Clinical Kidney Journal, 2022, vol. 15, no. 10, 1932–1945

https://doi.org/10.1093/ckj/sfac139
Advance Access Publication Date: 12 May 2022
Original Article

ORIGINAL ARTICLE

The impact of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury on mortality and clinical outcomes: a meta-analysis

Inês Castro [1], Miguel Relvas [2], Joana Gameiro [3], José António Lopes [3], Matilde Monteiro-Soares [4,5] and Luís Coentrão [1,2,6]

[1]Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal, [2]Nephrology Department, Centro Hospitalar Universitário São João, Porto, Portugal, [3]Department of Medicine, Division of Nephrology and Renal Transplantation, Centro Hospitalar Lisboa Norte, Lisbon, Portugal, [4]Community Medicine Department, Information and Decision in Health (MEDCIDS), University of Porto, Porto, Portugal, [5]Centre for Health Technology and Services Research (CINTESIS), University of Porto, Porto, Portugal and [6]Nephrology & Infectious Diseases R&D, i3S - Institute for Research & Innovation in Health, Porto, Portugal

Correspondence to: Miguel Relvas; E-mail: mic21892@gmail.com

ABSTRACT

Background. Renal replacement therapy (RRT) is essential in the presence of life-threatening complications associated with acute kidney injury (AKI). In the absence of urgent indications, the optimal timing for RRT initiation is still under debate. This meta-analysis aims to compare the benefits between early and late RRT initiation strategies in critically ill patients with AKI.

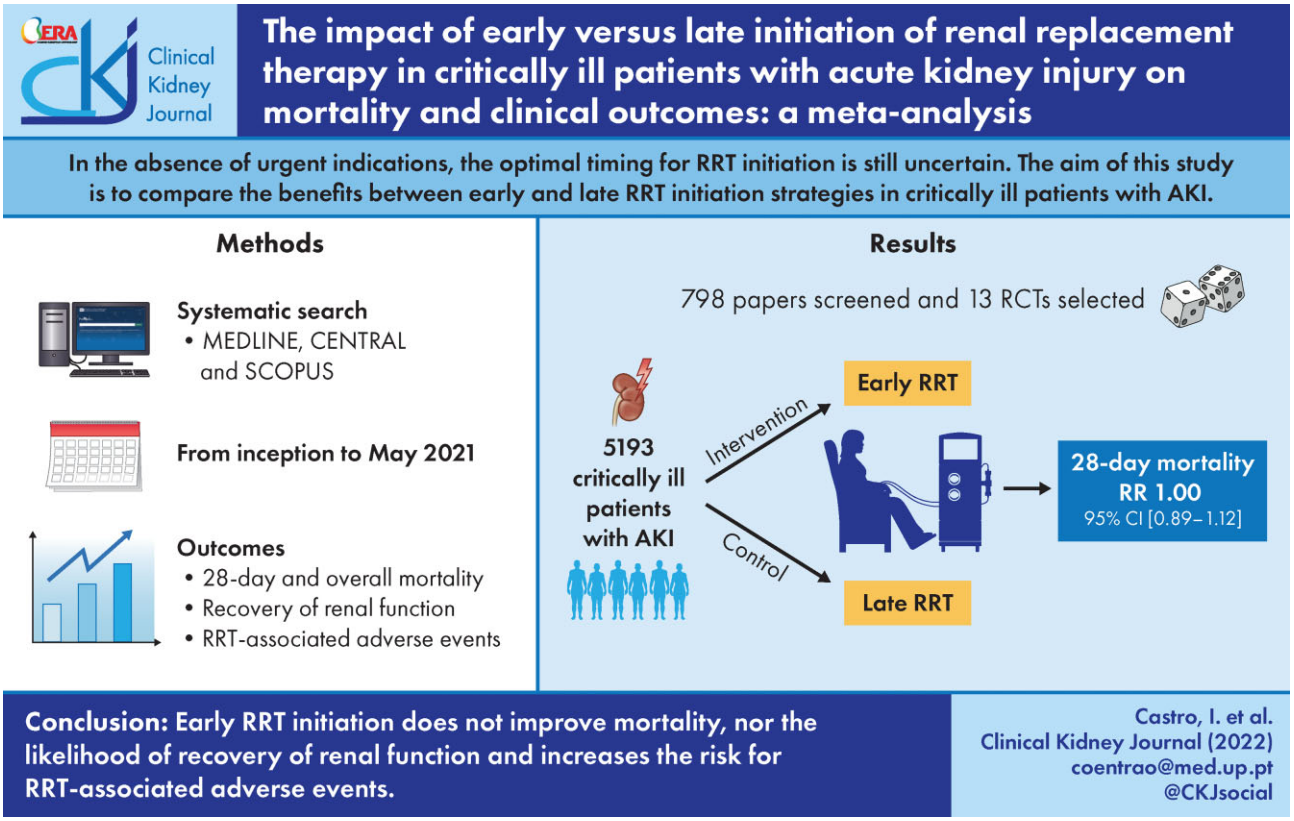
Methods. Studies were obtained from three databases [Medical Literature Analysis and Retrieval System Online (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus], searched from inception to May 2021. The selected primary outcome was 28-day mortality. Secondary outcomes included overall mortality, recovery of renal function (RRF) and RRT-associated adverse events. A random-effects model was used for summary measures. Heterogeneity was assessed through Cochrane I^2 test statistics. Potential sources of heterogeneity for the primary outcome were sought using sensitivity analyses. Further subgroup analyses were conducted based on RRT modality and study population.

Results. A total of 13 randomized controlled trials including 5193 participants were analysed. No significant differences were found between early and late RRT initiation regarding 28-day mortality [risk ratio (RR) 1.00; 95% confidence interval (CI) 0.89–1.12, $I^2 = 30\%$], overall mortality (RR 1.00; 95% CI 0.90–1.12, $I^2 = 42\%$) and RRF (RR 1.02; 95% CI 0.92–1.13, $I^2 = 53\%$). However, early RRT initiation was associated with a significantly higher incidence of hypotensive (RR 1.34; 95% CI 1.17–1.53, $I^2 = 6\%$) and infectious events (RR 1.83; 95% CI 1.11–3.02, $I^2 = 0\%$).

Conclusions. Early RRT initiation does not improve the 28-day and overall mortality, nor the likelihood of RRF, and increases the risk for RRT-associated adverse events, namely hypotension and infection.

Received: 8.10.2021; Editorial decision: 19.4.2022

GRAPHICAL ABSTRACT



Keywords: AKI, haemodialysis, intensive care, meta-analysis, renal replacement therapy

INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome defined as a sudden decrease in renal function [1]. AKI occurs in up to 50% of intensive care unit (ICU) patients and is associated with prolonged ICU and hospital stay, development of chronic kidney disease (CKD) and increased short and long-term mortality [2–4]. Renal replacement therapy (RRT) initiation in critically ill patients with life-threatening complications of AKI (e.g. pulmonary oedema, hyperkalaemia or refractory metabolic acidosis) is unanimously accepted [5]. However, in the absence of clearly urgent indications, the ideal timing for initiating RRT is still uncertain [6].

Early initiation of RRT may improve fluid and electrolyte balance, remove uraemic toxins and prevent other AKI-associated complications. However, many patients spontaneously recover from AKI with no need for RRT. Thus, a pre-emptive strategy may occasionally expose the patient unnecessarily to dialysis-related complications such as hypotension, infection, arrhythmia, or bleeding [5, 6]. Those patients could benefit from conventional or late initiation, where RRT is only started when a life-threatening complication emerges.

Various observational studies and small-randomized controlled trials (RCTs) [7–11] suggest early RRT initiation may improve survival, consistent with the ELAIN (Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury) trial's findings [12]—a large single-centre RCT focussed on the topic. Other RCTs [Initiation of Dialysis EArly Versus deLayed in Intensive Care Unit (IDEAL-ICU) or Artificial Kidney Initiation in Kidney Injury (AKIKI)] [13, 14] have failed to demonstrate significant differences in survival between early and delayed RRT initiation strategies. STandard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) [15], published in 2020, is the largest-to-date multinational RCT assessing RRT timing—it suggested that an accelerated RRT strategy is not associated with a lower risk of death at 90 days. Given the conflicting evidence available and to guide future clinical practice, the authors decided to conduct an updated meta-analysis comparing the impact on mortality, recovery of renal function (RRF) and RRT-associated complication rates of early versus late RRT initiation strategies in critically ill adult patients presenting with AKI.

MATERIALS AND METHODS

This meta-analysis was registered on International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021256868) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. The PRISMA checklist is presented in Supplementary data, Table S1.

Information sources and search strategy

Studies were identified by searching electronic databases and manually reviewing the reference lists of the selected articles. Three electronic databases were used, Medical Literature Analysis and Retrieval System Online (MEDLINE) (1991–2021), Scopus (1973–2021) and the Cochrane Central Register of

Controlled Trials (CENTRAL) (1945–2021). There were no restrictions on language, and the last search was run on 31 May 2021. Details regarding the search strategy used for each database are provided in the Supplementary data, File S1.

Eligibility criteria

We included studies that met the following inclusion criteria:

(i) Study population: critically ill patients ≥18 years with AKI;
(ii) Intervention: early RRT initiation;
(iii) Comparison intervention: late initiation of RRT;
(iv) Outcome: described outcomes had to include patient mortality;
(v) Study design: RCTs.

The criteria for AKI and the classification as early or late RRT are reported as in the individual study. The authors did not implement any restrictions on RRT modalities in this meta-analysis.

Study selection

After removing duplicate articles, two investigators (I.C. and M.R.) independently screened the titles and abstracts. The full texts of the identified eligible RCTs were then independently assessed to determine whether they should be included in the analysis. Disagreements between the two reviewers were resolved by a third reviewer (L.C.).

Data collection process and data items

Two authors (I.C. and M.R.) independently extracted the following data publication information (authors, year), study characteristics (country, design, sample size), participant demographics (mean age, percentage of males), definition and criteria for early and late RRT initiation and RRT modality. The primary outcome was 28-day mortality. Secondary outcomes included RRF, adverse events (hypotension, arrhythmia, bleeding and infection) and overall mortality (extrapolated from the last available data regarding mortality in each study). Disagreements between the two reviewers were resolved by a third reviewer (L.C.).

Assessment of the risk of bias in the included studies

Two authors (I.C., M.R.) assessed the risk of bias using Cochrane Collaboration's tool [17]. Adequate generation of a randomized sequence and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of the outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other possible sources of bias were evaluated independently. Funnel plots were used to ascertain publication bias. Disagreements were resolved by the other two reviewers (M.M.-S. and L.C.) or through consensus-based discussion.

Data analysis

The results of the selected RCTs were statistically combined using Review Manager version 5.3. (Cochrane Collaboration). Dichotomous outcome results were expressed using risk ratios (RR) with a 95% confidence interval (CI) and a *P*-value <.05 was set as the threshold for statistical significance. Statistical heterogeneity was anticipated due to clinical and methodological differences between the included trials (e.g. distinct RRT modalities and population characteristics). In order to incorporate both within-study and between-study variance, summary measures were performed using a random-effects model (Mantel-Haenszel method). Heterogeneity was assessed using I^2 tests, with substantial heterogeneity being defined as I^2 >50% [18]. Sensitivity analyses were performed to investigate potential sources of heterogeneity for the primary outcome, including consecutive removal of individual trials and removal of studies with a non-low risk of bias for each domain. Further subgroup analyses were conducted based on the RRT modality and study population.

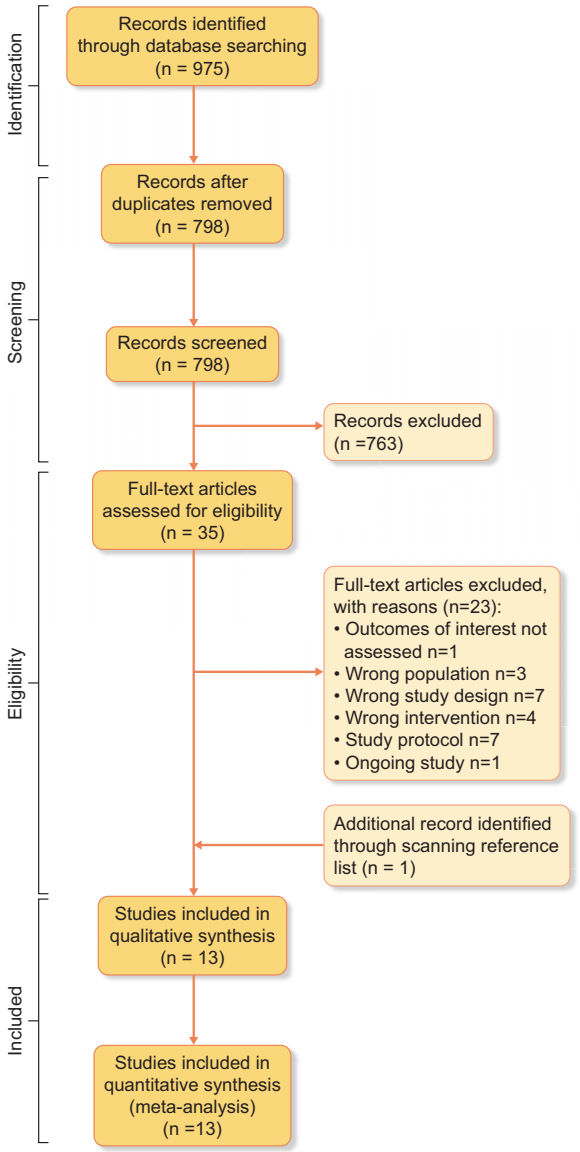


FIGURE 1: PRISMA flow diagram describing the study selection process.

RESULTS

Study selection

Figure 1 summarizes the study selection flow of the meta-analysis. In total, 975 articles were identified through electronic searches in the three selected databases, of which 177 were

Table 1. Study characteristics

Study	Country	Population and design	Patients (number)	Male (%)	Mean age (year)	Criteria for RRT initiation		RRT modality	Primary outcome
						Early	Late		
Bouman, 2002 [19]	Netherlands	Medical/surgery RCT, Multicentre	Total: 106 Early: 70 Late: 36	Early: 59 Late: 61	Early: 69 Late: 67	Renal replacement therapy (RRT) within 12 h if urine output <30 mL/h for >6 h, creatinine clearance <20 mL/min and mechanical ventilation.	Urea >40 mmol/L or hyperkalaemia (>6.5 mmol/L) or severe pulmonary oedema[a].	Continuous	28-day survival
Durmaz, 2003 [10]	Turkey	Cardiac surgery RCT, single-centre	Total: 44 Early: 21 Late: 23	Early: 76 Late: 83	Early: 58 Late: 54	Postoperative serum creatinine (SCr) increased by 10%.	Postoperative SCr increased by 50% or urine output <400 mL/24 h.	Intermittent	30-day mortality
Sugahara, 2004 [11]	Japan	Cardiac surgery RCT, single-centre	Total: 28 Early: 14 Late: 14	Early: 64 Late: 64	Early: 65 Late: 64	Urine output <30 mL/h for 3 h or urine output <750 mL/24 h.	Urine output <20 mL/h for 2 h or urine output <500 mL/24 h.	Continuous	14-day survival
Jamale, 2013 [20]	India	Medical RCT, single-centre	Total: 208 Early: 102 Late: 106	Early: 61 Late: 75	Early: 43 Late: 42	Blood urea nitrogen (BUN) >25 mmol/L and/or SCr >619 μmol/L.	Refractory hyperkalaemia, volume overload, acidosis, uraemic nausea and anorexia.	Intermittent	3-months mortality

Table 1. Continued

Study	Country	Population and design	Patients (number)	Male (%)	Mean age (year)	Criteria for RRT initiation Early	Late	RRT Modality	Primary Outcome
Combes, 2015 [21]	France	Cardiac surgery RCT, multicentre	Total: 224 Early: 112 Late: 112	Early: 79 Late: 80	Early: 61 Late: 58	Persistent postoperative shock after cardiac surgery[b].	Life-threatening hyperkalaemia, SCr >354 μmol/L or threefold of the preoperative SCr, serum urea >36 mmol/L, or urine output <0.3 mL/kg/h for 24 h.	Continuous	30-day mortality
Wald, 2015 [22]	Canada	Medical/surgery RCT, multicentre	Total. 100 Early: 48 Late: 52	Early: 73 Late: 71	Early: 62 Late: 64	RRT started within 12 h of fulfilling eligibility criteria[c].	Hyperkalaemia (K >6.0 mmol/L) or serum bicarbonate <10 mmol/L or PaO_2/FiO_2 <200 with infiltrates on chest radiograph suggestive of pulmonary oedema.	Continuous and/or Intermittent	90-day mortality
Gaudry, 2016 [14]	France	Medical/surgery RCT, multicentre	Total: 619 Early: 311 Late: 308	Early: 67 Late: 64	Early: 65 Late: 67	RRT within 6 h of diagnosis of KDIGO stage 3[d].	K >5.5 mmol/L or metabolic acidosis (pH <7.5) or pulmonary oedema or BUN >40 mmol/L or oliguria >72 h.	Continuous and/or Intermittent	60-day mortality
Zarbock, 2016 [12]	Germany	Surgery RCT, single-centre	Total: 231 Early: 112 Late: 119	Early: 70 Late: 57	Early: 66 Late: 68	RRT within 8 h of diagnosis of KDIGO stage 2[e].	RRT within 12 h of diagnosis of KDIGO stage 3[d], serum urea ≥100 mg/dL; severe hyperkalemia (>6 mmol/L), serum magnesium >4 mmol/L, urine output <200 ml in 12 h or anuria or organ oedema.	Continuous	90-day mortality
Barbar, 2018 [13]	France	Medical/surgery RCT, multicentre	Total: 488 Early: 246 Late: 242	Early: 58 Late: 64	Early: 69 Late: 69	RTT within 12 h after The diagnosis of Failure-stage of RIFLE Classification[f].	Hyperkalaemia (>6.5 mmol/L); pulmonary oedema refractory to diuretics; or metabolic acidosis (pH <7.15) or no renal function recovery after 48 h.	Continuous and/or Intermittent	90-day mortality

Table 1. Continued

Study	Country	Population and design	Patients (number)	Male (%)	Mean age (year)	Criteria for RRT initiation Early	Late	RRT Modality	Primary Outcome
Lumlertgul, 2018 [23]	Thailand	Medical/surgery RCT, multicentre	Total: 118 Early: 58 Late: 60	Early: 50 Late: 48	Early: 68 Late: 67	RRT started within 6 h of randomization[g].	BUN ≥36.5 mmol/L; hyperkalemia (>6 mmol/L); metabolic acidosis (pH < 7.15 or serum bicarbonate <12 mmol/L) pulmonary oedema or PaO_2/FiO_2 <200	Continuous	28-day mortality
Srisawat, 2018 [24]	Thailand	Medical/surgery RCT, multicentre	Total: 40 Early: 20 Late: 20	Early: 55 Late: 55	Early: 63 Late: 71	RRT was started within 12h of randomization[h].	Refractory metabolic acidosis (pH < 7.20 or serum bicarbonate <15 mEq/L), refractory hyperkalemia (>6.2 mmol/L); severe pulmonary edema, severe peripheral edema, no response to diuretics; persistent oliguria or anuria; BUN >22 mmol/L.	Continuous	28-day mortality
Xia, 2019 [25]	China	Medical/surgery RCT, single-centre	Total: 60 Early: 30 Late: 30	Early: 50 Late: 60	Early: 65 Late: 67	Sepsis and urinary neutrophil gelatinase-associated lipocalin (NGAL) ≥ 1310 ng/mL.	Hyperkalemia (>6.5 mmol/l) or pulmonary oedema or severe metabolic acidosis (pH < 7.20).	Continuous	28-day mortality
Bagshaw, 2020 [15]	15 countries[i]	Medical/surgery RCT, multicentre	Total: 2927 Early: 1465 Late: 1462	Early: 68 Late: 68	Early: 65 Late: 65	RRT within 12 h after patients had met full eligibility criteria[j].	Hyperkalaemia (≥6.0 mmol/L), pH ≤ 7.20 or a serum bicarbonate level ≤12 mmol/L, evidence of severe respiratory failure based on PaO_2/FiO_2 ≤200 and clinical perception of volume overload, or persistent acute kidney injury (AKI) for at least 72 h after randomization.	Continuous and/or Intermittent	90-day mortality

RRT, renal replacement therapy; SCr, serum creatinine; BUN, blood urea nitrogen; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of renal function and End-stage renal disease criteria; NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury. [a]Define as central venous pressure or pulmonary artery occlusion pressure >16 mmHg and lung oedema on radiograph in all quadrants, with positive end expiratory pressure of ≥10 cm H_20 and PaO_2/FiO_2 <150 mm Hg. [b]Defined as requiring high-dose catecholamines [epinephrine >0.2 μg/kg/min, norepinephrine >0.4 μg/kg/min, or epinephrine + (norepinephrine/2) >0.2 μg/kg/min] or cardiovascular assistance using extracorporeal membrane oxygenation/ extracorporeal life support within 3–24 h after intensive care unit admission. [c]The inclusion criteria are: presence of severe AKI (defined by the presence of two of the following three criteria: a twofold increase in serum creatinine from baseline, urine output <6 mL/kg in the preceding 12 h or whole-blood NGAL ≥400 ng/mL), the absence of urgent indications for RRT initiation (defined as serum potassium ≤5.5 mmol/L and serum bicarbonate ≥15 mmol/L) and low likelihood of volume-responsive AKI (defined as central venous pressure ≥8 mmHg). [d]Defined as SCr ≥4 mg/dL or threefold increase in SCr compared with baseline level or urine output <0.3 mL/kg/24h or anuria for ≥12 h. [e]Defined as a twofold increase in SCr compared with baseline or urine output <0.5 mL/kg/h for ≥12 h. [f]Defined as urine output <0.3 mL/kg/24 h or anuria ≥12 h or a SCr level 3 times the baseline level or SCr ≥4 mg/dL. [g]This RCT included patients with AKI at any stage (defined by KDIGO criteria). [h]This RCT included patients with AKI defined by RIFLE criteria. [i]Australia Austria, Belgium, Brazil, Canada, China, Finland, France, Germany, Ireland, Italy, New Zealand, Switzerland, United Kingdom, United States. [j]This RCT included patients with AKI defined by as a stage 2 or 3 of KDIGO classification.

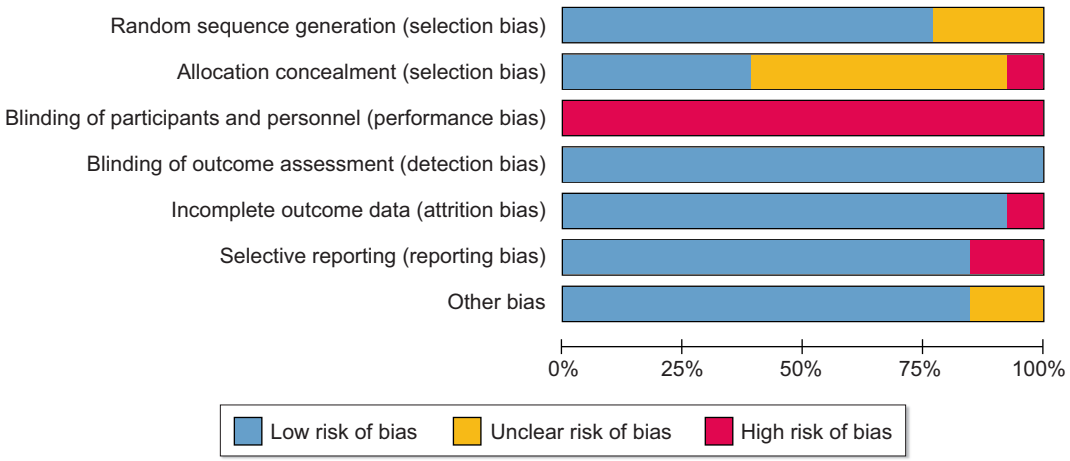


FIGURE 2: Included studies' risk of bias graph.

duplicates. The remaining 798 papers had their titles and abstracts screened for eligibility—in the process, 763 were excluded for failing to meet the set inclusion criteria. After assessing the remaining 35 articles and scanning their bibliographic references, 13 RCTs were included in the meta-analysis [10–15, 19–25].

Study characteristics

Details of the included trials, such as population characteristics, criteria for RRT initiation, RRT modality and primary outcomes, are described in Table 1

This meta-analysis included studies conducted between 2002 and 2020, with an aggregate of 5193 participants. Sample sizes ranged from 28 to 2927 patients, with a median of 118 participants. In all, five RCTs (38.5%) were single-centre studies [10–12, 20, 25] and eight (61.5%) were multicentre [13–15, 19, 21–24], four trials (30.8%) [10–12, 21] had limited inclusion to surgical patients—three pertained to cardiovascular surgery only [10, 11, 21]. The remaining nine (69.2%) studies involved medical [20] and mixed (medical/surgical) patients [13–15, 19, 22–25].

In all, seven studies (53.8%) focussed on continuous techniques [11, 12, 19, 21, 23–25] and two trials (15.4%) [10, 20] employed intermittent modalities. The remaining four studies (30.8%) [13–15, 22] used either intermittent, continuous, or combined RRT modalities.

The selected studies used variable criteria for early and late initiation of RRT. In most cases, dialytic support was based on trial-specific, or Kidney Disease: Improving Global Outcomes (KDIGO)/RIFLE-defined biochemical or urinary output cut-offs. In two cases, Srisawat *et al.* [24] and Xia *et al.* [25], quantification of a novel biomarker—neutrophil gelatinase-associated lipocalin (NGAL)—was the basis for early RRT initiation with cut-off values of 400 and 1310 ng/mL, respectively. Late initiation, as in most other cases, was based on traditional indications for dialysis—refractory metabolic acidosis, severe hyperkalaemia, or pulmonary oedema.

Risk of bias within and across studies

The authors used the Cochrane Collaboration risk of bias tool [17] to assess the risk of each included paper across seven domains. For most items, the selected studies were generally assessed at low risk of bias. However, given the nature of the intervention, effective blinding of the participants and clinicians was unattainable. Thus, this item was assessed at a high risk of bias for all included RCTs. The risk of bias assessments is summarized in Figs 2 and 3.

Funnel plots were used to evaluate the possibility of publication bias (Supplementary data, Fig. S1). Visual inspection showed no significant asymmetries for all outcomes but RRF.

Synthesis of results

Primary outcome. The primary outcome was 28-day mortality. Aggregate mortality rates were 37.18 and 37.15% for early and late RRTs respectively. No significant difference was found between the two groups (RR 1.00; 95% CI 0.89–1.12; $P = 1.00$). Moderate heterogeneity was present ($I^2 = 30\%$, Fig. 4).

A sensitivity analysis with exclusion of each trial and removal of studies with a non-low risk of bias for each domain (Supplementary data, Tables S2 and S3) was performed to identify potential sources of heterogeneity. A meta-analysis conducted after exclusion of each trial factoring in the risk of bias showed no significant effect on the pooled estimate and 95% CI. Results were identical using both the random-effects and fixed-effect models. Further subgroup analyses based on the RRT modality demonstrated no significant difference in the overall effect estimates (Fig. 5).

From the subgroup analyses based on the study population (Fig. 6), no significant differences in 28-day mortality were detected between the two strategies when assessing RCTs that included only medical patients (RR 1.68; 95% CI 0.89–3.17; $P = .11$), surgical participants (RR 0.60; 95% CI 0.33–1.09; $P = .10$) or a mixed population (RR 1.02; 95% CI 0.95–1.10; $P = .52$, $I^2 = 0\%$). In the subgroup that exclusively included surgical patients, significant heterogeneity was found ($I^2 = 70\%$; $P = .02$).

Secondary outcomes

Overall mortality. Overall mortality was calculated using the last reported data in each study [10–15, 19–25]. No significant difference in overall mortality was found between the two groups (RR 1.00; 95% CI 0.90–1.12; $P = .98$, $I^2 = 42\%$, Supplementary data, Fig. S2).

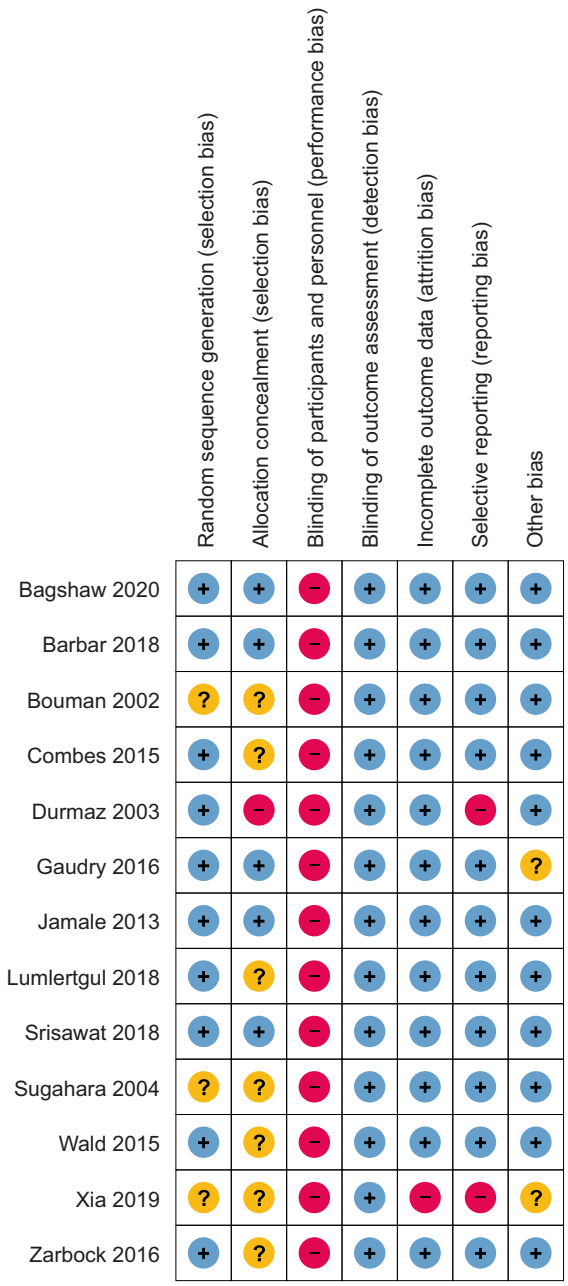


FIGURE 3: Included studies' risk of bias summary.

Recovery of renal function. Due to the general lack of data regarding the patients' baseline renal function, this meta-analysis used RRT independence as a surrogate indicator for RRF, using data from the last available follow-up. A total of 12 RCTs with 5122 patients were included in the analysis [11–15, 19–25]. No significant association was found between the timing of RRT initiation and RRF (RR 1.02; 95% CI: 0.92–1.13; $P = .75$, $I^2 = 53\%$, Supplementary data, Fig. S3).

Hypotension. A total of seven of the selected trials reported this outcome [12, 13, 15, 20–23]. In total, 15.4 and 10.9% of the patients in the early and late RRT groups respectively developed hypotension. Early RRT initiation was associated with a significantly higher incidence of hypotensive events (RR 1.34; 95% CI 1.17–1.53; $P < .0001$; $I^2 = 6\%$, Fig. 7).

Infection. RRT-associated infection was defined as a catheter-related or unexplained bloodstream infection. This outcome was reported in six RCTs [14, 15, 19, 20, 22, 23]. In the early RRT group, 2.1% of the patients developed infectious complications, in contrast to a 1.1% infection rate in the late RRT group. Early RRT initiation was associated with a significantly higher incidence of RRT-associated infectious events (RR 1.83; 95% CI 1.11–3.02; $P = .02$; $I^2 = 0\%$, Fig. 8).

Arrhythmia. In all, seven trials, with 4601 patients, reported this outcome [10, 12–15, 22, 23]. No significant association was found between the timing of RRT initiation and the incidence of arrhythmic complications (RR 1.28, 95% CI 0.92–1.78; $P = .14$; $I^2 = 39\%$, Fig. 9).

Bleeding. A total of 10 trials, with 5130 patients in total, reported this outcome [10, 12–15, 19, 20–23]. No significant association was found between the timing of RRT initiation and the incidence of bleeding complications (RR 0.95, 95% CI 0.78–1.16; $P = .62$; $I^2 = 0\%$, Fig. 10).

DISCUSSION

This meta-analysis included 13 studies comparing early and late RRT initiation strategies among 5193 critically ill adult patients with AKI. The definition for early RRT initiation was highly variable, including patients with AKI stages 1–3 (AKIN or KDIGO). In the late group, RRT was generally initiated in the presence of life-threatening complications of AKI refractory to medical treatment (e.g. pulmonary oedema, hyperkalaemia and refractory metabolic acidosis). We aimed to compare the benefits of early and late RRT initiation strategies in critically ill patients with AKI. Some other articles have focussed on this matter, however, this meta-analysis benefits from the inclusion of the most recent and largest clinical trial on this topic (Bagshaw *et al.*) which significantly increased the aggregate sample size and the robustness of our findings [26].

No significant difference on 28-day and overall mortality was established between the two approaches, even after subgroup analysis according to continuous and/or intermittent RRT, which is consistent with other recent meta-analysis focussing on RCTs [27–31]. We found neither strategy was associated with an increased chance of RRF. Furthermore, early initiation was associated with a significantly higher risk of RRT-related adverse events (hypotension and infectious complications), which goes against the findings of other authors [32, 33].

The majority of the included RCTs selected both medical and surgical patients [13–15, 19, 22–25], combining different AKI aetiologies. For this mixed population, no significant difference on 28-day mortality was found between an early and late RRT strategies. These results are robust and precise, supported not only by a narrow CI and a non-detectable heterogeneity, but also by the low risk of bias of the included studies.

However, particular attention should be placed on the subgroup analysis based on the study population. Restriction to surgical patients [10, 11, 21] seems to favour early RRT initiation. A total of 3/4 RCTs suggest a decrease on the 28-day mortality with early RRT initiation, one [11] of which with statistical significance. Although the combined results of the four RCTs showed non-significant differences between the two strategies,

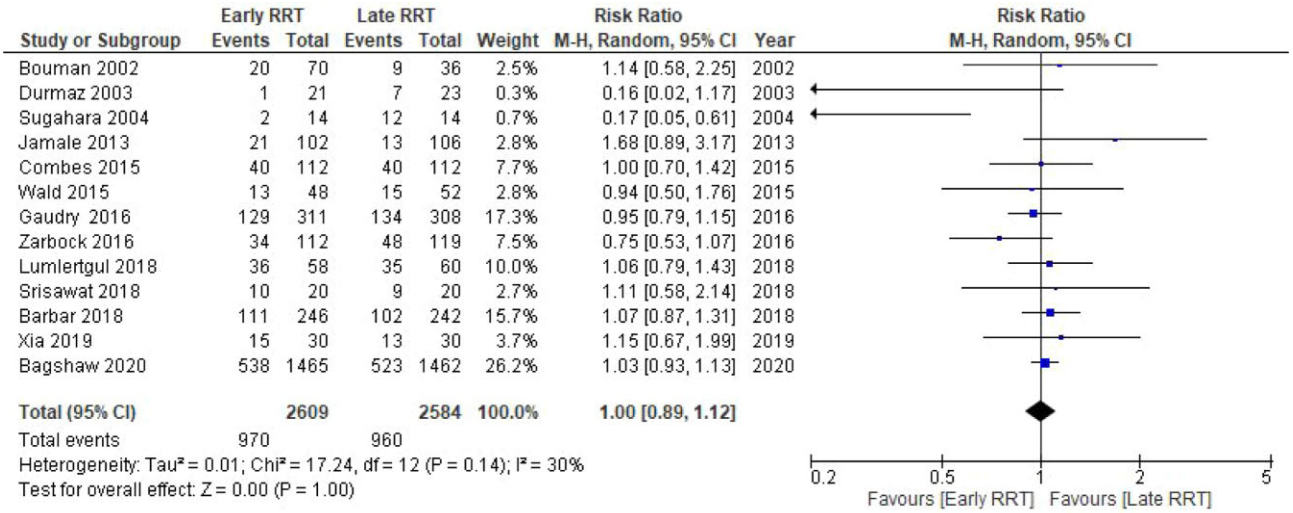


FIGURE 4: Forest-plot for the risk of 28-day mortality between early and late renal replacement therapy.

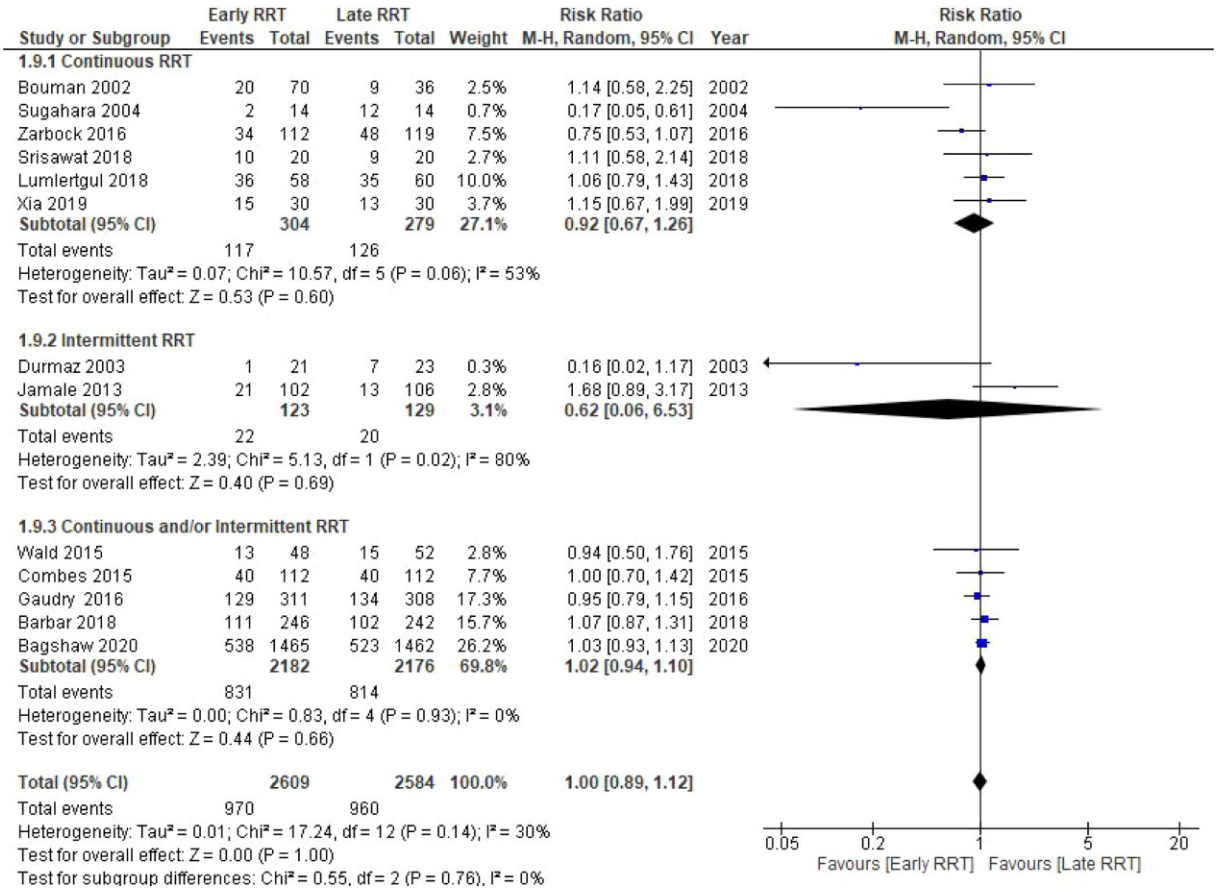


FIGURE 5: Subgroup analysis for the risk of 28-day mortality between early and late renal replacement therapy based on its modality (continuous and/or intermittent).

this analysis is limited by the uncertainty associated with the wider CI and high grade of heterogeneity detected.

To produce a satisfactory answer to whether the summary effect varies in relation to specific characteristics of the participants and different AKI aetiologies, RCTs with a different design are necessary. For future research, we suggest that authors should focus on a detailed characterization and selection of the study population, based on clinical characteristics and diagnoses (e.g, patients with AKI due to sepsis, cardiac failure or cardiothoracic surgery). Although determining a specific

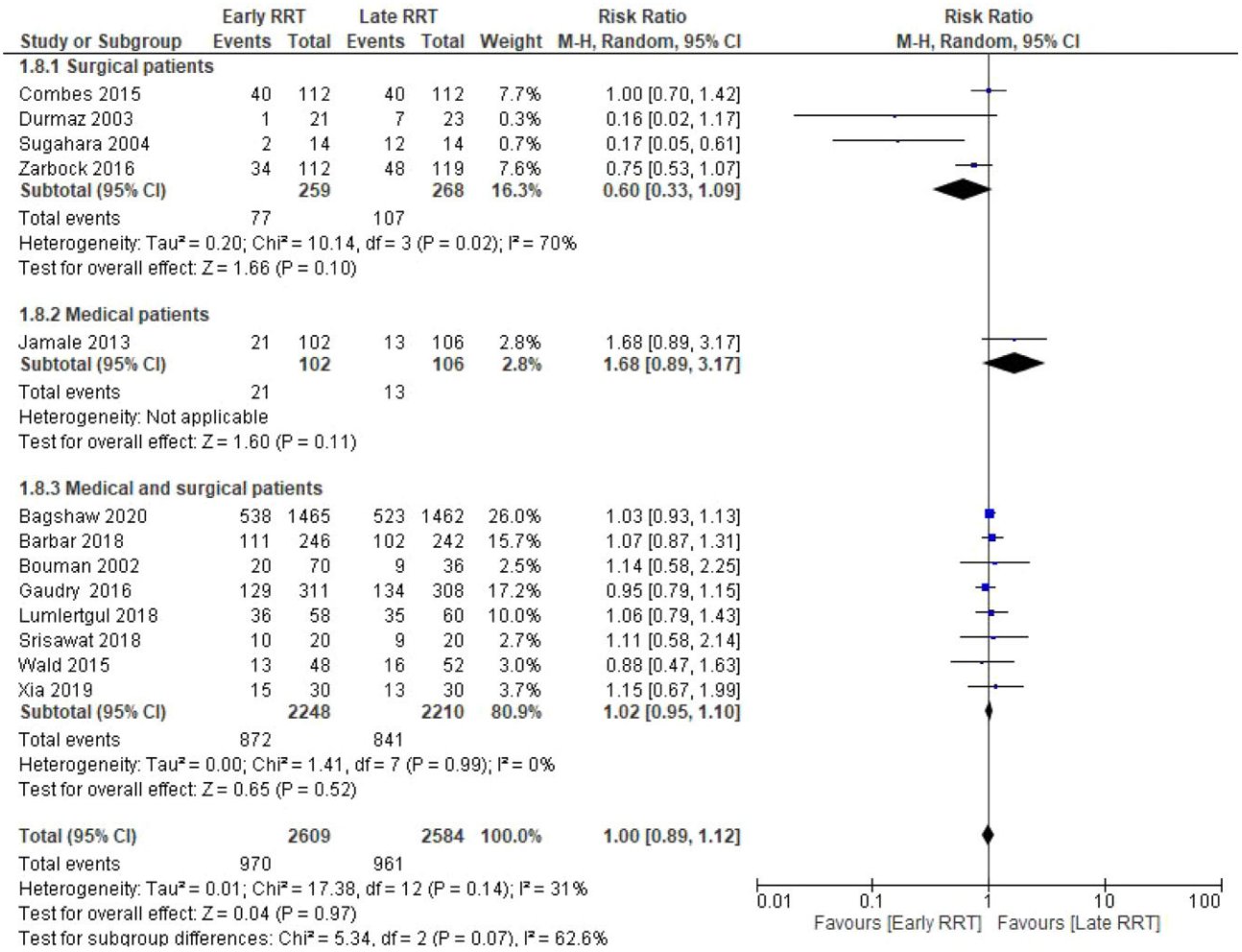


FIGURE 6: Subgroup analysis for the risk of 28-day mortality between early and late renal replacement therapy based on the study population (surgical, medical or mixed population).

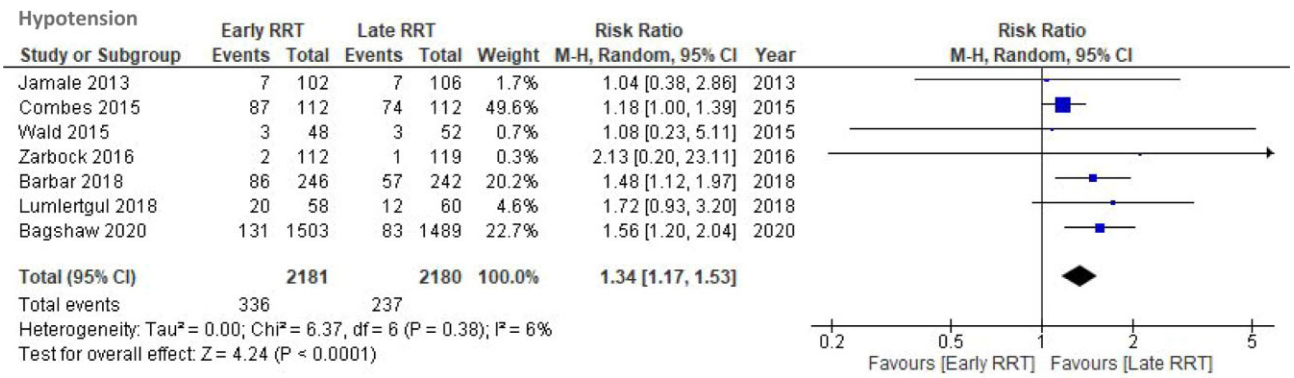


FIGURE 7: Forest-plot for the risk of hypotension between early and late renal replacement therapy.

aetiology for AKI is frequently difficult, especially in the presence of multifactorial mechanisms, comparisons of the results in these subpopulations would provide further data on the way different AKI mechanisms influence RRT outcomes and potentially identify patient subgroups that would benefit from early RRT introduction.

Various other meta-analyses have addressed the impact of early RRT initiation on patient mortality and different RRT-related outcomes with mixed results. Some have suggested a potential benefit on survival using a pre-emptive approach [34–37]; however, most of the studies included in those reviews have an observational design and suffer from pertinent methodological

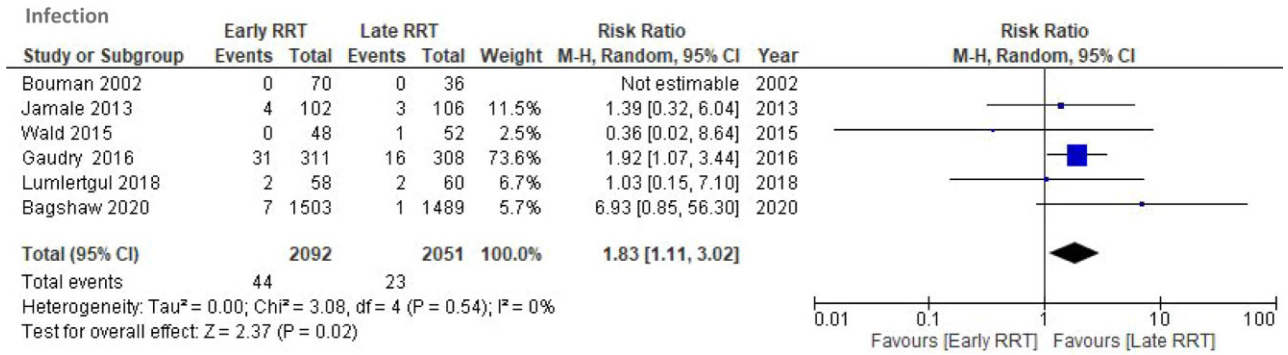


FIGURE 8: Forest-plot for the risk of infection between early and late renal replacement therapy.

FIGURE 9: Forest-plot for the risk of arrhythmia between early and late renal replacement therapy.

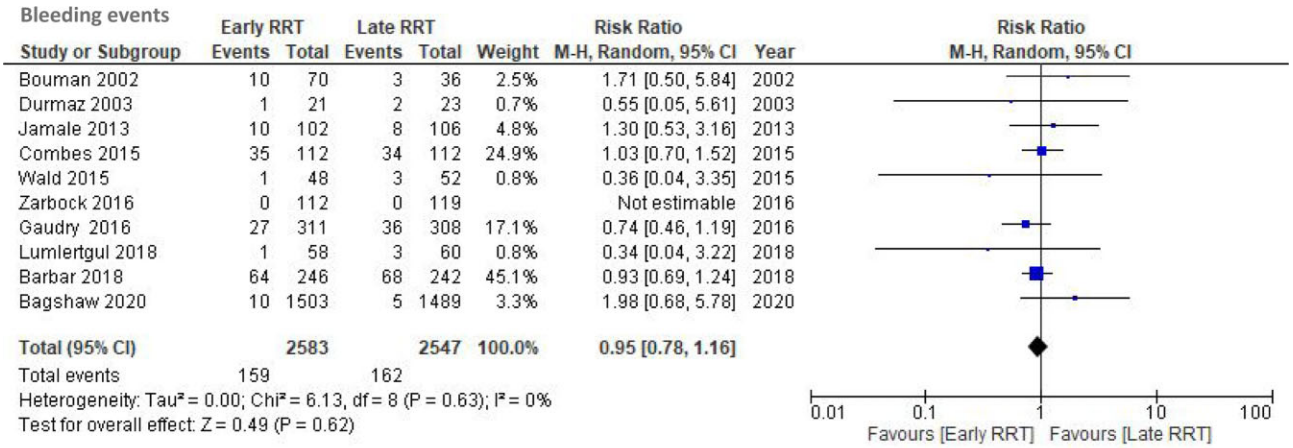


FIGURE 10: Forest-plot for the risk of bleeding events between early and late renal replacement therapy.

limitations. Observational studies tendentially focussed on patients who received RRT, dismissing patients with AKI that recover without RRT (some of which would belong in the late RRT initiation group), consequently potentially overestimating the benefits of an early RRT strategy [34–37].

The high short-term mortality associated with AKI in critically ill patients is widely acknowledged and was once again demonstrated in this meta-analysis.

Emerging biomarkers of kidney stress and injury have the potential not only to detect AKI in earlier stages but also to stratify the risk of severe AKI, renal recovery, or progression to chronic kidney disease (CKD). These biomarkers could also help to distinguish multiple clinical phenotypes of AKI, that have diverse aetiologies, pathogenesis, different outcomes and treatment responses [38–41].

Therefore, one must question if the results presented in this meta-analysis would be different if the selection of critically ill patients with AKI simultaneously included these novel biomarkers, besides serum creatinine (SCr) or urine output, in all RCTs. Their inclusion could help clinicians identify AKI patients at

high risk for persistent AKI who are more likely to profit from early RRT initiation. In the future, their integration in decision algorithms will probably allow clinicians to tailor their therapeutic approach to each patient as dialysis is not, by any means, a one-size-fits-all treatment [39].

Finally, one must also acknowledge that despite the lack of evidence favouring early RRT initiation, protracted delays in RRT may also pose harm to critically ill patients with AKI. This was recently reinforced by the AKIKI 2 trial [42] which compared a delayed and a more-delayed strategy for RRT initiation in this population. Patients were randomly assigned to one of the two strategies if they developed a blood urea nitrogen (BUN) concentration between 112 and 140 mg/dL (40–50 mmol/L) and/or oligo-anuria for more than three consecutive days [42]. In the delayed group, RRT was started within 12 h after randomization, whereas in the more-delayed group, RRT was postponed until an urgent indication emerged or BUN exceeded 140 mg/dL (50 mmol/L) [42]. RRT-free days did not differ between the strategies. However, a pre-specified multivariable analysis revealed higher 60-day mortality in the more-delayed group. According to the experts' opinion [43], this finding is potentially related to the effects of prolonged untreated AKI, exaggerated non-renal organ dysfunction [44] and modified recovery from critical illness [45].

Strengths and limitations

This study benefits from a comprehensive search strategy that focussed on RCTs. Selected articles were then critically analysed to guarantee the quality of the data included in the meta-analysis. The inclusion of a diversified group of outcomes in the analysis (mortality, RRF and four different adverse events) with sensitivity and subgroup analysis for the primary outcome further strengthened this study.

However, this meta-analysis also has important limitations. Firstly, clinical heterogeneities amongst the included trials limit the validity of this meta-analysis. Definitions for early and late RRT initiation varied significantly across RCTs—some authors opted for analytical-based criteria while others opted for time-based classifications (e.g. time after randomization, time relative to the development of AKI). Thus, what may represent an early intervention in one trial, could fulfil the criteria for late RRT in another RCT. Heterogeneity is also present in the population characteristics, RRT modalities and duration of follow-up. Additionally, adequate blinding of the participants and clinicians was unattainable, which presents a potentially significant source of bias. Furthermore, the asymmetrical appearance of the funnel plot related to RRF suggests publication bias regarding this outcome. A significant underestimation of the impact of an early/late RRT strategy on RRF cannot be excluded. Possible explanations for funnel plot asymmetry include variations in methodological quality, heterogeneity in intervention effects and small-study effects—a tendency for intervention effects estimated in smaller studies [11, 25] to differ from those estimated in larger studies [46].

CONCLUSIONS

This updated meta-analysis shows that early RRT initiation does not significantly improve 28-day and overall mortality, nor the likelihood of RRF in critically ill patients with AKI. Furthermore, a pre-emptive approach appears to increase the risk for RRT-associated adverse events, namely hypotension and infection. Future trials comparing RRT timing strategies should focus on specific AKI subpopulations that may benefit from earlier dialytic support.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. I.C., M.R. and L.C. developed the search strategy, material preparation, data collection and analysis. The first draft of the article was written by I.C. and M.R. All authors commented on previous versions of the article and contributed to the interpretation of data. M.M.-S., J.G., J.A.L. and L.C. critically revised the work. All authors read and approved the final article.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been previously published.

REFERENCES

1. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. *Lancet* 2019; **394**: 1949–1964
2. Hoste EA, Bagshaw SM, Bellomo R *et al*. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015; **41**: 1411–1423
3. Vaara ST, Pettilä V, Kaukonen KM *et al*. The attributable mortality of acute kidney injury: a sequentially matched analysis. *Crit Care Med* 2014; **42**: 878–885
4. Bagshaw SM, George C, Bellomo R *et al*. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. *Crit Care* 2007; **11**: R68
5. Bagshaw SM, Wald R. Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury. *Kidney Int* 2017; **91**: 1022–1032
6. Wald R, Bagshaw SM. The timing of renal replacement therapy initiation in acute kidney injury: is earlier truly better?. *Crit Care Med* 2014; **42**: 1933–1934
7. Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. *Intensive Care Med* 1999; **25**: 805–813
8. Demirkiliç U, Kuralay E, Yenicesu M *et al*. Timing of replacement therapy for acute renal failure after cardiac surgery. *J Card Surg* 2004; **19**: 17–20
9. Elahi MM, Lim MY, Joseph RN *et al*. Early hemofiltration improves survival in post-cardiotomy patients with acute renal failure. *Eur J Cardiothorac Surg* 2004; **26**: 1027–1031
10. Durmaz I, Yagdi T, Calkavur T *et al*. Prophylactic dialysis in patients with renal dysfunction undergoing on-pump coronary artery bypass surgery. *Ann Thorac Surg* 2003; **75**: 859–864
11. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. *Hemodial Int* 2004; **8**: 320–325

12. Zarbock A, Kellum JA, Schmidt C *et al*. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA* 2016; **315**: 2190–2199
13. Barbar SD, Clere-Jehl R, Bourredjem A *et al*. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018; **379**: 1431–1442
14. Gaudry S, Hajage D, Schortgen F *et al*. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016; **375**: 122–133
15. STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group, Bagshaw SM, Wald R, Adhikari NKJ *et al*. Timing of initiation of renal-replacement therapy in acute kidney injury. *N Engl J Med* 2020; **383**: 240–251
16. Moher D, Liberati A, Tetzlaff J *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097
17. Higgins JP, Altman DG, Gøtzsche PC *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–1558
19. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG *et al*. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med* 2002; **30**: 2205–2211
20. Jamale TE, Hase NK, Kulkarni M *et al*. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. *Am J Kidney Dis* 2013; **62**: 1116–1121
21. Combes A, Bréchot N, Amour J *et al*. Early high-volume hemofiltration versus standard care for post-cardiac surgery shock. The HEROICS Study. *Am J Respir Crit Care Med* 2015; **192**: 1179–1190
22. Wald R, Adhikari NK, Smith OM *et al*. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int* 2015; **88**: 897–904
23. Lumlertgul N, Peerapornratana S, Trakarnvanich T *et al*. Early versus standard initiation of renal replacement therapy in furosemide stress test non-responsive acute kidney injury patients (the FST trial). *Crit Care* 2018; **22**: 101
24. Srisawat N, Laoveeravat P, Limphunudom P *et al*. The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: A feasibility study. *J Crit Care* 2018; **43**: 36–41
25. Xia Y, Shi H, Wu W *et al*. Effect of urinary NGAL on the timing of renal replacement therapy in patients with acute renal injury associated with sepsis. *Med J Chin PLA* 2019; **44**: 605–610
26. Bagshaw SM, Hoste EA, Wald R. When should we start renal-replacement therapy in critically ill patients with acute kidney injury: do we finally have the answer? *Crit Care* 2021; **25**: 179
27. Wierstra BT, Kadri S, Alomar S *et al*. The impact of 'early' versus 'late' initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis. *Crit Care* 2016; **20**: 122
28. Moreira FT, Palomba H, Chaves RCF *et al*. Early versus delayed initiation of renal replacement therapy for acute kidney injury: an updated systematic review, meta-analysis, meta-regression and trial sequential analysis of randomized controlled trials. *Rev Bras Ter Intensiva* 2018; **30**: 376–384
29. Lin WT, Lai CC, Chang SP *et al*. Effects of early dialysis on the outcomes of critically ill patients with acute kidney injury: a systematic review and meta-analysis of randomized controlled trials. *Sci Rep* 2019; **9**: 18283
30. Gaudry S, Hajage D, Benichou N *et al*. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet* 2020; **395**: 1506–1515
31. Li X, Liu C, Mao Z *et al*. Timing of renal replacement therapy initiation for acute kidney injury in critically ill patients: a systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. *Crit Care* 2021; **25**: 15
32. Yang XM, Tu GW, Zheng JL *et al*. A comparison of early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *BMC Nephrol* 2017; **18**: 264
33. Pasin L, Boraso S, Tiberio I. Early initiation of renal replacement therapy in critically ill patients: a meta-analysis of randomized clinical trials. *BMC Anesthesiol* 2019; **19**: 62
34. Liu Y, Davari-Farid S, Arora P *et al*. Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth* 2014; **28**: 557–563
35. Wang X, Jie Yuan W. Timing of initiation of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Ren Fail* 2012; **34**: 396–402
36. Karvellas CJ, Farhat MR, Sajjad I *et al*. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit Care* 2011; **15**: R72
37. Seabra VF, Balk EM, Liangos O *et al*. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. *Am J Kidney Dis* 2008; **52**: 272–284
38. Ronco C. Acute kidney injury: from clinical to molecular diagnosis. *Crit Care* 2016; **20**: 201
39. Hoste E, Bihorac A, Al-Khafaji A *et al*. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. *Intensive Care Med* 2020; **46**: 943–953
40. Pickkers P, Darmon M, Hoste E *et al*. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Med* 2021; **47**: 835–850
41. Kellum JA, Prowle JR. Paradigms of acute kidney injury in the intensive care setting. *Nat Rev Nephrol* 2018; **14**: 217–230
42. Gaudry S, Hajage D, Martin-Lefevre L *et al*. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. *Lancet* 2021; **397**: 1293–1300

43. Bagshaw SM, Hoste EA, Wald R. When should we start renal-replacement therapy in critically ill patients with acute kidney injury: do we finally have the answer? *Crit Care* 2021; **25**: 179
44. Siew ED, Fissell WH, Tripp CM *et al*. Acute kidney injury as a risk factor for delirium and coma during critical illness. *Am J Respir Crit Care Med* 2017; **195**: 1597–1607
45. Abdel-Kader K, Girard TD, Brummel NE *et al*. Acute kidney injury and subsequent frailty status in survivors of critical illness: a secondary analysis. *Crit Care Med* 2018; **46**: e380–e388
46. Sterne JA, Sutton AJ, Ioannidis JP *et al*. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011; **343**: d4002