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

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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 I² 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.

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Impact of RRT timing in critically ill patients

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 RCT's (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.

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) | Mean age (year) | Criteria for RRT initiation | RRT modality | Primary outcome |
|-----------------|---------------|--------------------------------|-------------------|-----------------|-----------------------------|--------------|-----------------|
| Bouman, 2002    | Netherlands   | Medical/surgery RCT, Multicentre | Total: 106        | Early: 59       | Renal replacement therapy (RRT) within 12 h if urine output < 30 mL/h for > 6 h, creatinine clearance < 20 mL/min and mechanical ventilation. | Continuous   | 28-day survival |
|                 |               |                                | Early: 70         | Late: 61        | Urea > 40 mmol/L or hyperkalaemia (> 6.5 mmol/L) or severe pulmonary oedema. |              |                 |
|                 |               |                                | Late: 36          | Late: 67        |                             |              |                 |
| Durmaz, 2003    | Turkey        | Cardiac surgery RCT, single-centre | Total: 44         | Early: 76       | Postoperative serum creatinine (Scr) increased by 10%. | Intermittent | 30-day mortality |
|                 |               |                                | Early: 21         | Late: 83        | Postoperative Scr increased by 50% or urine output < 400 mL/24 h. |              |                 |
|                 |               |                                | Late: 23          | Late: 54        |                             |              |                 |
| Sugahara, 2004  | Japan         | Cardiac surgery RCT, single-centre | Total: 28         | Early: 64       | Urine output < 30 mL/h for 3 h or urine output < 750 mL/24 h. | Continuous   | 14-day survival |
|                 |               |                                | Early: 14         | Late: 64        | Urine output < 20 mL/h for 2 h or urine output < 500 mL/24 h. |              |                 |
|                 |               |                                | Late: 14          | Late: 64        |                             |              |                 |
| Jamale, 2013    | India         | Medical RCT, single-centre     | Total: 208        | Early: 61       | Blood urea nitrogen (BUN) > 25 mmol/L and/or Scr > 619 μmol/L. | Intermittent | 3-months mortality |
|                 |               |                                | Early: 102        | Late: 43        | Refractory hyperkalaemia, volume overload, acidosis, uraemic nausea and anorexia. |              |                 |
|                 |               |                                | Late: 106         | Late: 42        |                             |              |                 |
| Study               | Country     | Population and design       | Patients (number) | Male (%) | Mean age (year) | Criteria for RRT initiation | RRT Modality | Primary Outcome |
|---------------------|-------------|-----------------------------|-------------------|----------|----------------|-----------------------------|--------------|-----------------|
| Combes, 2015 [21]  | France      | Cardiac surgery RCT, multicentre | Total: 224        | Early: 79 | Late: 80        | Persistent postoperative shock after cardiac surgery<sup>3</sup>. | Continuous   | 30-day mortality |
| Wald, 2015 [22]    | Canada      | Medical/surgery RCT, multicentre | Total: 100        | Early: 73 | Late: 71        | RRT started within 12 h of fulfilling eligibility criteria<sup>4</sup>. | Continuous   | 90-day mortality |
| Gaudry, 2016 [14]  | France      | Medical/surgery RCT, multicentre | Total: 619        | Early: 67 | Late: 64        | RRT within 6 h of diagnosis of KDIGO stage<sup>5</sup>. | Continuous and/or Intermittent | 60-day mortality |
| Zarbock, 2016 [12] | Germany     | Surgery RCT, single-centre  | Total: 231        | Early: 70 | Late: 57        | RRT within 8 h of diagnosis of KDIGO stage<sup>5</sup>. | Continuous   | 90-day mortality |
| Barbar, 2018 [13]  | France      | Medical/surgery RCT, multicentre | Total: 488        | Early: 58 | Late: 64        | RRT within 12 h after The diagnosis of Failure-stage of RIFLE Classification<sup>1</sup>. | Continuous and/or Intermittent | 90-day mortality |
| Study                  | Country            | Population and design          | Patients (number) | Male (%) | Mean age (year) | Criteria for RRT initiation | RRT Modality     | Primary Outcome |
|-----------------------|--------------------|--------------------------------|-------------------|----------|-----------------|----------------------------|-----------------|-----------------|
| Lumlergul, 2018 [23]  | Thailand           | Medical/surgery RCT, multicentre | Total: 118        | Early: 50 | Early: 68       | RRT started within 6 h of randomization<sup>2</sup>. | Continuous       | 28-day mortality |
|                       |                    |                                | Early: 58         | Late: 48 | Late: 67        | BUN ≥ 36.5 mmol/L; hyperkalemia (<6 mmol/l); metabolic acidosis (pH < 7.15 or serum bicarbonate <12 mmol/l) pulmonary oedema or PaO<sub>2</sub>/FiO<sub>2</sub> < 200 |                 |                 |
|                       |                    |                                | Late: 60          |          |                 | Refractory metabolic acidosis (pH < 7.20 or serum bicarbonate <15 mEq/l), refractory hyperkalemia (<6.2 mmol/l); severe pulmonary edema, severe periphenal edema, no response to diuretics; persistent oliguria or anuria; BUN >22 mmol/l. |                 |                 |
| Srisawat, 2018 [24]   | Thailand           | Medical/surgery RCT, multicentre | Total: 40         | Early: 55 | Early: 63       | RRT was started within 12h of randomization<sup>3</sup>. | Continuous       | 28-day mortality |
|                       |                    |                                | Early: 20         | Late: 20 | Late: 71        | Sepsis and urinary neutrophil gelatinase-associated lipocalin (NGAL) ≥ 13 10 ng/mL. |                 |                 |
|                       |                    |                                |                    |          |                 | Hyperkalemia (<6.5 mmol/l) or pulmonary oedema or severe metabolic acidosis (pH < 7.20). |                 |                 |
| Xia, 2019 [25]        | China              | Medical/surgery RCT, single-centre | Total: 60         | Early: 50 | Early: 65       |                       | Continuous       | 28-day mortality |
|                       |                    |                                | Early: 30         | Late: 60 | Late: 67        | Sepsis and urinary neutrophil gelatinase-associated lipocalin (NGAL) ≥ 13 10 ng/mL. |                 |                 |
| Bagshaw, 2020 [15]    | 15 countries<sup>4</sup> | Medical/surgery RCT, multicentre | Total: 2927       | Early: 68 | Early: 65       | RRT' within 12 h after patients had met full eligibility criteria<sup>2</sup>. | Continuous and/or Intermittent | 90-day mortality |
|                       |                    |                                | Early: 1465       | Late: 68 | Late: 65        | Hyperkalemia (<6.0 mmol/l), pH ≤ 7.20 or a serum bicarbonate level ≤ 12 mmol/l, evidence of severe respiratory failure based on PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 200 and clinical perception of volume overload, or persistent acute kidney injury (AKI) for at least 72 h after randomization. |                 |                 |

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.  
<sup>1</sup>Defined 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<sub>2</sub>O and PaO<sub>2</sub>/FiO<sub>2</sub> < 150 mm Hg.  
<sup>2</sup>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.  
<sup>3</sup>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).  
<sup>4</sup>Defined as SCR ≥ 4 mg/dL or threefold increase in SCR compared with baseline level or urine output <0.3 mL/kg/24 h or anuria for ≥ 12 h.  
<sup>5</sup>Defined as two-fold increase in SCR compared with baseline or urine output >0.5 mL/kg/h for ≥ 12 h.  
<sup>6</sup>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.  
<sup>7</sup>This RCT included patients with AKI at any stage (defined by KDIGO criteria).  
<sup>8</sup>This RCT included patients with AKI defined by KDIGO criteria.  
<sup>9</sup>Australia Austria, Belgium, Brazil, Canada, China, Finland, France, Germany, Ireland, Italy, New Zealand, Switzerland, United Kingdom, United States.  
<sup>10</sup>This RCT included patients with AKI defined by as a stage 2 or 3 of KDIGO classification.
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 cutoff 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; \(P = .38, I^2 = 42\%\), Supplementary data, Fig. S2).
**Impact of RRT timing in critically ill patients**

**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).

**Hyptension.** 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 hyptensive events. Early RRT initiation was associated with a significantly higher incidence of hyptensive 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 (hyptension 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,
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 4: Forest-plot for the risk of 28-day mortality between early and late renal replacement therapy.](image)

![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).](image)
Impact of RRT timing in critically ill patients

The 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
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

**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.
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. 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.

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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.C., 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.

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