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Accelerated-strategy renal replacement therapy for critically ill patients:
A systematic review and meta-analysis

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Abstract

Background: The aim of this study was to investigate the clinical effect and safety of accelerated-strategy initiation of renal replacement therapy (RRT) in critically ill patients.

Methods: PubMed, Embase, OVID, EBSCO, and the Cochrane Library databases were searched for relevant articles from inception to December 30, 2020. Only RCTs that compared the clinical efficacy and safety between accelerated-strategy RRT and standard-strategy RRT among critically ill adult patients with acute kidney injury (AKI) were included. The primary outcome was 28-day mortality.

Results: A total of 5279 patients in 12 RCTs were included in this meta-analysis. The 28-day mortality rates of patients treated with accelerated and standard RRT were 37.3% (969/2596) and 37.9% (976/2573), respectively. No significant difference was observed between the groups (OR, 0.92; 95% CI, 0.70–1.12; I^2 = 60%). The recovery rates of renal function were 54.5% and 52.5% in the accelerated- and standard-RRT groups, respectively, with no significant difference (OR, 1.03; 95% CI, 0.89–1.19; I^2 = 56%). The rate of RRT dependency was similar in the accelerated- and standard-RRT strategies (6.7% vs 5.0%; OR, 1.11; 95% CI, 0.71–1.72; I^2 = 20%). The accelerated-RRT group displayed higher risks of hypotension, catheter-related infection, and hypophosphatemia than the standard-RRT group (hypotension: OR, 1.26; 95% CI, 1.10–1.45; I^2 = 36%; catheter-related infection: OR, 1.90; 95% CI, 1.17–3.09; I^2 = 0%; hypophosphatemia: OR, 2.11; 95% CI, 1.43–3.15; I^2 = 67%).

Conclusions: Accelerated RRT does not reduce the risk of death and does not improve the recovery of kidney function among critically ill patients with AKI. In contrast, an increased risk of adverse events was observed in patients receiving accelerated RRT. However, these findings were based on low quality of evidence. Further large-scale RCTs is warranted.

Abbreviations: AKI = acute kidney injury, CRRT = continuous renal replacement therapy, IHD = intermittent hemodialysis, RCT = randomized controlled trials, RRT = replacement therapy.

Keywords: accelerated renal replacement therapy, adverse event, mortality, renal function

1. Introduction

Organ dysfunction is an almost inevitable complication during the intensive care unit (ICU) stay of critically ill patients. Moreover, multiorgan failure is the most common cause of death, and acute kidney injury (AKI) is one of the most common condition reported, developing in over half of ICU patients.[1] Furthermore, AKI is associated with a longer hospital stay and higher mortality and health care costs.[1–4] Renal replacement therapy (RRT) is the most important measure to provide renal support to ICU patients with AKI. Appropriate RRT can help maintain acid–base balance, mitigate excess fluid, correct electrolyte abnormalities, and remove fatal toxins in patients with renal failure. Most importantly, timely and effective RRT can save lives and improve the outcomes in patients with AKI-related complications.[4] However, the optimal timing for initiating RRT in critically ill patients with AKI remains unclear.

Initiation of RRT before the onset of overt complications of kidney failure is reported to restore and correct mild acid–base abnormalities, modify the fluid status, and prevent the accumulative metabolic hazards caused by untreated AKI.[4] By contrast, the accelerated-RRT strategy could be introduced in patients who survived and spontaneously recovered

kidney function without the need for RRT. RRT also carries the risk of several adverse events, including hemodynamic disturbance, electrolyte imbalance, undesired substance removal (e.g., antibiotics, micronutrients), and dialysis catheter–associated complications. Although numerous randomized controlled trials (RCTs)[5–16] have been conducted to compare the accelerated-strategy and standard-strategy RRT among critically ill patients, the findings seem to conflict. Therefore, we conducted this systematic review and meta-analysis of RCTs to assess the clinical effect and safety of accelerated-strategy RRT in critically ill patients.

2. Methods

2.1. Study search and selection

PubMed, Embase, OVID, EBSCO and the Cochrane Library databases were searched for relevant articles from inception to December 30, 2020. The following search terms were used: "early," "accelerate," "timing," "dialysis," "renal replacement," "hemodialysis," "hemofiltration," "hemodiafiltration," "acute kidney," "acute renal," "anuria," "oliguria," "acidosis," "organ failure," "RCT," and "random." Only RCTs that compared the clinical efficacy and safety of accelerated-strategy RRT with standard-strategy RRT among critically ill adult patients with AKI were included. The reference lists of the relevant articles were also searched manually to identify additional eligible articles. No language limitations were applied. Two authors (SHL and LCL) independently reviewed the identified abstracts and selected articles for full review. Disagreements were resolved by the third author (WTL). This systematic review followed the guidelines of the preferred reporting items for systematic reviews and meta-analyses and registered in PROSPERO (CRD42020221342).[17]

2.2. Patient and public involvement

This is a meta-analysis based on study-level data, and no individual-level data were involved in the study or in defining the research question or outcome measures.

2.3. Study selection and data extraction

Three investigators independently screened and reviewed each study. Studies were included if they met the following criteria: (1) patients with AKI, (2) age ≥ 18 years, (3) accelerated-strategy RRT intervention compared with standard-strategy RRT, (4) RCT design, and (5) efficacy and adverse events as the outcomes. In vitro research, animal studies, and pharmacokinetic–pharmacodynamic assessments were excluded. In cases of disagreements, fourth and fifth investigators were consulted. For each included study, the following data were extracted: year of publication, study design, study period, study population, clinical outcomes, and risk of adverse events (AEs).

2.4. Outcome measurement

The primary outcome was 28-day mortality. Secondary outcomes were 14-day mortality, 30-day mortality, 60-day mortality,
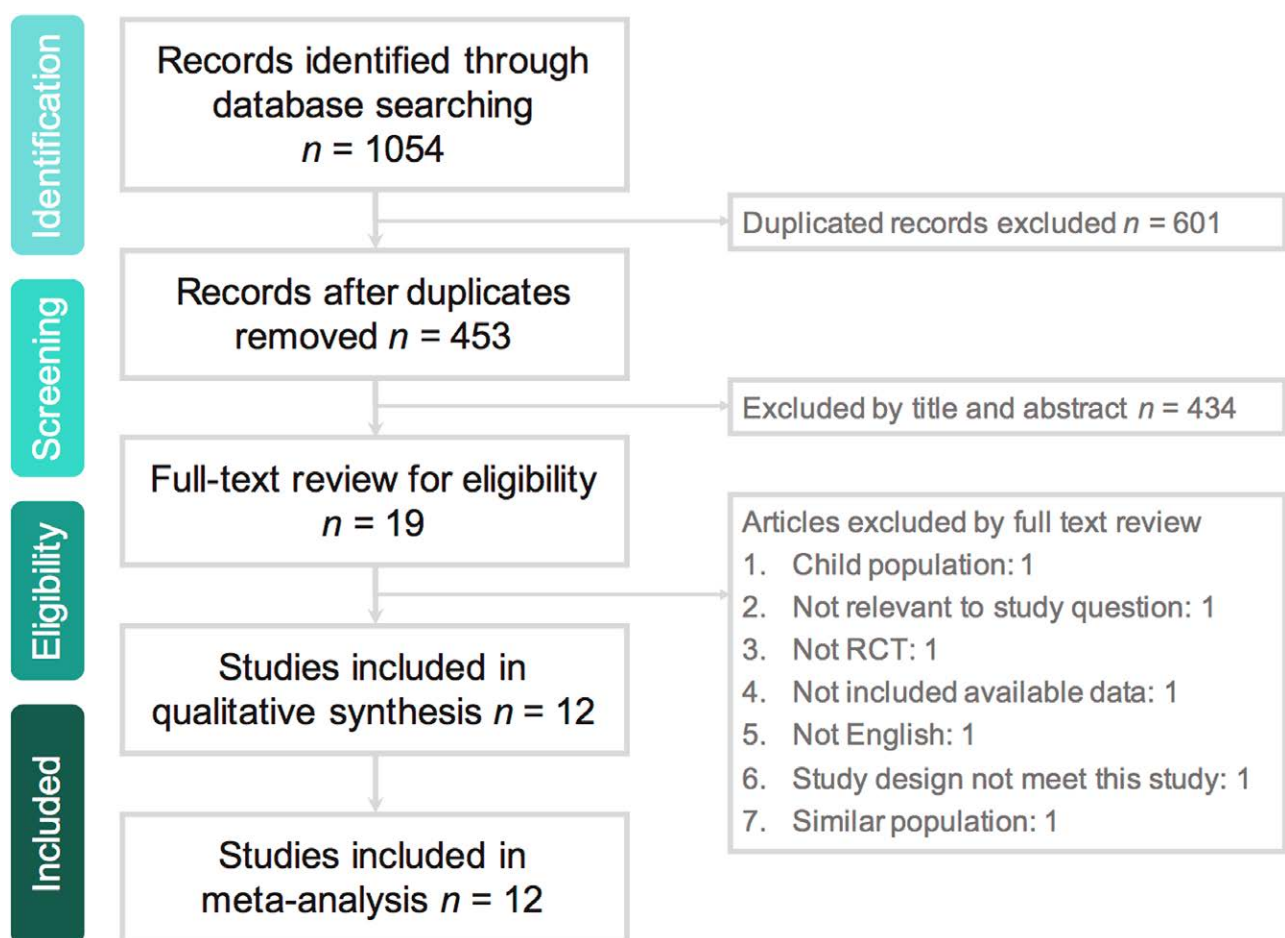

Figure 1. Flowchart of the study selection for meta-analysis.

90-day mortality, ICU length of stay (LOS), hospital LOS, recovery of renal function, RRT dependence, and risk of complications.

2.5. Data analysis

The Cochrane risk-of-bias tool was used to assess the quality of the included RCTs and their associated risk of bias.[18] Statistical analyses were performed using the Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark), with a random-effects model. Pooled odds ratios (ORs) was used to assess categorical variables; pooled mean and standard difference were used to assess continuous variables; 95% confidence intervals (CIs) were calculated for all outcome analyses.

3. Results

The search of online databases yielded 1054 studies, among which 601 duplicates were excluded. Moreover, 434 studies were determined to be irrelevant after the title and abstract were screened, and 7 studies were excluded after the full text was screened. Therefore, 12 RCTs[5–16] were included in the meta-analysis (Fig. 1).

3.1. Study characteristics

Overall, 5279 patients in 12 RCTs were included in this meta-analysis (Table 1). Except for 4 RCTs[9,11,14,16] conducted in

a single center and one RCT[7] conducted in 2 centers, the studies were multicenter. Except for one multinational RCT,[5] the studies were conducted in one country, including Turkey (n = 1), Japan (n = 1), India (n = 1), Germany (n = 1), Canada (n = 1), Thailand (n = 1), the Netherlands (n = 1), and France (n = 4). Only 3 studies focused on surgical patients, and cardiovascular surgery was the most common surgery among these patients.[9,14,16] The risk of bias in each study is displayed in Figure 2. All 12 RCTs had a high risk of bias regarding allocation concealment and blinding of participants and personnel. Furthermore, 7 RCTs were determined to have a high risk of detection bias.[5,6,10–12,15,16]

3.2. Clinical efficacy

Overall, the 28-day mortality rates of patients assigned to the accelerated- and standard-RRT groups were 37.3% (969/2596), and 37.9% (976/2573). No significant difference was observed between the groups (OR, 0.92; 95% CI, 0.70–1.12; I^2 = 60%; Fig. 3). This similarity in terms of mortality between the accelerated- and standard-RRT group remained unchanged at different assessment times (ICU mortality: OR, 1.02; 95% CI, 0.89–1.17; I^2 = 0%. In-hospitality mortality: OR, 1.18; 95% CI, 0.83–1.67; I^2 = 48%. 60-day mortality: OR, 0.96; 95% CI, 0.75–1.23; I^2 = 31%. 90-day mortality: OR, 0.99; 95% CI, 0.78–1.25; I^2 = 44%). The leave-one-out sensitivity analysis revealed that the magnitude of association of different strategy of RRT with mortality was not influenced by individual studies.

Table 1.

Characteristics of the included studies.

Study, year	Study design	Study period	Study site	No. of patients	Accelerated RRT modality	Study population
Bouman et al, 2002[7]	Prospective, randomized, controlled trial	1998–2000	2 ICUs in the Netherlands	106	CRRT	Ventilated, severely ill patients who were oliguric despite massive fluid resuscitation, inotropic support, and high-dose intravenous diuretics
Durmaz et al, 2003[9]	Prospective, randomized controlled trial	1999–2001	1 center in Turkey	44	IHD	Patients with preoperative creatinine levels over 2.5 mg/dL but not requiring dialysis and undergoing primary elective CABG
Sugahara et al 2004[14]	Prospective, randomized controlled trial	1995–1997	1 center in Japan	40	CRRT	Patients with AKI following CABG
Payen et al, 2009[13]	Prospective, randomized open trial	1997–2000	12 mixed ICUs in France	80	CRRT	Clinically identified patients with an infection associated with at least 2 SIRS criteria and sepsis-induced organ failures within the 24 hours
Jamale et al, 2013[11]	Prospective, open-label, randomized controlled trial	2010–2012	1 center in India	208	IHD	Adult patients with severe AKI
Combes et al, 2015[8]	Prospective, randomized controlled trial	2009–2012	Multicenter in France	224	CRRT	Patients with severe shock requiring high-dose catecholamines 3–24 h postcardiac surgery
Wald et al, 2015[15]	Open-label, parallel-arm feasibility, randomized controlled trial	2012–2013	12 centers in Canada	101	IHD/CRRT/SLED	Critically ill adults with volume replete severe AKI
Zarbock et al, 2016[16]	Parallel-group, randomized controlled trial	2013–2015	1 center in Germany	231	CRRT	Critically ill patients with AKI KDIGO stage 2 and a plasma neutrophil gelatinase-associated lipocalin level of >150 ng/mL
Gaudry et al, 2016[10]	Prospective, open-label, 2-group randomized trial	2013–2016	31 ICUs in France	620	IHD/CRRT	Adult patients with severe AKI KDIGO classification (stage 3) requiring mechanical ventilation, catecholamine infusion, or both.
Lumlertgul et al, 2018[12]	Prospective, open-label, 2-group randomized trial	2016–2017	5 ICUs in Thailand	118	CRRT	Adult patients with AKI and FST-nonresponsiveness (urine output <200 mL in 2 h)
Barbar et al, 2018[6]	Randomized, controlled, open-label trial	2012–2016	29 ICUs in France	488	IHD/CRRT	Patients with early-stage septic shock and severe AKI at the failure stage of the RIFLE classification system but without life-threatening complications related to AKI
Bagshaw et al, 2020[5]	Randomized, open-label, controlled trial	2015–2019	168 hospitals in 15 countries	3019	NA	Adult patient (≥18 years) admitted to an ICU with kidney dysfunction and severe acute kidney injury categorized as stage 2 or 3 as per the KDIGO classification

AKI, acute kidney injury; CABG, coronary artery bypass grafting; CRRT: continuous renal replacement therapy; FST, furosemide stress test; IHD: intermittent hemodialysis; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable; RIFLE, risk, injury, failure, loss, and end-stage kidney disease; SIRS, systemic inflammatory response syndrome; SLED, Sustained low-efficiency dialysis.
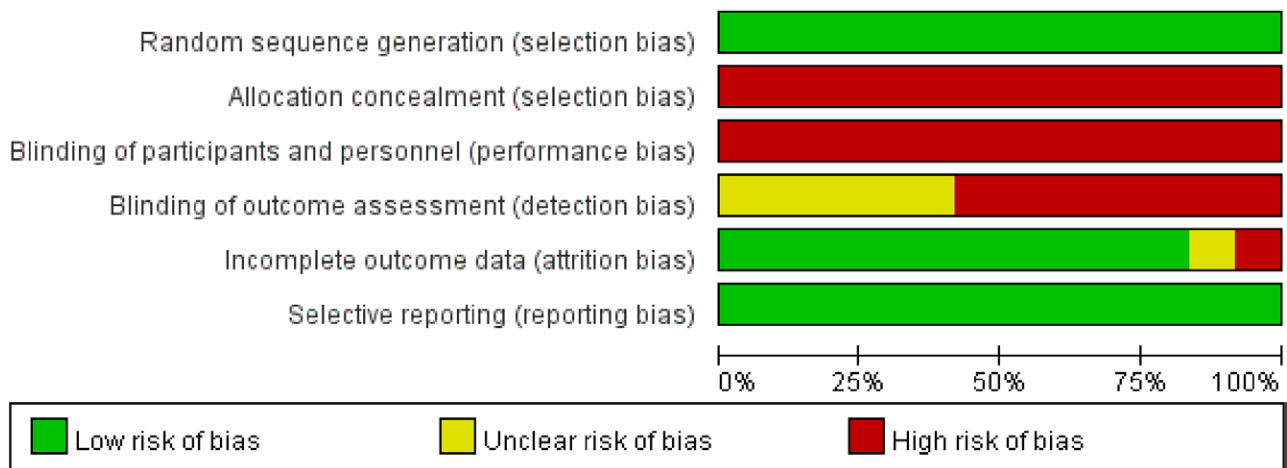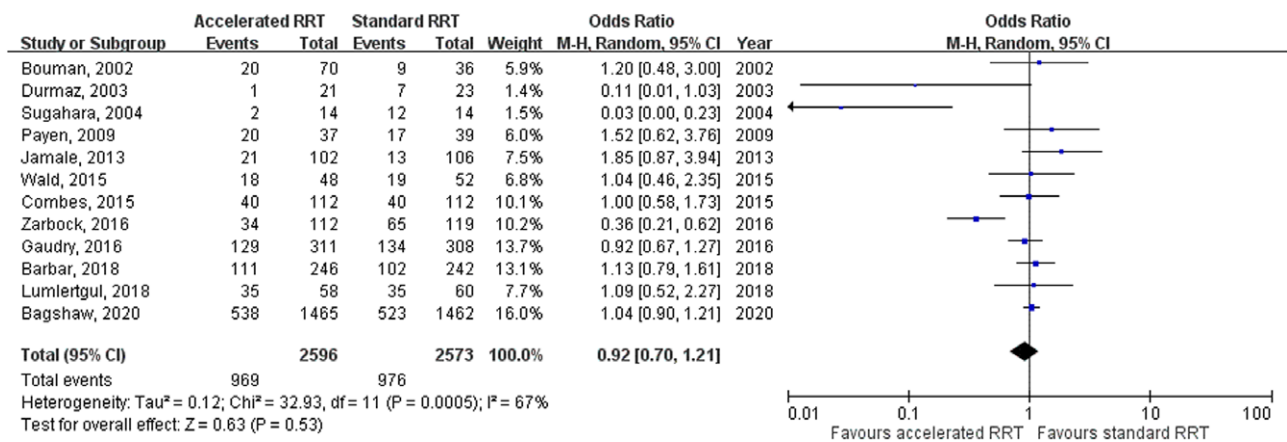
Figure 2. Summary of risk of bias.

Figure 3. Forest plot for 28-day mortality.

The recovery rates of renal function were 54.5% and 52.5% in the accelerated- and standard-RRT groups, respectively, with no statistical difference (OR, 1.03; 95% CI, 0.89–1.19; I^2 = 56%, Fig. 4). The rate of RRT dependency was similar between the accelerated- and standard-RRT strategies (6.7% vs 5.0%; OR, 1.11; 95% CI, 0.71–1.72; I^2 = 20%, Fig. 5), and the survival rates with RRT on day 28 were also similar between the accelerated- and standard-RRT strategies (OR, 0.8; 95% CI, 0.61–1.28; I^2 = 0%). Finally, the length of ICU stay was similar between the accelerated- and standard-RRT groups (standard mean difference: –0.3; 95% CI, –00.71 to 0.07; I^2 = 90%)

3.3. Risk of AEs

The accelerated-RRT group displayed higher risks of hypotension (OR, 1.26; 95% CI, 1.10–1.45; I^2 = 36%), catheter-related infection (OR, 1.90; 95% CI, 1.17–3.09; I^2 = 0%), and hypophosphatemia (OR, 2.11; 95% CI, 1.43–3.15; I^2 = 67%) than the standard-RRT group. By contrast, no significant difference was observed between the accelerated- and standard-RRT groups in the risks of hemorrhage (OR, 0.91; 95% CI, 0.65–1.27; I^2 = 7%), arrhythmia (OR, 1.28; 95% CI, 0.92–1.77; I^2 = 38%), hypokalemia (OR, 1.07; 95% CI, 0.83–1.37; I^2 = 0%), and hyperkalemia (OR, 0.52; 95% CI, 0.17–1.61; I^2 = 57%). The accelerated-RRT group displayed a lower risk of metabolic acidosis than the standard-RRT group (OR, 0.60; 95% CI, 0.39–0.90; I^2 = 0%).

4. Discussion

In this meta-analysis, 12 RCTs[5–16] comprising 5279 patients were reviewed to compare the efficacy and safety of accelerated-strategy RRT and standard-strategy RRT in the treatment of critically ill patients with AKI. We did not observe additional survival benefit of accelerated RRT in this meta-analysis. This finding was supported by the following evidence. First, the 28-day all-cause mortality did not differ between the patient receiving the accelerated-RRT and standard-RRT strategies. Second, this finding did not change in the leave-one-out sensitivity analysis. Third, the similarity between the accelerated-RRT and standard-RRT strategies in terms of mortality remained unchanged at different assessment times, including ICU, in-hospital, 60-day, and 90-day mortality. These findings were consistent with those of a meta-analysis by Gaudry et al,[19] which included 10 RCTs with 2143 patients; individual patient data were available for 9 studies (2083 patients) for analysis. A total of 1879 patients had severe AKI, and 946 and 933 patients were randomly assigned to the delayed and early RRT, respectively. Gaudry et al determined that 28-day mortality rate did not significantly differ between the delayed and early RRT group (366 [44%] of 837 vs 355 [43%] of 827; risk ratio 1.01 [95% CI, 0.91–1.13]; *P* = .80).[19] Our meta-analysis included one of the largest and most recent RCTs,[5] which comprised 3019 patients who had undergone randomization. This RCT was not included in the study by Gaudry et al[19] Our meta-analysis included 5279 patients who underwent randomization and could thus provide more
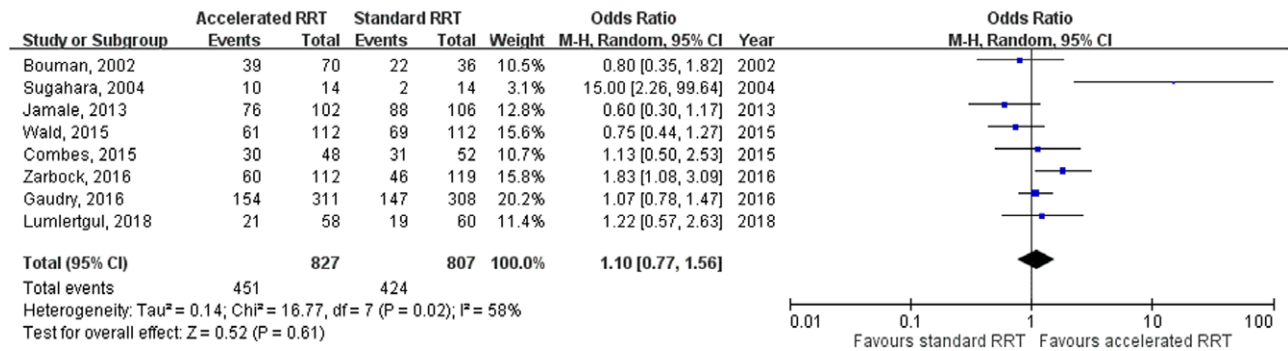
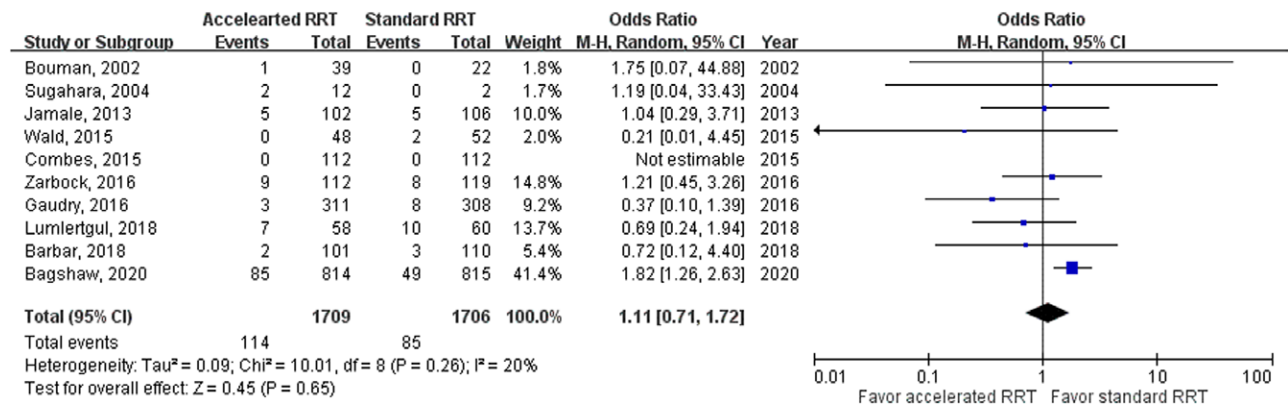**Figure 4.** Forest plot of the recovery of renal function.

Figure 5. Forest plot of renal replacement dependency.

robust and updated information than previous meta-analyses.[19–23] In summary, no difference in terms of mortality was observed between patients assigned to the accelerated- and standard-RRT strategies.

Furthermore, we also assessed the effect of accelerated RRT on renal outcomes. We did not observe any difference in terms of renal function recovery and RRT dependency between accelerated- and standard-RRT groups. Moreover, the survival rates with RRT dependency on day 28 did not differ between these 2 groups. These findings were consistent with previous studies[22,24] and suggested that accelerated RRT was not associated with a better renal outcome than standard RRT.

Finally, concerns are warranted regarding the AE associated with the accelerated-RRT strategy. In this meta-analysis, we determined that accelerated RRT was associated with higher risks of hypotension, catheter-related infection, and hypophosphatemia than standard RRT. However, a lower risk of metabolic acidosis was observed in the accelerated-RRT group than in the standard-RRT group. Furthermore, the risks of accelerated RRT associated with other AEs, including hemorrhage, arrhythmia, and the abnormality of potassium, were similar to those of standard RRT. Overall, our findings suggest that although the accelerated-RRT strategy may help with early correction of metabolic acidosis, this strategy is associated with an increased risk of several AEs, including hypotension, catheter-related infection, and hypophosphatemia. Therefore, clinicians should be aware of these possible complications during the implementation of the accelerated-RRT strategy for critically ill patients.

This meta-analysis had the major strength of including the most patients and the most updated studies. The study findings can thus provide more solid conclusions and timely information on this topic. However, this study had several limitations. First, the RCTs included in this meta-analysis had various study designs and populations. In addition, the diagnosis of

AKI, the RRT technology, and the inclusion criteria were not consistent across all included studies. These issues can cause high heterogeneity. In this study, we did the leave-one-out sensitivity analysis and still revealed that the magnitude of association of different strategy of RRT with mortality was not influenced by individual studies. Moreover, we conducted the subgroup analysis of 3 studies,[5, 6,10] which had clear AKI definitions for accelerated strategy RRT and standard-strategy RRT, and showed that no significant difference in 28-day mortality was found between the study and the control group (OR, 1.03; 95% CI, 0.91–1.07; I^2 = 0%). However, further study is needed to confirm our findings. Second, all 12 RCTs carried a high risk of bias regarding allocation concealment and blinding of participants and personnel, and most of the studies also had a high risk of detection bias. These problems may be associated with the low level of evidence of this meta-analysis.

5. Conclusions

In conclusion, this meta-analysis found that accelerated RRT does not reduce the risk of death and does not improve the recovery of kidney function among critically ill patients with AKI. In contrast, an increased risk of AEs was observed in patients receiving accelerated RRT. Therefore, our findings based mainly on the low quality of the evidence did not support the accelerated RRT strategy. However, further large-scale RCT is warranted to investigate the appropriate timing of implementing RRT for the critically ill patients.

Author contributions

SHL, CCL, SPC, SHH, and WTL designed the study. SHL, SPC, and LCL designed the search strategy and performed the search. SHL, CCL, SPL, LCL, and SHH performed abstract screening,

full text screening, data extraction, and risk of bias assessment. SHL, SPC, and LCL performed data analysis. CCL, SPC, LCL, and WTL helped in finalizing the full text screening, and in data interpretation. SHL and LCL participated in the statistical analysis, risk of bias assessment, and the rating of the certainty of evidence. CCL, SHH, and WTL drafted the manuscript. All authors revised the manuscript and read and approved the final manuscript.

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