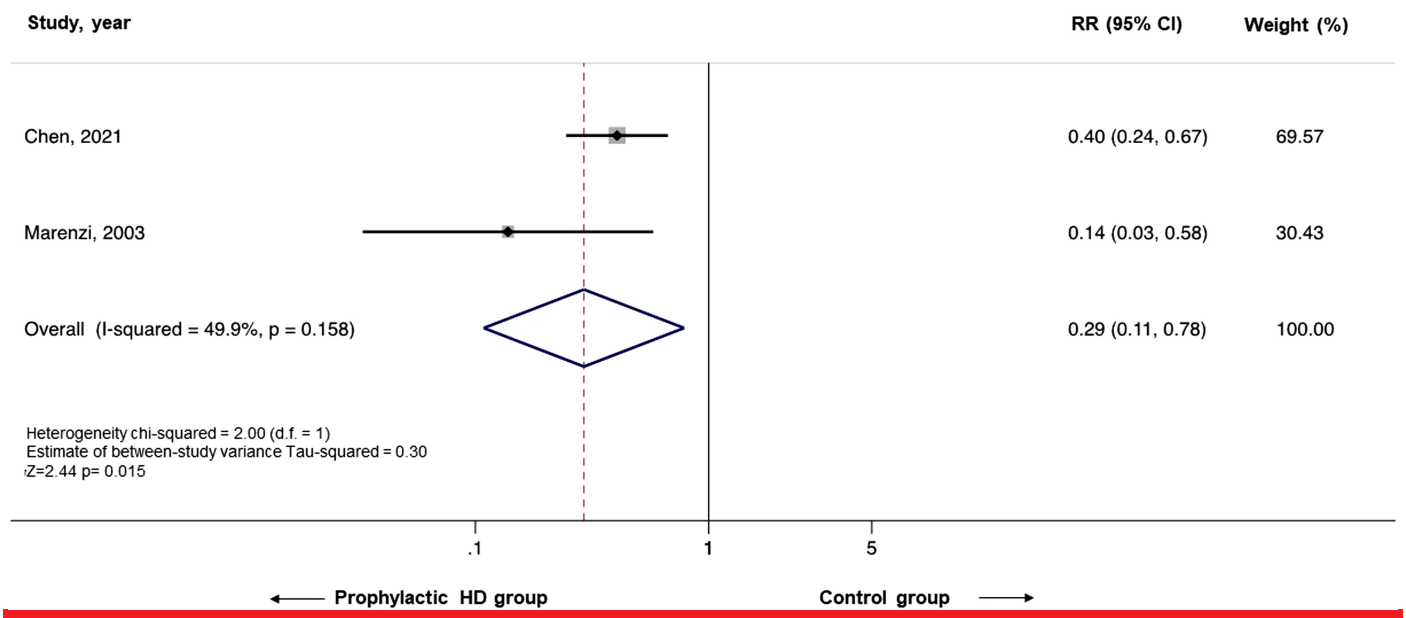

Figure 4. Forest plot of the included studies assessing the association between prophylactic HD and RRT required in 1 year among patients with CKD who underwent coronary angiography. CKD, chronic kidney disease; HD, hemodialysis; RRT, renal replacement therapy.

contrast volume >200 mL). Thus, significant benefits could be more noticeable in studies performed on patients undergoing complex coronary intervention requiring high contrast volume.

Modalities of RRT are another considered factor. Hemodialysis can induce hypovolemia, consequently, reduce renal blood flow, and result in renal ischemic injury.[43] A hemofiltration is a continuous form of RRT that provides a hemodynamic stability[44,45] and prevents periods of hypovolemia that may occur during the hemodialysis.[26] These effects are helpful in patients undergoing coronary intervention with critical conditions such as pulmonary edema, valvular heart disease, or left ventricular dysfunction. Two studies in our meta-analysis used hemofiltration as RRT and showed significant 1-year mortality benefits compared to the control group.[25,26] Song et al[34] demonstrated that continuous RRT is more effective than HD in preventing CA-AKI. Hemofiltration has some limitations, including increased hospital costs and close monitoring in the intensive care unit. However, the prophylactic strategy with hemofiltration may be applied to critically ill cardiac patients exposed to a high volume of contrast agents from complex coronary procedures.

Study Limitations

There are some limitations in our meta-analysis. First, our study included only 5 studies, which may underpower

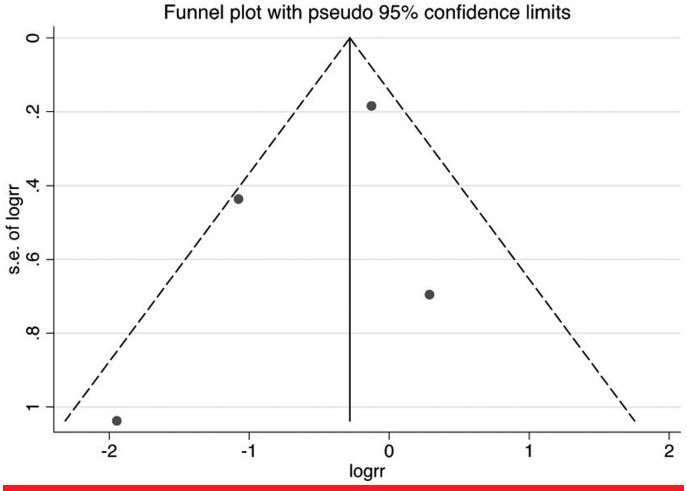

Figure 5. Funnel plot of prophylactic HD in patients with CKD who underwent coronary angiography and 1-year mortality. Circles represent observed published studies. CKD, chronic kidney disease; HD, hemodialysis.

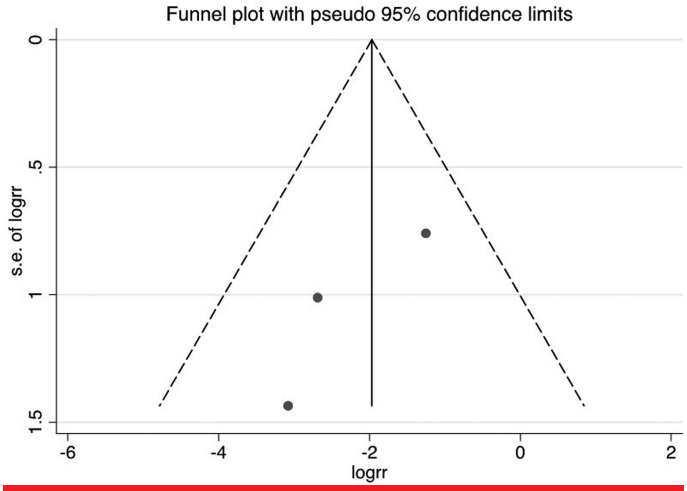

Figure 6. Funnel plot of prophylactic HD in patients with CKD who underwent coronary angiography and dialysis during hospitalization. Circles represent observed published studies. CKD, chronic kidney disease; HD, hemodialysis.

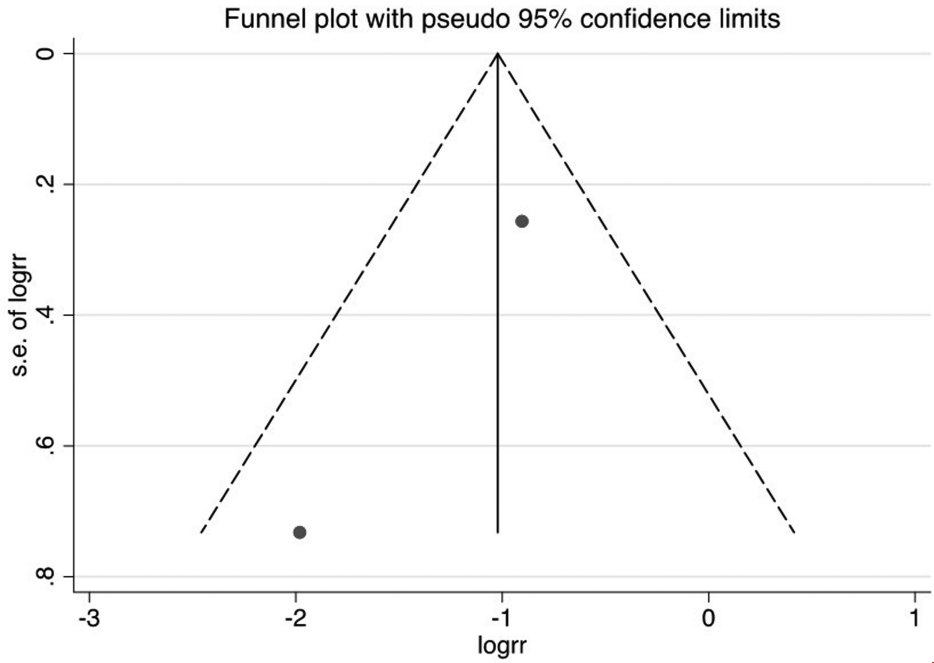

Figure 7. Funnel plot of prophylactic HD in patients with CKD who underwent coronary angiography and RRT required in 1 year. Circles represent observed published studies. CKD, chronic kidney disease; HD, hemodialysis; RRT, renal replacement therapy.

Table 2. Protocol of Renal Replacement Therapy of Included Trials

		Hemodialysis			
Author (year)	**Time from Contrast Exposure to the Start of RRT**	**Duration of Dialysis (hours)**	**Blood Flow (mL/min)**	**Dialysate Flow (mL/min)**	**Membrane**
Hsieh Y et al, 2004	NA	4	200	500	High
Chen H et al, 2021	Within 2 hours	4	150	500	High flux polysulfone
Lee P et al, 2007	81 ± 32 minutes	4	150	500	High of low flux
		Hemofiltration			
Author (year)	Timing of Hemofiltration		Blood Flow (mL/min)	Isotonic Replacement Fluid Flow (mL/h)	
Marenzi G et al, 2003	4-6 hours before the scheduled coronary procedure; treatment was resumed after the procedure was completed and continued for 18-24 hours.		100	1000 No net fluid loss resulted	
Marenzi G et al, 2015	3-hour treatment with veno-venous hemodiafiltration within 1 hour after PCI		200-250	2000	

PCI, percutaneous coronary intervention; RRT, renal replacement therapy.

our results and conclusion. Second, there is a lack of ethnic diversity as all included studies were conducted in only Taiwan and Italy. Finally, our analysis included participants with a range of coronary diseases, such as patients who underwent elective coronary angiography and patients with acute coronary syndrome who required emergent cardiac catheterization. The different profiles of coronary heart disease and urgency of cardiac catheterization may have other vulnerabilities of CA-AKI. According to our results, large randomized control trials are required to provide more information that will lead to specific interventions to prevent CA-AKI in CKD patients undergoing cardiac catheterization.

CONCLUSION

Our study demonstrated that prophylactic RRT after cardiac catheterization and PCI appeared to reduce the risk of HD during hospitalization and RRT required in 1 year. Although, this improvement in renal outcome may not translate into a 1-year mortality benefit. Further studies with a large patient population are needed to understand better the role of prophylactic RRT in patients undergoing cardiac catheterization and coronary intervention. In clinical practice, either HD or hemofiltration, RRT could be considered in a high-risk population, especially in patients with advanced CKD exposed to a high volume of contrast agents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.T., S.S.; Design – Y.T., S.S., W.V.; Supervision – W.V.; Analysis and/or Interpretation – Y.T., S.S., W.V.; Literature Search – Y.T., S.S., W.V.; Writing – Y.T.; Critical Review – S.S., W.V.

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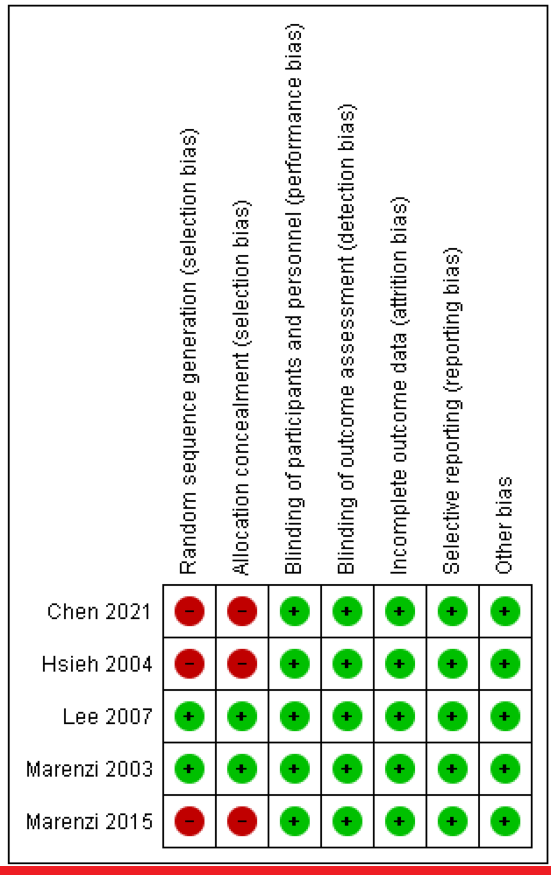
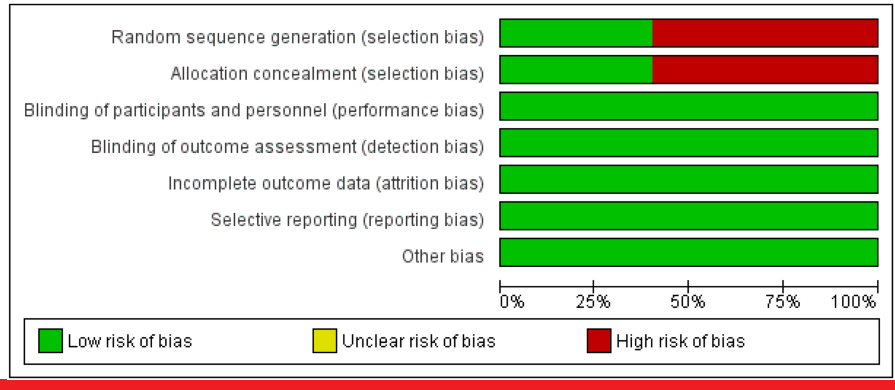
Supplementary Table 1. Newcastle-Ottawa Scale Assessment of Included Studies

Newcastle-Ottawa Scale items	Chen H et al 2021	Hsieh Y et al 2004	Lee P et al 2007	Marenzi G et al 2003	Marenzi G et al 2015
Representativeness of the exposed cohort	1	1	1	1	1
Selection of the non-exposed cohort	1	1	1	1	1
Ascertainment of exposure	1	1	1	1	1
Demonstration that outcome of interest was not present at start of study	1	1	1	1	1
Comparability	1	1	1	1	1
Assessment of outcome	1	1	1	1	1
Follow-up was long enough for outcomes to occur	1	1	0	1	1
Adequacy of follow-up of cohorts	1	1	1	1	1
Total score	8	8	7	8	8



Supplementary Figure 1. Risk of bias summary of included studies.



Supplementary Figure 2. Risk of bias graph of included studies.