

# The role of continuous renal replacement therapy in sepsis-associated acute kidney injury: a systematic review and meta-analysis

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## Abstract

**Background:** Continuous renal replacement therapy (CRRT) is commonly used to manage sepsis-associated acute kidney injury (SA-AKI) as a form of extracorporeal blood purification. However, the current consensus report from the 28th Acute Disease Quality Initiative workgroup does not provide explicit recommendations for the use of CRRT in SA-AKI, because of insufficient high-quality evidence regarding its efficacy. This study aimed to evaluate whether CRRT provides clinical benefits compared with non-CRRT therapy in patients with SA-AKI.

**Methods:** All randomized controlled trials published up to October 11, 2025, in 9 Chinese and English databases were reviewed and included in the study. A meta-analysis was performed on the experimental group (CRRT group) and control group (non-CRRT group) using risk ratios (RRs), weighted mean differences (WMDs), and 95% confidence intervals (CIs). The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach.

**Results:** A total of 37 studies involving 3120 subjects were included. Compared with the non-CRRT group, CRRT was associated with reduced 28-day mortality (RR: 0.46, 95% CI: 0.34–0.61,  $P < 0.01$ ), hospital mortality (RR: 0.39, 95% CI: 0.28–0.54,  $P < 0.01$ ), and incidence of cardiovascular events (RR: 0.39, 95% CI: 0.28–0.55,  $P < 0.01$ ). CRRT was also associated with shorter intensive care unit length of stay (WMD: -3.97, 95% CI: -4.71 to -3.22,  $P < 0.01$ ) and in-hospital length of stay (WMD: -4.51, 95% CI: -5.51 to -3.51,  $P < 0.01$ ).

**Conclusion:** The pooled estimates from the included studies favored CRRT with respect to 28-day mortality, hospital mortality, incidence of cardiovascular events, ICU length of stay, and in-hospital length of stay; however, the certainty of evidence was low to very low because of methodological limitations, heterogeneity in CRRT definitions and treatment protocols, small study sizes, and limited geographic generalizability. These findings should not be interpreted as establishing a routine clinical benefit of CRRT in SA-AKI or as supporting CRRT initiation in patients without standard indications for kidney replacement therapy. Further independent, prospectively registered, multicenter randomized controlled trials with standardized CRRT protocols are needed to confirm these findings.

**Keywords:** Acute kidney injury, Continuous renal replacement therapy, Meta-analysis, Sepsis

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Introduction

Acute kidney injury (AKI) is a critical condition prevalent in hospitals worldwide, posing a threat to human health. AKI has a high incidence; up to 57% of intensive care unit (ICU) patients are affected. Sepsis is the leading cause of AKI and contributes to 40%–50% of cases among ICU patients.<sup>[1,2]</sup> Every year, 19 million cases of sepsis or septic shock occur worldwide, with up to 11 million cases of sepsis-associated AKI (SA-AKI).<sup>[3]</sup> According to the consensus report issued by the 28th Acute Disease Quality Initiative workgroup, SA-AKI is defined as the manifestation of AKI within 7 days after the onset of sepsis.<sup>[4]</sup> Compared with patients without SA-AKI, those with SA-AKI typically have a more severe condition, a higher disease burden, and are associated with greater hemodynamic instability, increased need for mechanical ventilation, longer hospital stays, and higher hospital mortality rates.<sup>[5]</sup> Mortality rates in patients with SA-AKI have been reported to reach as high as 70.2%; despite a recent decrease because of medical advancements, it remains substantial, ranging from 28% to 51.4%.<sup>[6]</sup> Furthermore, nearly 30% of patients with SA-AKI do not achieve complete kidney recovery and are at risk of deteriorating kidney function, chronic kidney disease, and a shortened life expectancy.<sup>[7]</sup>

Mechanisms underlying SA-AKI are complex and remain unclear. Several mechanisms can lead to SA-AKI, including the dysfunction of both large and small blood vessels, renal glomerular ischemia-reperfusion injury, endothelial cell damage, inflammatory response, oxidative stress, mitochondrial dysfunction, metabolic reprogramming, and programmed cell death processes in renal tubular epithelial cells (RTECs), such as apoptosis, necroptosis, pyroptosis, autophagy, and ferroptosis.<sup>[1, 3, 8–12]</sup>

Continuous renal replacement therapy (CRRT) is an important extracorporeal blood purification (EBP) method in the management of patients with SA-AKI. CRRT effectively clears inflammatory factors, primarily small-to-medium-sized molecules, from the body, thereby reducing damage caused by the inflammatory response and improving inflammatory status.<sup>[13]</sup> In addition, CRRT can clear pathogens, microbial toxins, and toxic metabolites.<sup>[4]</sup> Research suggests that CRRT can effectively enhance renal function and microcirculatory status in patients with SA-AKI, thereby positively improving prognosis.<sup>[14]</sup> However, because of the insufficient evidence, consensus reports from the Acute Disease Quality Initiative workgroup, and expert opinions jointly formulated by the joint commission of the Italian Society of Anesthesiology and Critical Care (SIAARTI) and the Italian Society of Nephrology (SIN), only mention that EBP may be used for the treatment of SA-AKI without providing specific recommendations.<sup>[4, 15]</sup>

Recently, many hospitals worldwide have conducted clinical trials on SA-AKI. CRRT is one of the intervention measures most frequently used by physicians. Currently, the effect of CRRT on patients with SA-AKI remains unclear. This meta-analysis aimed to combine data from all randomized controlled trials (RCTs) to evaluate the effects of CRRT on patients with SA-AKI and to offer supporting evidence for EBP in future SA-AKI consensus guidelines.

## Methods

This study was registered with PROSPERO (ID: CRD42023463623) and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

### Data sources and search strategy

Two reviewers developed a comprehensive and advanced search strategy for the meta-analysis. Searches were conducted across 5 major English databases, including PubMed, Scopus, Web of Science, Embase, and Cochrane, and 4 Chinese databases, including WanFang, China Science and Technology Journal Database (VIP), Chinese Biomedical Literature (CBM), and Chinese National Knowledge Infrastructure (CNKI). A literature search was conducted from establishing the databases to October 11, 2025. No language restrictions were applied in the literature search. Any disagreements in developing the search strategy were resolved through the intervention of a third reviewer until a consensus was reached. The keywords used in this search are listed in Table S1, Supplemental Digital Content, <https://links.lww.com/ECCM/A110>.

### Inclusion criteria

(1) Adult patients clinically diagnosed with SA-AKI, defined as those meeting the diagnostic criteria for sepsis—primarily based on sepsis-3 or, for earlier studies, the 1992/2001 Society of Critical Care Medicine and American College of Chest Physicians consensus definition, or subsequent Surviving Sepsis Campaign guidelines—and subsequently developing AKI as described in the original

studies.<sup>[16–18]</sup> When not explicitly stated, SA-AKI was considered present if both sepsis and AKI were reported based on standard clinical and laboratory findings; and (2) each study included both an experimental group and a control group. Both groups received standard treatments for SA-AKI, including anti-infection therapy, fluid resuscitation, and nutritional support. The experimental group received additional CRRT. In this meta-analysis, CRRT was defined according to the terminology used in the original studies, including continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF), or continuous blood purification approaches reported as CRRT-related interventions by the investigators. The control group did not receive any form of kidney replacement therapy, including CRRT, during the study period.

### Exclusion criteria

Studies were excluded if they did not meet the prespecified eligibility criteria regarding study design, population, intervention, comparator, or outcomes; were reviews, meta-analyses, guidelines, animal studies, or non-randomized studies; included non-adult populations; had duplicate or overlapping data; were unavailable in full text; or did not provide sufficient extractable data for at least one prespecified outcome. When numerical data were unclear or internally inconsistent, the original report was rechecked, and data that could not be reliably verified were not included in the quantitative synthesis.

### Definition of outcomes

The primary outcomes were 28-day and hospital mortality rates. The secondary outcomes included the incidence of cardiovascular events, ICU length of stay, and in-hospital length of stay. Cardiovascular events refer to the incidence of complications such as acute myocardial infarction, sudden cardiac death, and persistent angina.

### Literature screening and data extraction

Two reviewers (different from those involved in the search process) independently screened the articles, extracted the data, and assessed study quality. Any disagreements were resolved through discussion or adjudication by a third reviewer. A single comprehensive table was constructed to summarize the key characteristics of each included study, including the first author, publication year, sample size, sex, mean age, serum creatinine level, and detailed CRRT parameters (mode, blood flow, replacement fluid flow, therapeutic dose, treatment time, and frequency).

### Quality assessment

The same 2 reviewers individually evaluated the quality of the included studies using the Cochrane Risk of Bias (RoB) tool version 1.0.<sup>[19]</sup> These criteria encompass 7 aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, selective reporting, incomplete outcome data, and other sources of bias. For the selective reporting domain, judgements were based on the consistency between outcomes prespecified or described in the Methods and those reported in the Results, together with protocol or trial-registration information when available; absence of trial registration alone was not considered evidence of selective reporting bias. If discrepancies arose, a third reviewer was involved to facilitate consensus.

## Statistical analysis

Statistical analyses were performed using RevMan software (version 5.3, The Nordic Cochrane Center; The Cochrane Collaboration, Copenhagen, Denmark) and Stata software (version 14; StataCorp, College Station, TX). Risk ratios (RRs) with corresponding 95% confidence intervals (CIs) were calculated for dichotomous variables, whereas continuous variables were analyzed using weighted mean differences (WMDs) with 95% CIs. Heterogeneity among studies was assessed using the  $I^2$  statistic. The meta-analysis model was selected based on statistical heterogeneity ( $I^2$ ), and clinical and methodological heterogeneity, such as differences in infection sites, CRRT modalities, and standard treatment protocols across studies. Based on this comprehensive assessment, a random-effects model was applied for all pooled analyses to provide a more conservative and generalized estimate. Eggers test was used to evaluate potential publication bias. When significant publication bias was detected ( $P < 0.05$ ), the trim-and-fill method was used to adjust the pooled results. In addition, subgroup analyses were conducted based on CRRT modality, distinguishing between studies using continuous veno-venous hemofiltration (CVVH) and those using other or unspecified CRRT modes. Sensitivity analyses were conducted by sequentially omitting each study to assess the robustness and stability of the pooled results. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering 5 domains: RoB, inconsistency, indirectness, imprecision, and publication bias. A summary of the findings table was constructed accordingly.

## Results

### Literature retrieval

A total of 1056 articles were identified through the database searches. After removing 416 duplicate articles, 640 remained for further screening. After title and abstract screening, 591 articles were excluded because of irrelevant study types, populations, interventions, or outcomes. The remaining 49 full-text articles were sought for retrieval and successfully obtained. After a full-text review of the 49 retrieved articles, 12 non-RCTs were excluded. Ultimately, 37 studies were included in the final analysis.<sup>[20–56]</sup> All included studies were conducted in China. Figure 1 illustrates the review procedure.

### Characteristics of the included studies

Data from 37 studies conducted between 2011 and 2025 were analyzed, involving 3120 subjects. All control groups received standard therapy for SA-AKI, including anti-infection therapy, fluid resuscitation, nutritional support, and respiratory support. In each study, the experimental group (CRRT group) received CRRT in addition to standard therapy administered to the control group (non-CRRT group). Among the included studies, 18 used CVVH, while the remaining 19 employed other modes such as continuous veno-venous hemodialysis and continuous veno-venous hemodiafiltration, or did not specify the mode used. No significant differences were reported in baseline data between the CRRT and non-CRRT groups ( $P > 0.05$ ) across the studies. Table 1 summarizes the included RCTs and CRRT intervention details.

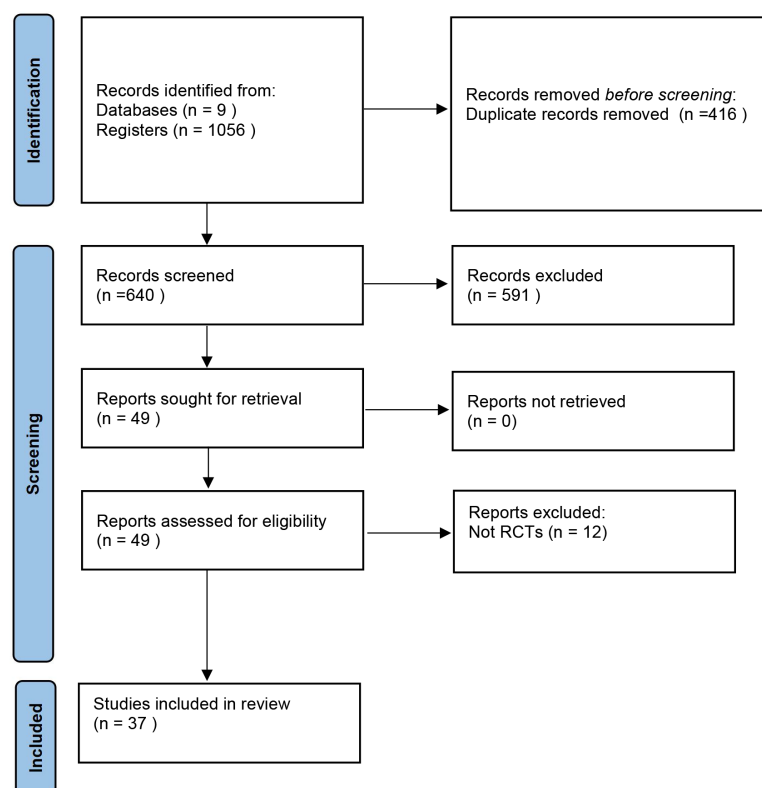


**Figure 1.** Flowchart of the literature screening process. RCT, randomized controlled trial.

Table 1

Summary of Included RCTs and CRRT Intervention Details

| Number | Study                              | Sample Size (N)          | Sex Distribution             | Mean Age                                   | Serum Creatinine (Before Treatment) (μmol/L)     | CRRT  |                     |                        |                            |                                                                   |
|--------|------------------------------------|--------------------------|------------------------------|--------------------------------------------|--------------------------------------------------|-------|---------------------|------------------------|----------------------------|-------------------------------------------------------------------|
|        |                                    |                          |                              |                                            |                                                  | Mode  | Blood Flow mL/min   | Replacement Fluid Flow | Therapeutic Dose (mL/kg/h) | Treatment Time and Frequency                                      |
| 1      | Lai, 2025 <sup>[23]</sup>          | N = 100 (E: 50; C: 50)   | E/M/F: 25/25<br>C/M/F: 26/24 | E: (52.92 ± 2.32)<br>C: (51.35 ± 2.43)     | E: (318.45 ± 34.89)<br>C: (312.45 ± 35.21)       | CVVH  | 150–200             | 25–35 mL/kg/h          | UN                         | 8–12 h/d, Consecutive for 3–7 days                                |
| 2      | Wang and Cao, 2025 <sup>[21]</sup> | N = 100 (E: 50; C: 50)   | E/M/F: 28/22<br>C/M/F: 26/24 | E: (56.31 ± 4.25)<br>C: (56.23 ± 4.15)     | E: (362.28 ± 30.69)<br>C: (362.26 ± 29.65)       | UN    | 180–200             | 1800–2300 mL/h         | UN                         | 8 h/d, Consecutive for 1 wk                                       |
| 3      | Wei, 2025 <sup>[20]</sup>          | N = 200 (E: 100; C: 100) | E/M/F: 65/35<br>C/M/F: 64/36 | E: (55.07 ± 14.62)<br>C: (53.76 ± 14.65)   | E: (393.54 ± 50.45)<br>C: (390.52 ± 50.73)       | CVVHD | 100–180             | 25–35 mL/kg/h          | UN                         | Once every 24–48 h                                                |
| 4      | An et al., 2023 <sup>[30]</sup>    | N = 89 (E: 39; C: 50)    | E/M/F: 18/21<br>C/M/F: 29/21 | E: 74.5 (65.0–83.3)<br>C: 76.0 (68.2–85.1) | E: 247.0 (209.0–265.0)<br>C: 242.0 (181.8–261.3) | UN    | 183.4 (173.8–193.9) | UN                     | UN                         | 33.5 (18.5–45.5) h                                                |
| 5      | Gao, 2023 <sup>[29]</sup>          | N = 70 (E: 35; C: 35)    | E/M/F: 20/15<br>C/M/F: 23/12 | E: (56.3 ± 4.2)<br>C: (56.0 ± 3.7)         | E: (365.2 ± 30.1)<br>C: (364.8 ± 25.9)           | UN    | 180–200             | 1800–2300 mL/h         | UN                         | 8 h/d, Consecutive for 1 wk                                       |
| 6      | He, 2023 <sup>[28]</sup>           | N = 100 (E: 50; C: 50)   | E/M/F: 26/24<br>C/M/F: 27/23 | E: (70.67 ± 1.56)<br>C: (71.04 ± 1.02)     | E: (415.2 ± 115.9)<br>C: (416.3 ± 116.1)         | CWH   | 200                 | 2000 mL/h              | UN                         | Once a day                                                        |
| 7      | Liu et al., 2023 <sup>[27]</sup>   | N = 80 (E: 40; C: 40)    | E/M/F: 23/17<br>C/M/F: 25/15 | E: (61.61 ± 10.03)<br>C: (61.76 ± 9.93)    | E: (177.11 ± 22.63)<br>C: (176.32 ± 21.35)       | UN    | 150–200             | 1000–2100 mL/h         | UN                         | Once every 24–48 h, at least twice a week, for a duration of 1 wk |
| 8      | Zhang, 2023 <sup>[26]</sup>        | N = 66 (E: 33; C: 33)    | E/M/F: 17/16<br>C/M/F: 18/15 | E: (70.94 ± 1.59)<br>C: (70.83 ± 1.47)     | E: (178.87 ± 25.02)<br>C: (181.24 ± 24.36)       | CWH   | 200–300             | UN                     | UN                         | Treat for 2 h each time                                           |
| 9      | Zhao et al., 2023 <sup>[25]</sup>  | N = 56 (E: 28; C: 28)    | E/M/F: 14/14<br>C/M/F: 13/15 | E: (58.45 ± 2.68)<br>C: (58.12 ± 2.46)     | UN                                               | CWH   | 180–220             | 50–80 mL/kg/h          | UN                         | Once every 48 h                                                   |
| 10     | Zheng, 2023 <sup>[24]</sup>        | N = 94 (E: 47; C: 47)    | E/M/F: 28/19<br>C/M/F: 27/20 | E: (56.04 ± 8.17)<br>C: (55.26 ± 8.43)     | UN                                               | CWHDF | 120–200             | 1600–1900 mL/h         | UN                         | Treat for 4–5 h each time, 3 times a week for 4 wk                |
| 11     | Zhu and Zhou, 2023 <sup>[23]</sup> | N = 53 (E: 27; C: 26)    | E/M/F: 15/12<br>C/M/F: 14/12 | E: (61.25 ± 3.49)<br>C: (61.39 ± 3.24)     | E: (360.48 ± 45.23)<br>C: (361.05 ± 45.12)       | CWH   | 150–250             | 4–10 L/h               | 35–40                      | UN                                                                |
| 12     | Jin et al., 2022 <sup>[34]</sup>   | N = 103 (E: 50; C: 53)   | E/M/F: 28/22<br>C/M/F: 31/22 | E: 57 (54–63)<br>C: 58 (54–66)             | E: 348.2 (256.1–419.6)<br>C: 265.1 (189.2–394.0) | CWH   | 180.5 (170.2–190.1) | UN                     | 47.1 (40.5–53.2)           | 35.6 (20.5–42.0) h                                                |
| 13     | Xia et al., 2022 <sup>[33]</sup>   | N = 80 (E: 40; C: 40)    | E/M/F: 22/18<br>C/M/F: 21/19 | E: (68.77 ± 8.14)<br>C: (68.34 ± 8.09)     | E: (189.34 ± 23.18)<br>C: (188.76 ± 22.45)       | CWH   | 150–200             | 40 mL/kg/h             | UN                         | 12 h/d, Consecutive for 3 d                                       |
| 14     | Xiao et al., 2022 <sup>[32]</sup>  | N = 50 (E: 25; C: 25)    | E/M/F: 15/10<br>C/M/F: 14/11 | E: (43.28 ± 9.55)<br>C: (43.51 ± 10.20)    | UN                                               | CWH   | 200–250             | UN                     | UN                         | 8 h/d, Consecutive for 1 wk                                       |
| 15     | Yao et al., 2022 <sup>[31]</sup>   | N = 60 (E: 30; C: 30)    | E/M/F: 15/15<br>C/M/F: 18/12 | E: (63.15 ± 14.31)<br>C: (62.34 ± 13.22)   | E: (369.24 ± 23.88)<br>C: (369.78 ± 23.70)       | UN    | 150–200             | 2000 mL/h              | UN                         | 8–12 h/d, Consecutive for 7 d                                     |

(Continued)

Table 1

Continued

| Number | Study                              | Sample Size (N)        | Sex Distribution           | Mean Age                                 | Serum Creatinine (Before Treatment) (μmol/L) | CRRT |                   |                        |                            |                                                                                                                            |
|--------|------------------------------------|------------------------|----------------------------|------------------------------------------|----------------------------------------------|------|-------------------|------------------------|----------------------------|----------------------------------------------------------------------------------------------------------------------------|
|        |                                    |                        |                            |                                          |                                              | Mode | Blood Flow mL/min | Replacement Fluid Flow | Therapeutic Dose (mL/kg/h) | Treatment Time and Frequency                                                                                               |
| 16     | Chen, 2021 <sup>[37]</sup>         | N = 110 (E: 51; C: 59) | UN                         | UN                                       | UN                                           | UN   | 100–300           | UN                     | 25–35                      | UN                                                                                                                         |
| 17     | Lei et al., 2021 <sup>[38]</sup>   | N = 90 (E: 45; C: 45)  | E/MF: 25/20<br>C/MF: 27/18 | E: (61.34 ± 6.87)<br>C: (61.77 ± 7.21)   | E: (362.58 ± 46.33)<br>C: (351.46 ± 44.21)   | CWHD | 150–200           | 40 mL/kg/h             | UN                         | 12 h/d, Consecutive for 6 d                                                                                                |
| 18     | Zhang, 2021 <sup>[39]</sup>        | N = 62 (E: 31; C: 31)  | E/MF: 29/2<br>C/MF: 28/3   | E: (90.02 ± 8.01)<br>C: (89.54 ± 7.79)   | E: (391.02 ± 54.61)<br>C: (391.22 ± 54.38)   | UN   | 150–200           | UN                     | UN                         | UN                                                                                                                         |
| 19     | Han et al., 2020 <sup>[43]</sup>   | N = 68 (E: 34; C: 34)  | E/MF: 21/13<br>C/MF: 20/14 | E: (56.29 ± 7.30)<br>C: (55.59 ± 7.56)   | E: (356.2 ± 32.5) C: (352.7 ± 33.1)          | UN   | 180–250           | 2000–3000 mL/h         | UN                         | Consecutive or 7 d                                                                                                         |
| 20     | Liu, 2020 <sup>[42]</sup>          | N = 126 (E: 63; C: 63) | E/MF: 39/24<br>C/MF: 37/26 | E: (61.5 ± 10.5) C: (61.2 ± 10.7)        | E: (149.36 ± 29.58) C: (148.75 ± 28.59)      | UN   | UN                | UN                     | UN                         | The first continuous treatment lasts for more than 72 h, followed by daily or alternate treatment lasting 8–12 h each time |
| 21     | Liu et al., 2020 <sup>[41]</sup>   | N = 106 (E: 53; C: 53) | E/MF: 30/23<br>C/MF: 31/22 | E: (70.25 ± 8.30)<br>C: (73.02 ± 8.40)   | E: (405.37 ± 40.26) C: (403.26 ± 42.15)      | UN   | 180–220           | 35 mL/kg/h             | UN                         | UN                                                                                                                         |
| 22     | Pan et al., 2020 <sup>[40]</sup>   | N = 95 (E: 48; C: 47)  | E/MF: 30/18<br>C/MF: 28/19 | E: (55.02 ± 4.63)<br>C: (55.17 ± 4.75)   | UN                                           | CWH  | 150–200           | 40 mL/kg/h             | UN                         | 12 h/d, Consecutive for 3 d                                                                                                |
| 23     | Qiu and Lin 2020 <sup>[39]</sup>   | N = 82 (E: 41; C: 41)  | E/MF: 27/14<br>C/MF: 26/15 | E: (53.41 ± 7.68)<br>C: (52.63 ± 8.13)   | E: (156.83 ± 24.56) C: (156.37 ± 26.23)      | CWH  | UN                | UN                     | 65                         | 12 h/d, Consecutive for 5 d                                                                                                |
| 24     | Wang et al., 2020 <sup>[38]</sup>  | N = 80 (E: 40; C: 40)  | E/MF: 25/15<br>C/MF: 26/14 | E: (61.26 ± 14.31)<br>C: (60.37 ± 15.22) | E: (295.73 ± 80.37) C: (302.15 ± 78.18)      | UN   | 118–188           | 40 mL/kg/h             | UN                         | UN                                                                                                                         |
| 25     | Sun et al., 2019 <sup>[46]</sup>   | N = 100 (E: 50; C: 50) | E/MF: 33/17<br>C/MF: 32/18 | E: (46.23 ± 8.59)<br>C: (48.14 ± 9.37)   | E: (358.23 ± 36.46) C: (364.58 ± 38.92)      | CWHD | 200–250           | 2.5–3 L/h              | UN                         | 8 h/d, Consecutive for 1 wk                                                                                                |
| 26     | Yue et al., 2019 <sup>[45]</sup>   | N = 72 (E: 36; C: 36)  | E/MF: 20/16<br>C/MF: 22/14 | E: (51.7 ± 9.8) C: (51.3 ± 10.7)         | UN                                           | CWH  | 150–200           | 40 mL/kg/h             | UN                         | 12 h/d, Consecutive for 3 d                                                                                                |
| 27     | Zhang et al., 2019 <sup>[44]</sup> | N = 98 (E: 49; C: 49)  | E/MF: 32/17<br>C/MF: 30/19 | E: (56.2 ± 2.2) C: (55.2 ± 1.2)          | E: (417.1 ± 115.2) C: (415.6 ± 113.7)        | UN   | UN                | UN                     | UN                         | Treatments at intervals of 1–1.5 d for 2 d each                                                                            |
| 28     | Chen et al., 2018 <sup>[47]</sup>  | N = 70 (E: 35; C: 35)  | E/MF: 21/14<br>C/MF: 20/15 | E: (48.98 ± 8.68)<br>C: (48.86 ± 8.38)   | E: (370.52 ± 45.52) C: (370.29 ± 46.68)      | CWH  | 180–250           | 2000–3000 mL/h         | UN                         | UN                                                                                                                         |
| 29     | Jiang, 2017 <sup>[48]</sup>        | N = 84 (E: 42; C: 42)  | E/MF: 26/16<br>C/MF: 25/17 | E: (58.3 ± 11.7) C: (57.6 ± 12.1)        | E: (390.5 ± 54.8) C: (393.7 ± 50.4)          | UN   | 150–200           | 40 mL/kg/h             | UN                         | UN                                                                                                                         |
| 30     | Luo, 2017 <sup>[48]</sup>          | N = 90 (E: 45; C: 45)  | E/MF: 25/20<br>C/MF: 26/19 | E: (51.24 ± 4.31)<br>C: (52.12 ± 4.41)   | UN                                           | CWH  | UN                | 1–2 L/h                | UN                         | UN                                                                                                                         |
| 31     | Deng, 2016 <sup>[53]</sup>         | N = 86 (E: 43; C: 43)  | E/MF: 27/16<br>C/MF: 25/18 | E: (56.1 ± 2.3) C: (55.7 ± 2.1)          | E: (417.2 ± 115.3) C: (415.7 ± 113.8)        | CWH  | UN                | UN                     | UN                         | Continuous treatment for more than 2 d                                                                                     |

(Continued)

Table 1  
Continued

| Number | Study                            | Sample Size (N)        | Sex Distribution             | Mean Age                              | Serum Creatinine (Before Treatment) (μmol/L) | CRRT       |                   |                        |                            |                                                                                                  |
|--------|----------------------------------|------------------------|------------------------------|---------------------------------------|----------------------------------------------|------------|-------------------|------------------------|----------------------------|--------------------------------------------------------------------------------------------------|
|        |                                  |                        |                              |                                       |                                              | Mode       | Blood Flow mL/min | Replacement Fluid Flow | Therapeutic Dose (mL/kg/h) | Treatment Time and Frequency                                                                     |
| 32     | Huang, 2016 <sup>[52]</sup>      | N = 106 (E: 53; C: 53) | E:M/F: 30/23<br>C:M/F: 30/23 | E: (52.4 ± 7.9) C: (50.5 ± 5.9)       | E: (445.9 ± 169.8) C: (441.5 ± 146.3)        | CWH        | 250–300           | 3500–4500 mL/h         | UN                         | 5–24 h/d                                                                                         |
| 33     | Tan, 2016 <sup>[51]</sup>        | N = 76 (E: 38; C: 38)  | E:M/F: 26/12<br>C:M/F: 24/14 | E: (53.6 ± 7.2) C: (55.2 ± 6.8)       | E: (420.3 ± 102.4) C: (416.4 ± 98.5)         | CWHDF      | UN                | 2000–3500 mL/h         | UN                         | Twice a week                                                                                     |
| 34     | Ye, 2016 <sup>[50]</sup>         | N = 30 (E: 15; C: 15)  | E:M/F: 9/6<br>C:M/F: 7/8     | E: (58.47 ± 15.39) C: (60.13 ± 18.42) | E: (206.3 ± 55.2) C: (208.6 ± 89.3)          | CWHDF + HP | UN                | UN                     | UN                         | UN                                                                                               |
| 35     | Cao et al., 2015 <sup>[54]</sup> | N = 92 (E: 40; C: 52)  | E:M/F: 21/19<br>C:M/F: 27/25 | E: (52.8 ± 4.3) C: (53.1 ± 3.9)       | E: (429.80 ± 124.43) C: (431.27 ± 125.64)    | CWH        | 160–200           | UN                     | UN                         | UN                                                                                               |
| 36     | Sun, 2013 <sup>[55]</sup>        | N = 42 (E: 21; C: 21)  | M/F: 28/14                   | 26–67                                 | E: (324.41 ± 164.38) C: (427.56 ± 154.88)    | CWH        | 170–200           | 3000–4000 mL/h         | UN                         | The initial treatment time exceeds 12 h, and subsequent treatment will be based on the condition |
| 37     | Su, 2011 <sup>[56]</sup>         | N = 54 (E: 26; C: 28)  | E:M/F: 16/10<br>C:M/F: 21/7  | E: (70.46 ± 6.58) C: (71.32 ± 8.41)   | E: (429.6 ± 226.2) C: (373.25 ± 150.07)      | CWH        | UN                | UN                     | 35                         | The initial treatment time exceeds 48 h, and subsequent treatment will be based on the condition |

Data are presented as mean ± SD unless otherwise indicated. Values for An Mengmeng 2023 and Jin Beibei 2022 are expressed as median (IQR). C, control group; CWH, continuous veno-venous hemofiltration; CWHDF, continuous veno-venous hemodiafiltration; E, experimental group; F, female; HP, hemoperfusion; IQR, interquartile range; M, male; NA, not applicable; RCT, randomized controlled trial; UN, unreported.

## Quality assessment

Two reviewers evaluated the studies, yielding consistent conclusions (Fig. 2A, B). First, 18 studies explicitly indicated that they used random sequences, but only 1 specified whether the randomization process was concealed. Second, only 1 study employed a double-blind design, and another implemented a single-blind approach. Finally, complete data were available for all studies, with no evidence of selective reporting or other potential biases.

## Outcomes

### 28-day mortality rate

Fifteen studies were included in the analysis ( $I^2 = 61\%$ , RR: 0.46, 95% CI: 0.34–0.61,  $P < 0.01$ ; Fig. 3). Subgroup analysis showed that both the CVVH group (7 studies) and the other modes group (8 studies) reduced the 28-day mortality rate ( $I^2 = 51\%$ , RR: 0.37, 95% CI: 0.22–0.62,  $P < 0.01$  vs.  $I^2 = 63\%$ ; RR: 0.52, 95% CI: 0.37–0.74,  $P < 0.01$ ).

### Hospital mortality rate

Nine studies were included in the analysis (RR: 0.39, 95% CI: 0.28–0.54,  $I^2 = 0\%$ ,  $P < 0.01$ ; Fig. 4). Most of the available evidence was derived from studies using CVVH (8 of 9), which consistently reported a reduction in hospital mortality. Only 1 study evaluated continuous veno-venous hemodiafiltration

modalities and reported a point estimate suggesting a potential reduction in hospital mortality (RR: 0.40, 95% CI: 0.14–1.16); however, this finding should be interpreted cautiously given the absence of data pooling and the exploratory nature of the evidence.

## Incidence of cardiovascular events

Seven studies were included in the analysis ( $I^2 = 0\%$ , RR: 0.39, 95% CI: 0.28–0.55,  $P < 0.01$ ; Fig. 5). Subgroup analysis indicated that both the CVVH group (3 studies) and the other modes (4 studies) group decreased the incidence of cardiovascular events ( $I^2 = 0\%$ , RR: 0.38, 95% CI: 0.22–0.66,  $P = 0.0006$  vs.  $I^2 = 0\%$ , RR: 0.40, 95% CI: 0.26–0.61,  $P < 0.01$ ).

## Intensive care unit length of stay (days)

Twenty studies were included in the analysis ( $I^2 = 85\%$ , WMD: -3.97; 95% CI: -4.71 to -3.22,  $P < 0.01$ ; Fig. 6). Subgroup analysis demonstrated that both the CVVH group (11 studies) and the other modes (9 studies) group reduced ICU length of stay ( $I^2 = 91\%$ , WMD: -3.87, 95% CI: -5.10 to -2.64,  $P < 0.01$  vs.  $I^2 = 43\%$ , WMD: -4.11, 95% CI: -4.73 to -3.48,  $P < 0.01$ ). Although substantial statistical heterogeneity was observed ( $I^2 = 85\%$ ), the direction of effect was consistent across the studies, with all pooled estimates favoring CRRT.

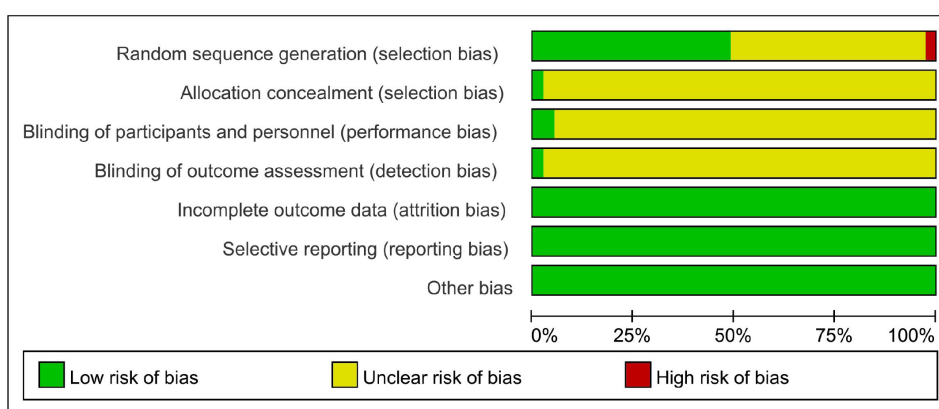


Figure 2. Risk of bias assessment of included studies. (A) Risk of bias graph. (B) Risk of bias summary.

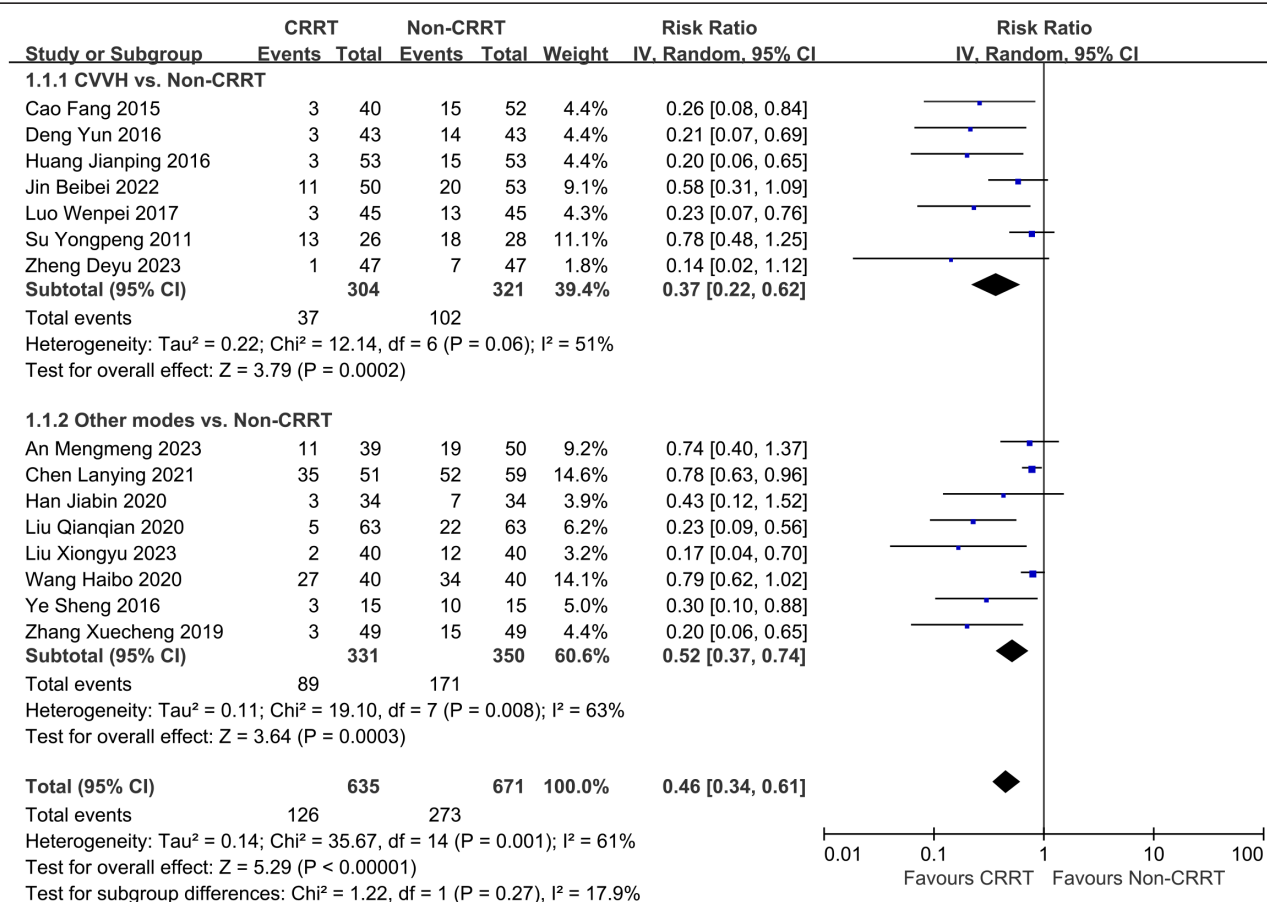


**Figure 3.** Forest plot of 28-day mortality. CI, confidence interval; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; IV, inverse variance.

### In-hospital length of stay (days)

Seven studies were included in the analysis (WMD:  $-4.51$ , 95% CI:  $-5.51$  to  $-3.51$ ,  $P < 0.01$ ,  $I^2 = 70\%$ ; Fig. 7). Exploratory subgroup analyses based on CRRT modality suggested a similar direction of effect in both the CVVH subgroup (2 studies) and the other modes subgroup (5 studies). However, substantial heterogeneity was observed in the CVVH subgroup ( $I^2 = 92\%$ ), and the

limited number of studies precluded firm conclusions. Therefore, the subgroup findings should be interpreted with caution.

### Publication bias

Eggers test suggested potential publication bias for the 28-day mortality rate and incidence of cardiovascular events (both  $P < 0.01$ ). The trim-and-fill method was subsequently applied to these 2 outcomes. The trim-and-fill procedure did not impute

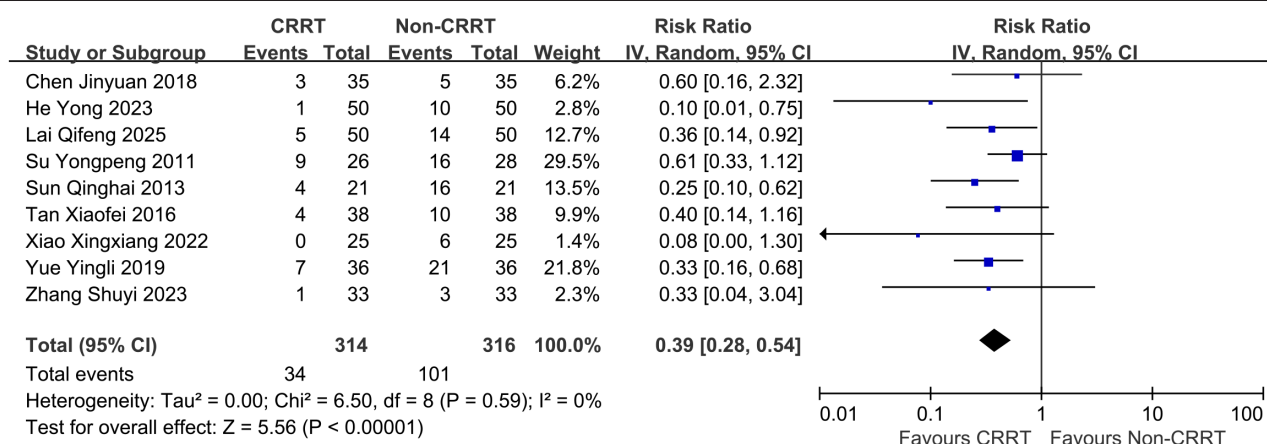


**Figure 4.** Forest plot of hospital mortality. CI, confidence interval; CRRT, continuous renal replacement therapy; IV, inverse variance.

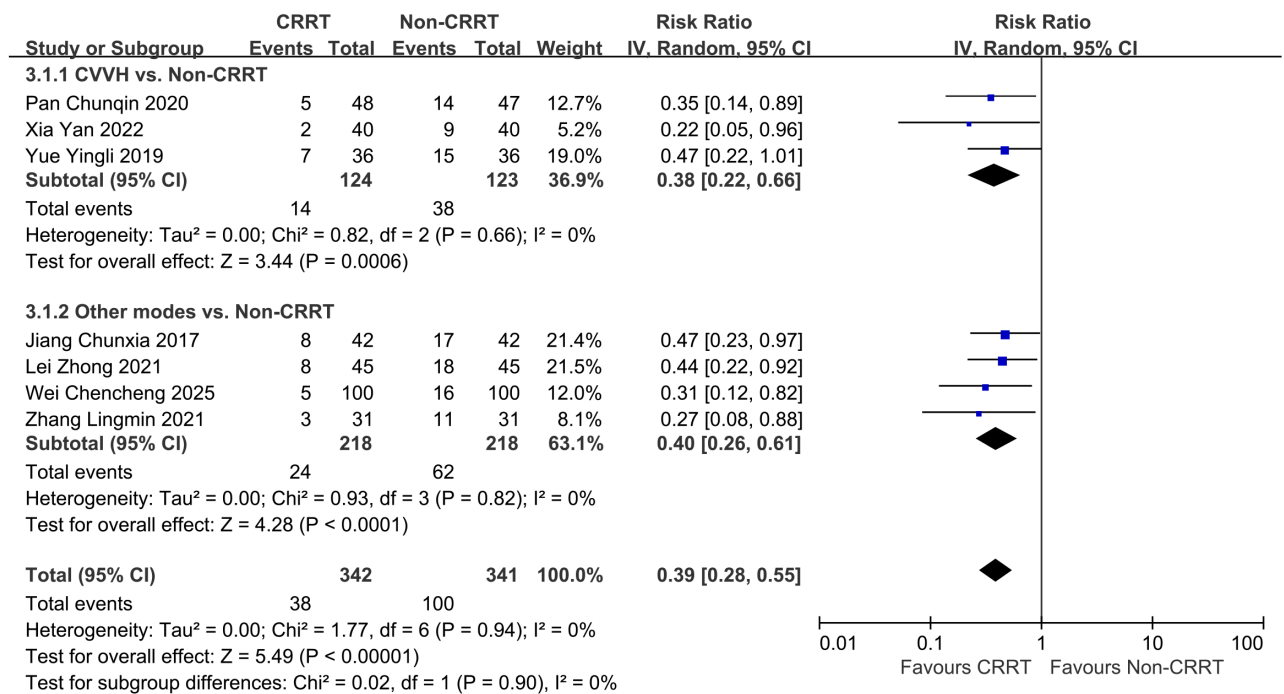


**Figure 5.** Forest plot of cardiovascular event incidence. CI, confidence interval; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; IV, inverse variance.

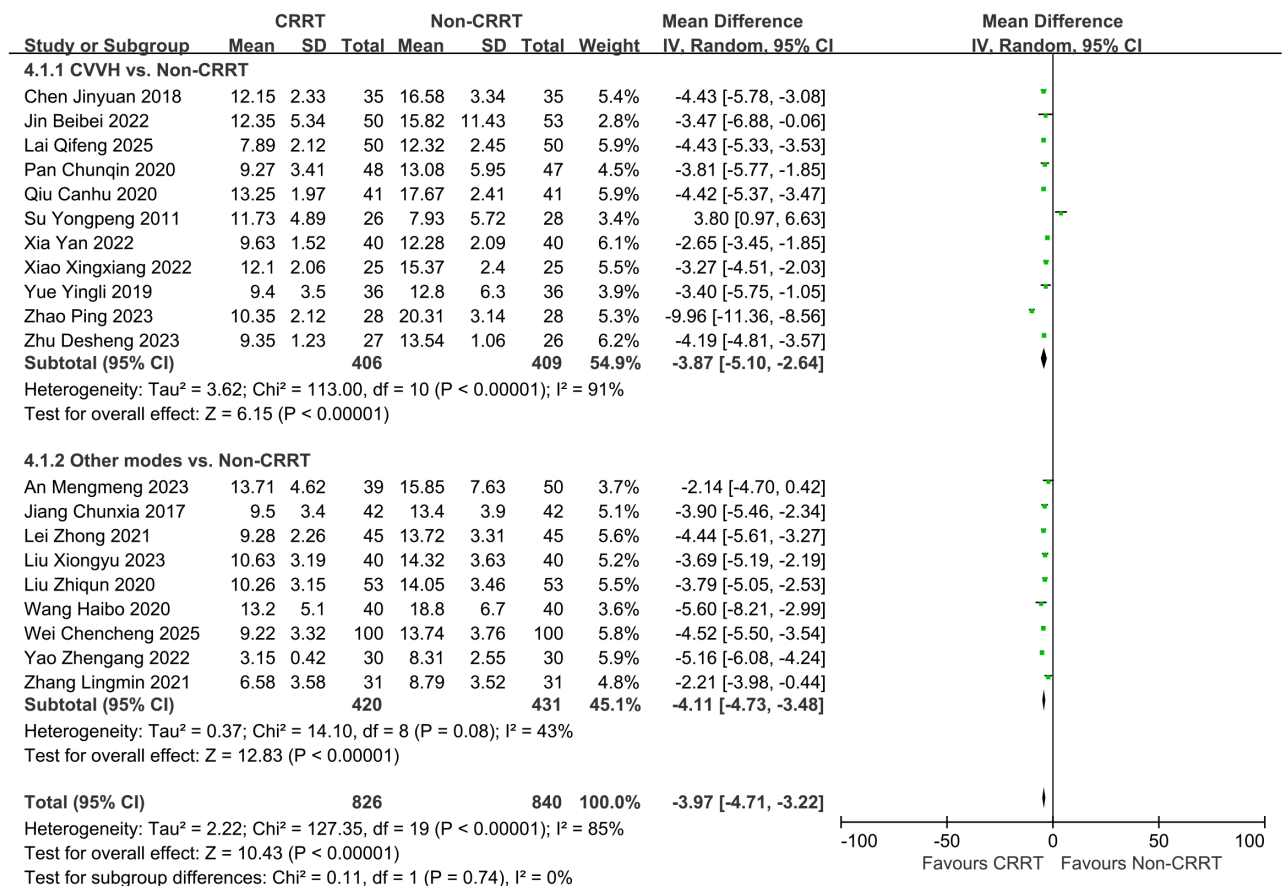


**Figure 6.** Forest plot of ICU length of stay. CI, confidence interval; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; ICU, intensive care unit; IV, inverse variance.

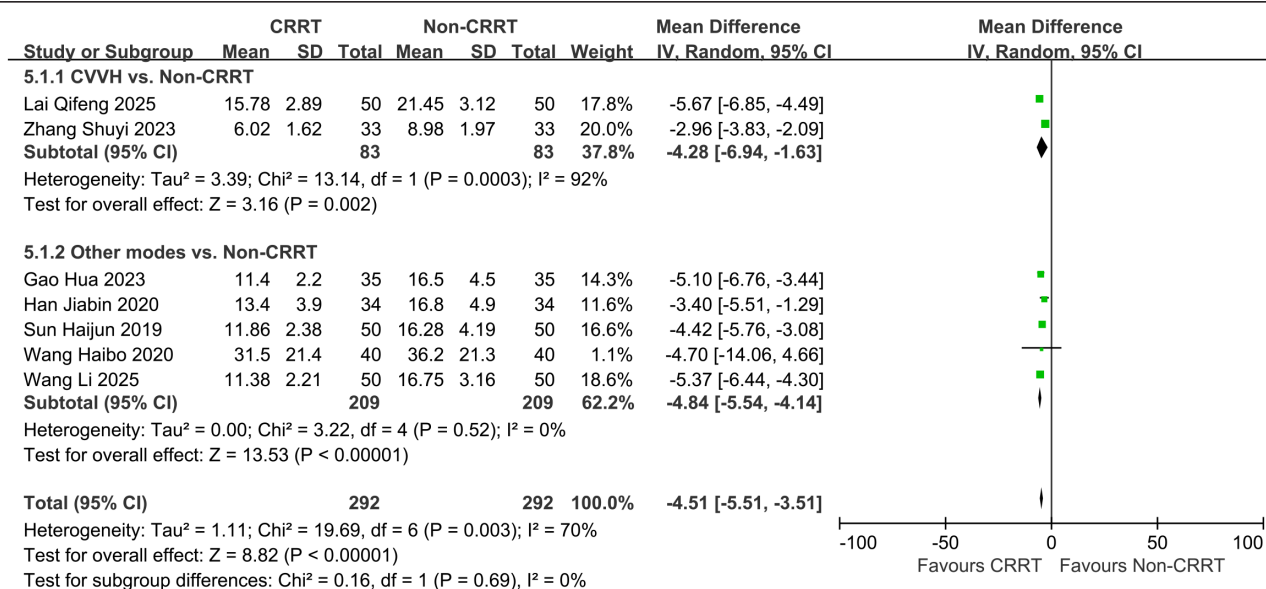


**Figure 7.** Forest plot of in-hospital length of stay. CI, confidence interval; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; IV, inverse variance.

any additional studies and therefore did not change the pooled estimates (28-day mortality rate: RR 0.46, 95% CI 0.34–0.61,  $P < 0.01$ ; incidence of cardiovascular events: RR 0.39, 95% CI 0.28–0.55,  $P < 0.01$ ). However, this finding does not exclude the possibility of publication bias or establish the robustness of the pooled estimates, particularly given the relatively small number of studies and the limited methodological reporting of the included trials.

### Sensitivity analysis

Sensitivity analyses were performed for all key outcomes (28-day mortality rate, hospital mortality rate, incidence of cardiovascular events, ICU length of stay, and in-hospital length of stay) using a leave-one-out approach. Each study was sequentially excluded to assess the influence of individual trials on the pooled estimates. No material changes in effect sizes or statistical significance were observed for any outcome, confirming the stability of the findings.

### Grading of Recommendations Assessment, Development and Evaluation assessment

All outcomes were rated as having low or very low certainty (Table 2). The main reasons for downgrading were as follows: (1) unclear or high RoB in most studies, mainly due to inadequate blinding and incomplete reporting of randomization or allocation concealment, (2) potential inconsistency across studies, particularly in CRRT dose and modality, (3) indirectness, as all included trials were conducted in China, which may limit generalizability, and (4) possible publication bias in several outcomes. Therefore, the overall quality of evidence supporting CRRT in SA-AKI remains low, and the results should be interpreted with caution.

### Discussion

Our meta-analysis results suggest that compared with the non-CRRT group, the CRRT group had a lower 28-day mortality

**Table 2**  
**The Summary of Findings**

| Outcomes                           | Number of Studies | Number of Participants | Effect                      | P value | Certainty (GRADE) | Comments                                                        |
|------------------------------------|-------------------|------------------------|-----------------------------|---------|-------------------|-----------------------------------------------------------------|
| 28-d Mortality rate                | 15 RCTs           | 1306                   | RR: 0.46 (0.34–0.61)        | <0.01   | Very low          | Downgraded for risk of bias, indirectness, and publication bias |
| Hospital mortality rate            | 9 RCTs            | 630                    | RR: 0.39 (0.28–0.54)        | <0.01   | Low               | Downgraded for risk of bias and indirectness                    |
| Incidence of cardiovascular events | 7 RCTs            | 683                    | RR: 0.39 (0.28–0.55)        | <0.01   | Very low          | Downgraded for risk of bias, indirectness, and publication bias |
| ICU length of stay (d)             | 20 RCTs           | 1666                   | WMD: -3.97 (-4.71 to -3.22) | <0.01   | Low               | Downgraded for risk of bias and indirectness                    |
| In-hospital length of stay (d)     | 7 RCTs            | 584                    | WMD: -4.51 (-5.51 to -3.51) | <0.01   | Low               | Downgraded for risk of bias and indirectness                    |

GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICU, intensive care unit; NA, not applicable; RCT, randomized controlled trial; RR, risk ratio; WMD, weighted mean difference.

rate, hospital mortality rate, incidence of cardiovascular events, ICU length of stay, and in-hospital length of stay. These findings support the potential clinical benefits of CRRT for the management of SA-AKI. However, the interpretation of these results must also consider certain methodological considerations, particularly the inconsistencies in reporting CRRT dosing parameters across studies. We found that detailed reports on CRRT therapeutic dose were inconsistent across the included studies. Specifically, only 5 of the 37 RCTs explicitly reported the therapeutic dose in terms of mL/kg/h. While the majority of studies did not define the total effluent volume or standardized dose, many reported partial parameters, such as replacement fluid flow and blood flow rates. Nonetheless, 13 studies did not provide replacement fluid flow data, limiting our ability to compare treatment intensities across trials. This heterogeneity in therapeutic dose reporting reflects a broader challenge in the field and may affect the precision and generalizability of the pooled estimates. Future trials should aim to adhere to standardized CRRT reporting guidelines, including complete specifications of effluent flow rates and therapeutic doses, to improve the comparability and reproducibility of results.

SA-AKI is a syndrome arising from direct mechanisms linked to infection, the host's reaction to infection, or indirect mechanisms triggered by the unfavorable effects of sepsis or its management.<sup>[4]</sup> The clinical manifestations of SA-AKI include oliguria and diminished glomerular filtration rate, usually resulting in disturbances in electrolyte and acid–base balance, fluid overload, and accumulation of toxic metabolites and medications that rely on renal excretion. The various etiological subtypes of SA-AKI may have distinct underlying mechanisms that individually or jointly influence its pathophysiology.<sup>[11]</sup> Initial theories proposed that insufficient global renal perfusion results in acute renal tubular necrosis. The primary treatment goal has long been to elevate perfusion pressure and enhance renal blood flow (RBF). Nevertheless, animal experiments and human data have revealed that most SA-AKI animals or patients do not necessarily demonstrate reduced RBF. Surprisingly, animal models of sepsis and human patients show normal or elevated RBF.<sup>[1,9]</sup> It is now clear that SA-AKI can manifest even when there is no clear renal hypoperfusion or significant macrohemodynamic instability, with other pathophysiological mechanisms playing a more substantial role.<sup>[3]</sup>

Current research suggests that inflammatory responses, macrovascular and microvascular dysfunction, and abnormal cellular responses are the 3 cornerstones of the pathophysiological mechanisms of SA-AKI.<sup>[11]</sup> Systemic inflammatory response is a hallmark of sepsis pathophysiology and a pivotal contributor to subsequent complications, including kidney injury.<sup>[3]</sup> The cascade of reactions initiated by the release of numerous inflammatory factors is a critical factor that contributes to the development of SA-AKI.<sup>[13]</sup> Previous studies have shown that inflammatory factors can induce damage to renal tubular capillary endothelial cells, leading to renal tubular injury and functional impairment, ultimately resulting in AKI.<sup>[13]</sup> Elevated levels of inflammatory factors are associated with delayed renal recovery and high mortality rates in SA-AKI.<sup>[57]</sup> Furthermore, apoptosis is a pivotal contributor to SA-AKI.<sup>[58]</sup> Apoptosis is a cellular process that utilizes active energy to eliminate damaged cells.<sup>[59]</sup> Evidence suggests that RTECs undergo apoptosis in patients with SA-AKI, whereas patients with AKI caused by other factors do not experience cellular apoptosis.<sup>[58, 59]</sup> Apoptosis of RTECs is a primary observation in SA-AKI, and inflammation-induced cellular apoptosis may

be one of the pathogenic mechanisms.<sup>[58, 60]</sup> The addition of high concentrations of lipopolysaccharide and tumor necrosis factor to cultured RTECs and renal glomerular endothelial cells may increase the expression of proapoptotic mediators, especially Fas messenger RNA and Fas-associated death domain proteins, while decreasing the expression of the antiapoptotic protein Bcl-xL.<sup>[60]</sup> Inflammatory cytokines are moderately sized, water-soluble molecules (with molecular weights ranging from 0.5–60 kDa) in an unbound state within the bloodstream. Historically, the use of EBP techniques to eliminate cytokines has been suggested as a therapeutic approach to mitigate the excessive expression of these molecules. With advancements in EBP technology and membrane materials, CRRT has been widely used in critically ill patients. The efficiency of inflammatory cytokine removal depends on molecular weight, EBP technology, and membrane pore size. CRRT is more efficient in eliminating cytokines with lower molecular weights. The typical threshold for CRRT is set–30–40 kDa, and most inflammatory cytokines have molecular weights less than 40 kDa. As an illustration, tumor necrosis factor- $\alpha$  possesses a molecular weight of 17 kDa. Hence, most inflammatory cytokines can be gradually eliminated through standard CRRT.<sup>[57, 61]</sup> Inflammatory cytokines that enter the bloodstream exert autocrine and paracrine effects. Nonetheless, CRRT mitigates these detrimental effects by effectively arresting the continued advancement of the inflammatory response, protecting tissue cells from harm attributed to inflammatory cytokines, preventing endothelial cell death, enhancing vascular function and hemodynamics, rectifying sepsis-induced vascular dysfunction, and augmenting tissue perfusion.<sup>[8]</sup> CRRT removes inflammatory cytokines via convection, diffusion, or adsorption mechanisms.<sup>[8]</sup> Furthermore, in addition to CRRT's ability of CRRT to remove inflammatory cytokines and thereby alleviate RTECs apoptosis, different CRRT techniques may directly eliminate apoptotic factors in patients with SA-AKI. These advantages support the use of CRRT in patients with SA-AKI.<sup>[60]</sup>

In sepsis, inflammation leads to endothelial cell dysfunction, resulting in loss of venous tone and barrier function. This leads to a decrease in the average systemic pressure, a relative hypovolemic state, and a reduction in systemic vascular resistance, resulting in hypotension.<sup>[62]</sup> The rapid restoration of circulation through intravenous fluid administration is crucial for sepsis management. However, excessive fluid administration to treat hypotension often leads to oliguria and fluid retention, which can be harmful.<sup>[62–65]</sup> The inflammatory cascade, which involves various inflammatory cytokines, increases microvascular permeability and capillary leakage, leading to interstitial fluid accumulation, protein loss, and tissue edema.<sup>[63]</sup> An increase in intra-abdominal pressure because of edema can impede the drainage of renal veins, thereby worsening the elevation of renal vascular pressure.<sup>[62]</sup> Excess fluid is a frequent complication observed in AKI cases marked by oliguria or anuria. It is characterized by tissue swelling, dilution-related coagulation issues, low body temperature, diluted blood, and disruptions in electrolyte levels. This can lead to the development of multiple organ dysfunction syndrome, resulting in a lower survival rate in patients with SA-AKI.<sup>[63, 64]</sup> It is well-established that fluid overload is associated with increased mortality rates in patients with SA-AKI.<sup>[63–66]</sup> Although conservative fluid management and diuretics are commonly used to prevent fluid overload, CRRT is crucial for fluid control in patients with AKI. Earlier investigations have also shown that the use of CRRT to eliminate fluids is associated with enhanced results in individuals with AKI.<sup>[63]</sup>

Currently, there is consensus that metabolic reprogramming is a crucial pathophysiological mechanism of SA-AKI.<sup>[1, 3, 10, 12]</sup> Among the diverse cell types in the kidney, RTECs exhibit the highest metabolic activity and are particularly susceptible to injury associated with sepsis.<sup>[10]</sup> Under normal physiological conditions, oxidative phosphorylation accounts for over 95% of the cellular energy required for metabolic processes. However, in SA-AKI, the energy metabolism of RTECs is preferentially shifted towards the glycolytic pathway for energy generation, akin to the Warburg effect observed in cancer cells.<sup>[1, 3, 10, 12]</sup> Similarly, monocytes and lymphocytes undergo metabolic reprogramming, shifting toward a proinflammatory phenotype and triggering an inflammatory response.<sup>[3, 7]</sup> Metabolic reprogramming initiates inflammation and primes RTECs to endure excessive inflammation to eliminate pathogen elimination.<sup>[57]</sup> Hyperglycemia is one of the most common metabolic disturbances in patients with sepsis, possibly because of alterations in glycogen metabolism and severe insulin resistance.<sup>[67]</sup> Elevated blood glucose levels enhance aerobic glycolysis in immune cells by providing them with essential metabolic intermediates. However, substantial evidence has indicated that excessive metabolic reprogramming is detrimental.<sup>[7]</sup> Excessive metabolic reprogramming can lead to uncontrolled hyperglycemia and immune cell exhaustion, which are crucial for immunosuppression and secondary infections.<sup>[57]</sup> CRRT may remove elevated blood glucose and inflammatory cytokines, and alleviate the adverse consequences of excessive metabolic reprogramming. The heightened presence of inflammatory cytokines, such as interleukin-1 $\beta$  and interleukin-6, is a significant underlying factor in developing insulin resistance. Clearance of these cytokines by CRRT may potentially improve insulin sensitivity and influence metabolic homeostasis. CRRT may also remove glucagon (molecular weight, approximately 3.4 kDa), which has been proposed to influence the balance between gluconeogenesis and glycolytic metabolism; however, the clinical relevance of this mechanism remains uncertain.<sup>[57]</sup>

A 7-year observational study comprising 880 units across 46 countries showed that many ICU patients did not meet the recommended calorie and protein intake levels. This is particularly pronounced in patients with SA-AKI because of the inherent metabolic disruptions associated with AKI.<sup>[57]</sup> Research findings indicate that reduced calorie and protein intakes are correlated with an increased in-hospital mortality rate in patients with AKI.<sup>[68]</sup> Furthermore, malnutrition has been shown to significantly increase the 28-day mortality rate in patients with AKI.<sup>[69]</sup> The body assimilates glucose, citrate, or lactate to the replacement solution during CRRT, offering extra energy via the tricarboxylic acid cycle.<sup>[57]</sup> CRRT ensures that patients receive adequate nutritional support and better control metabolic abnormalities.<sup>[8]</sup>

As previously mentioned, CRRT can clear inflammatory factors, reduce fluid overload, mitigate the adverse consequences of cellular metabolic reprogramming, provide energy, and improve metabolism. CRRT can also control temperature, correct electrolyte and acid-base imbalances, and stabilize hemodynamics. These factors may be beneficial in patients with SA-AKI.<sup>[70]</sup>

Although CRRT remains the most widely used modality for patients with SA-AKI, several blood purification techniques have been explored in the broader context of sepsis management, including adsorptive filters, plasma exchange, and high-volume hemofiltration (HVHF). Emerging evidence regarding adjunctive blood purification modalities for sepsis provides an important context for our findings. For instance, using the oXiris adsorptive

hemofilter during CRRT has been associated with significantly reduced 28-day mortality and improved short-term endpoints in patients with septic shock. This specialized membrane, designed to adsorb endotoxins and cytokines, showed benefits in a recent meta-analysis, although the certainty of evidence remains low.<sup>[71]</sup> Similarly, a 2023 network meta-analysis comparing extracorporeal therapies in sepsis identified therapeutic plasma exchange (TPE) and polymyxin-B hemoperfusion as the top modalities linked to lower mortality. In that analysis, TPE and endotoxin adsorption each outperformed standard care, although based on low-quality data and with inconsistent results for polymyxin-B in different trials.<sup>[72]</sup> TPE has shown particular promise; a new systematic review reported a ~40% relative reduction in short-term mortality when TPE was added to standard therapy in septic adults with multiorgan failure.<sup>[73]</sup> This aligns with earlier trials suggesting improved hemodynamics and organ function with plasma exchange, although definitive proof from large RCTs is still pending.<sup>[73]</sup> In contrast, simply increasing the therapeutic dose of CRRT via HVHF does not seem to improve outcomes. A 2020 meta-analysis of HVHF in sepsis found no significant mortality benefit (pooled 28-day mortality RR ~0.96) or organ support advantage over standard-volume CRRT.<sup>[74]</sup> Collectively, these observations suggest that the efficacy of blood purification in sepsis lies more in blood removal rather than in the sheer intensity of dialysis. Adjunctive techniques targeting endotoxins or inflammatory mediators (e.g., specialized hemofilters, sorbents, or plasma exchange) may complement conventional CRRT in SA-AKI; however, simply increasing the filtration volume has fallen short. Importantly, these studies emphasize the need for high-quality trials to identify the optimal candidates and timing for such therapies. Integrating these modalities prudently, such as including patients with high endotoxin load, profound cytokine elevation, or coagulopathic septic shock, could further enhance outcomes.

## Limitations

This meta-analysis has several limitations. First, all included RCTs were conducted in China, which may have restricted the external validity of the results, and some studies had small sample sizes. Second, although Eggers test was performed to assess publication bias and the trim-and-fill method was applied to adjust the results, unpublished articles were not included, which may have led to potential publication bias. Third, approximately half of the studies omitted details regarding the random sequence, only 1 study mentioned utilizing allocation concealment methods, and only 1 study adopted double-blinding, resulting in an unclear RoB. Fourth, although most outcomes showed no heterogeneity, there may be significant clinical heterogeneity because of several factors: (1) differences in sepsis infection sites and severity, (2) the lack of clear diagnostic criteria or staging system for SA-AKI, which may have led to heterogeneity in the disease definitions and limited the comparability of the results, (3) differences in standard SA-AKI therapy protocols, and (4) variations in CRRT filter type, mode, blood flow, replacement fluid flow, therapeutic dose, treatment time and frequency, and anticoagulant type. ICU length of stay exhibited notably higher heterogeneity than mortality outcomes, which is unsurprising as it is a complex and highly context-dependent endpoint. Differences in ICU discharge criteria, local bed availability, step-down unit capacity, and post-ICU care pathways across institutions may substantially influence ICU length of stay independent of disease severity or CRRT

effects. In addition, variations in the timing of CRRT initiation, treatment duration, and fluid management strategies may further contribute to clinical heterogeneity. Importantly, despite the high  $I^2$  value, the direction of effect consistently favored CRRT across studies, and sensitivity analyses confirmed the stability of the pooled estimate. Finally, none of the included studies reported 60- or 90-day mortality rates, limiting our ability to explore longer-term outcomes; consequently, only 28-day and hospital mortality rates could be analyzed, which restricts assessment of the sustained clinical benefits of CRRT in patients with SA-AKI. Despite these limitations, this study provides evidence for the potential benefits of CRRT in patients with SA-AKI, which may encourage further research and ultimately improve patient outcomes.

## Conclusion

The pooled estimates from the included studies favored CRRT with respect to 28-day mortality, hospital mortality, incidence of cardiovascular events, ICU length of stay, and in-hospital length of stay; however, the certainty of evidence was low to very low because of methodological limitations, heterogeneity in CRRT definitions and treatment protocols, small study sizes, and limited geographic generalizability. These findings should not be interpreted as establishing a routine clinical benefit of CRRT in SA-AKI or as supporting CRRT initiation in patients without standard indications for kidney replacement therapy. Further independent, prospectively registered, multicenter randomized controlled trials with standardized CRRT protocols are needed to confirm these findings.

## Conflict of interest statement

The authors declare no conflict of interest.

## Author contributions

Zeng S, Guan C, and Wang H conceived and designed the study. Zeng S, Guan C, and Zheng J developed the search strategy. Li Y and Yao Z screened the literature. Yao Z and Li Y conducted the quality assessment. Zeng S, Yao Z, and Zheng J extracted the data. Zeng S and Wang H performed the data analysis. Zeng S drafted the manuscript, and Wang H and Zheng J revised it. All authors have read and approved the final manuscript.

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## Ethical approval of studies and informed consent

All studies included in this study followed the principles of the Declaration of Helsinki as revised in 2013.

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