

Timing of Renal Replacement Therapy Initiation in Patients with Septic Acute Kidney Injury; A Systematic Review and Meta-Analysis

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Abstract

Background; Acute kidney injury (AKI) is the most frequent complication seen in patients with septic shock and is an independent risk factor for death. Although renal-replacement therapy (RRT) is standard care for patients with severe septic AKI, the optimal timing of RRT initiation remains controversial.

Methods; The PubMed, Cochrane, and Embase databases were searched from their inception to June 2021 to identify the ideal timing of RRT initiation in patients with septic AKI by comparing 28- and 90-day mortality rates.

Results; Among a total of six studies including 1,058 patients, the 28-day mortality rate was significantly lower in the early RRT-treated group compared to the late group [RR=0.69; 95% CI (0.51-0.94); P=0.018]. Moreover, among the five studies including 938 patients, the 90-day mortality rate was also significantly lower in the early RRT-treated group than the late group [RR=0.61; 95% CI (0.47-0.80); P=0.01]. In a subgroup analysis for continuous RRT (CRRT), we also found significantly lower 28- and 90-day mortality rates in the early CRRT-treated group compared to the late group.

Conclusion; This study showed that early initiation of RRT might reduce 28- and 90-day mortality compared with late initiation in septic AKI patients.

Introduction

Acute kidney injury (AKI) is a frequent complication among patients in the intensive care unit (ICU) with septic shock[1–3], because the kidney is one of the first organs to sustain damage with AKI occurring in 51% of septic shock patients. Meanwhile, the mortality due to septic AKI remain substantial, despite the consistent efforts and advanced developments of medical technology[4]. Currently, septic AKI is associated with more severe hemodynamic instability, greater requirement of mechanical ventilation, longer hospital stay and higher hospital mortality compared with non-septic AKI[4, 5].

Renal replacement therapy (RRT) is a well-known treatment for AKI and benefits patients by controlling fluid balance and correcting acid-base and electrolyte imbalance[6–8]. However, the mortality rate among AKI patients with sepsis, still remains extremely high in spite of RRT treatment[4–9].

Recently, several studies have tried to identify the optimal timing of RRT initiation in critically ill patients[10–12], as there is no consensus on when to begin RRT. Moreover, there are even fewer studies on RRT initiation in septic AKI patients[13–18].

Therefore, we conducted a meta-analysis study by collecting the results of recently published trials in order to explore whether the early initiation of RRT decreases the mortality of septic AKI patients.

Materials And Methods

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[19] (Supplemental table 1).

Search strategy

We performed a comprehensive search of PubMed, EMBASE, the Cochrane Central Registry of Controlled Trials, and Web of Science from the inception of each database to June 2021 to identify randomized trials and cohort studies that assessed when RRT was initiated in septic patients with AKI. We restricted our search to clinical studies performed in adult populations and those that were published in the English language. Twelve keywords, which were “acute renal failure,” “acute kidney injury,” “acute kidney failure,” “continuous renal replacement therapy,” “renal replacement therapy,” “dialysis,” “renal dialysis,” “hemofiltration,” “sepsis,” “septic shock,” “time to treatment,” and “time factors” were used in the search. The

bibliographies of the obtained publications and the references of relevant reviews were also checked to ensure that no relevant studies were inadvertently omitted.

Study selection

Two reviewers (HO and NK) independently performed an initial eligibility screen of all retrieved titles and abstracts. Studies that reported original data that specifically mentioned applying RRT in septic patients with AKI were selected for further review. Full-text reviews were independently performed by the same two reviewers with the following eligibility criteria: 1) observational cohort and/or randomized clinical trial (RCT) design; 2) adult septic patients; 3) diagnosis of AKI; 4) description of factors related to the timing of RRT initiation; and 5) description of mortality outcomes. Any discrepancies were resolved in a consensus discussion mediated by a third reviewer (YC). Our study's protocol was registered in PROSPERO. The authors did not seek specific institutional review board or ethics committee approval for this study because the study was conducted with publicly available data obtained from online databases.

Assessment of risk of bias

The quality of the included RCTs was assessed using the Cochrane Collaboration Risk of Bias Tool[20](Supplemental table 2). The quality of the observational studies was evaluated using the Newcastle-Ottawa Scale (NOS)[21] (Supplemental table 3). Studies with NOS scores <7 were considered to have high risks of bias[22, 23].

Data extraction and statistical analysis

The author, publication year, study type, study location, RRT modality, RRT timing and mortality outcomes were extracted from each of the included studies. In addition, we contacted the authors of these studies for missing or incomplete data. The primary outcome was the 28-day mortality of patients in whom RRT was initiated. The 90-day mortality was the secondary outcome. A meta-analysis was performed using the package 'meta' and 'metafor' of the R package, version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria). Pooled estimates of risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using random effects models based on the restricted maximum-likelihood estimator of the between-study variance to take account for heterogeneity among studies. An additional subgroup analysis of CRRT and the impact of its initiation time on 28- and 90-day mortality was performed with the same protocol. Significant statistical heterogeneity was determined by the Q-statistic test ($P < .10$) and I-squared statistics ($I^2 \geq 50\%$). A P value $< .05$ was set as the threshold of statistical significance. Publication bias was assessed using Egger's regression model, and visualized with a contour-enhanced funnel plot. Additionally, the trim and fill method was performed to investigate potential effects due to unpublished studies.

Results

Study selection and quality assessment

We initially collected 5,566 articles from the three medical databases. After removing the duplicate articles, 4,478 remained. HO and NK then screened the titles and abstracts of the articles and deleted 4,439 irrelevant studies. Then, 39 articles underwent full-text assessment. Thirty-three articles were excluded as 12 were review or case studies and 21 were either conference papers, not written in English, or not full-text papers. Therefore, only 6 articles were chosen for the final analysis (Table 1 and Figure 1). Of the 6 articles, one was a RCT[14] and five were retrospective cohort studies[13, 15–18]. The results of our quality assessment are shown in Supplemental Table 1 and Supplemental Table 2. The RCT did not have a high risk of bias for sequence generation, addressing outcome data, selective reporting, or funding source. All of the retrospective studies had total bias scores of at least 7 based on NOS, which indicates a low risk of bias.

Table 1
The basic characteristics of studies included in meta-analysis

Author	Year	Country	Study period	Study design	Modality	No. of patients		Early criteria	Late criteria
						Early	Late		
Chon ¹⁹	2012	Korea	2009-2010	Retrospective cohort	CRRT	36	19	Time from sepsis to inception of CRRT ≤24h	Time from sepsis to inception of CRRT >24h
Shum ¹⁸	2013	China	2008-2011	Retrospective cohort	CRRT	31	89	Simplified RIFLE risk, GFR decrease >25% from baseline	Simplified RIFLE Injury or Failure, GFR decrease >50% from baseline
Oh ¹⁷	2016	Korea	2008-2013	Retrospective cohort	CRRT	30	30	Interval between the start of EGDT and CRRT initiation ≤26.4 h	Interval between the start of EGDT and CRRT initiation >26.4 h
Baek ¹⁶	2017	Korea	2014-2015	Retrospective cohort	CRRT	125	52	The time from the start of vasopressor infusion to the initiation of CRRT ≤24 h	The time from the start of vasopressor infusion to the initiation of CRRT > 24h
Barber ¹⁵	2018	France	2012-2016	Prospective, randomized controlled trial	RRT/CRRT	246	242	Renal-replacement therapy was started within 12 h after the onset of acute kidney injury that was determined to be at the failure stage of RIFLE classification	Renal-replacement therapy was initiated after a delay of 48 h if renal function did not spontaneously recover and if no condition meeting the criteria for emergency renal-replacement therapy developed
Yoon ¹⁴	2020	Korea	2016-2018	Retrospective cohort	CRRT	93	65	the interval time from AKI to CRRT initiation using the cut-of time by the AUROC curve <16.5h	the interval time from AKI to CRRT initiation using the cut-of time by the AUROC curve ≥ 16.5h

Abbreviations; No., number; CRRT, continuous renal replacement therapy; RIFLE, risk, injury, failure, loss and end-stage kidney disease; GFR, glomerular filtration rate; EGDT, early goal directed therapy; AUROC, area under the receiver operating characteristic

Study characteristics

There were 6 studies with a total of 1,058 patients included in our meta-analysis. Five studies were retrospective cohort studies conducted in a single center, and one was a randomized-controlled multi-center study. Four studies were performed in Korea, one in China, and another in France. In addition, we presented the different definitions of early and late RRT initiation used in each study in Table 1. Five studies explored how the timing of RRT initiation impacted 28- and 90-day mortality, whereas one study only investigated the impact of timing on 28-day mortality.

The effect of early RRT on 28-day mortality

Among a total of 6 studies including 1,058 patients, the 28-day mortality rate of patients with septic AKI was 44.5% [222/561 (39.6%) in the early RRT-treated group and 249/497 (50.1%) in the late group]. As a result of pooling risk ratios of 6 studies, the 28-day mortality rate was significantly lower in the early RRT-treated group compared with that in the late group [RR=0.69; 95% CI (0.51-0.94); P=0.018] with wild heterogeneity (Q=23.31, P<0.01) (Figure 2).

The effect of early RRT on 90-day mortality

Next, we compared 90-day mortality rates among 5 studies (with the study of Shum et al. being excluded) with a total of 938 patients, and the 90-day mortality rate was 56.5% [272/530 (51.3%) in the early RRT-treated group and 258/408 (63.2%) in the late group]. Moreover, the 90-day mortality rate was also significantly lower in the early RRT-treated group than in the late group [RR=0.61; 95% CI (0.47-0.80); P=0.01] with wild heterogeneity (Q=27.41, P<0.01) (Figure 3).

The effect of early CRRT on mortality

Among the six studies, only one included patients undergoing intermittent hemodialysis. However, we explored the impact of early CRRT initiation on 28- and 90-day mortality, and compared 28-day mortality between the early and late groups with 5 studies and 90-day mortality with 4 studies (excluding the study of Shum et al.).

The 28-day mortality was 45.3% [111/315 (35.2%) in the early CRRT-treated group and 147/255 (57.6%) in the late group], while the 90-day mortality was 56.9% [129/284 (45.4%) in the early group and 127/166 (76.5%) in the late group]. Moreover, Figure 4 and 5 showed that the 28- and 90-day mortality rates were also significantly lower in the early CRRT-treated group than the late group [for 28-day mortality; RR=0.61; 95% CI (0.47-0.80); P<0.001 with wild heterogeneity (Q=6.97, P=0.14), for 90-day mortality; RR=0.60; 95% CI (0.51-0.70); P<0.001] with wild heterogeneity (Q=0.11, P=0.99).

Publication bias

The results of Egger's tests show no significant bias in all studies (for the 28- and 90-day mortality of RRT-treated patients; P=0.170 and P=0.318, respectively, and for the 28- and 90-day mortality of CRRT-treated patients; P=0.564 and P=0.784, respectively) (Figure supplement 1). For 28-day mortality, the one missing study was estimated by the trim and fill method, and the adjusted pooled estimate was still significant after imputing the hypothetical study [RR=0.61; 95% CI (0.47-0.80); P=0.01]. Moreover, our study indicates that evidence quality was low due to the risk of bias, indirectness, and imprecision.

Discussion

Even though there have been several studies on the benefits of early RRT in critically ill patients, there is still debate on whether those benefits are worth early RRT initiation. Zarbock et al.[24] reported that the 90-day mortality rate of patients who received early RRT was significantly lower than that of patients who initiated RRT later, whereas neither Gaudry et al. [25] nor Bagshaw et al.[26] showed significant differences in mortality rates (28- and 60-day mortality for Gaudry et al. and 90-day mortality for Bagshaw et al.) between early and late RRT initiation. For septic AKI patients, Barbar et al.[14] found no significant difference in 90-day mortality between patients who received early and late RRT. Consistently with the findings of

Barbar et al., Li et al.[27] also found no significant differences in 28- and 90-day mortality rates according to RRT timing in their meta-analysis on septic AKI patients. Apparently, recent RCTs and meta-analysis did not show early RRT initiation as improving survival rates in critically ill patients with AKI including septic AKI.

However, it does not mean that we need to delay RRT as much as possible. Gaudry et al.[25] stated that their study should not be interpreted as suggesting that a “wait and see” approach is safe for all patients. Indeed, careful surveillance is mandatory when deciding to delay RRT in patients with severe AKI so that RRT can be initiated as soon as any complications are detected. Rather, the issue is how to identify a reasonable time point for beginning treatment. Moreover, Barbar et al.[14] demonstrated that the failure stage was not necessarily intended to identify patients who would require RRT, and a delay of only 48 hours may not be sufficiently long enough to allow renal function to recover in some patients or to cause a difference between early and late RRT initiation.

We realized that each study used different definitions to describe early and late RRT[14, 24–26]. Unlikely RCTs, most of the retrospective cohort studies showed that early initiation of RRT decreased mortality compared with delayed initiation[13, 15, 17, 18]. But all the patients included in this study were those who underwent RRT. Hence, the early RRT-treated group might have included several patients who would not need RRT if followed with close observation, and that might explain the better prognosis of the early group. Meanwhile, both Gaudry[25] and Barbar et al.[14] recognized that quite a few patients did not undergo RRT in the late group, with their renal functions spontaneously resolving. Barbar et al.[14] pointed out that 70 patients among the total of 242 patients in the late group (28.9%) did not receive RRT, which means “delay of RRT” in these studies might not be a true “delay” in practical condition, suggesting that could be one of the limitations in the Barbar’s study.

With the earlier initiation of dialysis in AKI, we expect to improve acid-base, electrolyte, and fluid balance, and thereby prevent more aggravating complications of AKI and perhaps also enhance the removal of toxins such as nonspecific pro-inflammatory or anti-inflammatory mediators through convection and adsorption[28]. Moreover, fluid therapy and usage of other drugs may be easily done through the fluid management of RRT[28]. These points suggest that RRT may be initiated without delay, when deemed necessary.

The strength of this meta-analysis was that it was conducted with only septic AKI patients that underwent RRT as well as CRRT, and we searched for all the related papers published until June of 2021. Several limitations still need to be discussed. First, small-sized studies were included. Most of the studies on RRT timing were for critically ill patients, not septic AKI patients. Only a few studies included septic AKI patients. Second, substantial heterogeneity was shown even in the few studies, which suggests that the findings of the current study should be interpreted with caution.

Conclusions

In conclusion, this study found that early initiation of RRT and CRRT might reduce 28- and 90-day mortality compared to late initiation in septic AKI patients. However, continuous studies are required with different criteria to identify the optimal timing of RRT and CRRT in septic AKI patients in the future.

Abbreviations

AKI
Acute kidney injury
RRT
renal-replacement therapy
CRRT
continuous renal-replacement therapy
RCT

randomized clinical trial

CIs

confidence intervals

Declarations

Authors' contributions

HJO, JHK, JYA, SJJ, JYC, JSY, YGS, NSK, and YEC have made substantial contributions to the conception and design of this study. HJO, IKM, RYH, NSK, and YEC have made contributions to the acquisition and interpretation of the data. IKM and RYH have made contributions to the statistical analysis. HJO, NSK, and YEC drafted the article and revised it for important intellectual content. All the authors took part in the manuscript writing and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Ethics approval and consent to participate

This study did not seek specific institutional review board or ethics committee approval because the study was conducted with publicly available data obtained from online database

Consent for publication

We obtained consent to publish from the participants for the reporting of individual patient data.

Competing interests

The authors declare that they have no competing interests.

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Figures

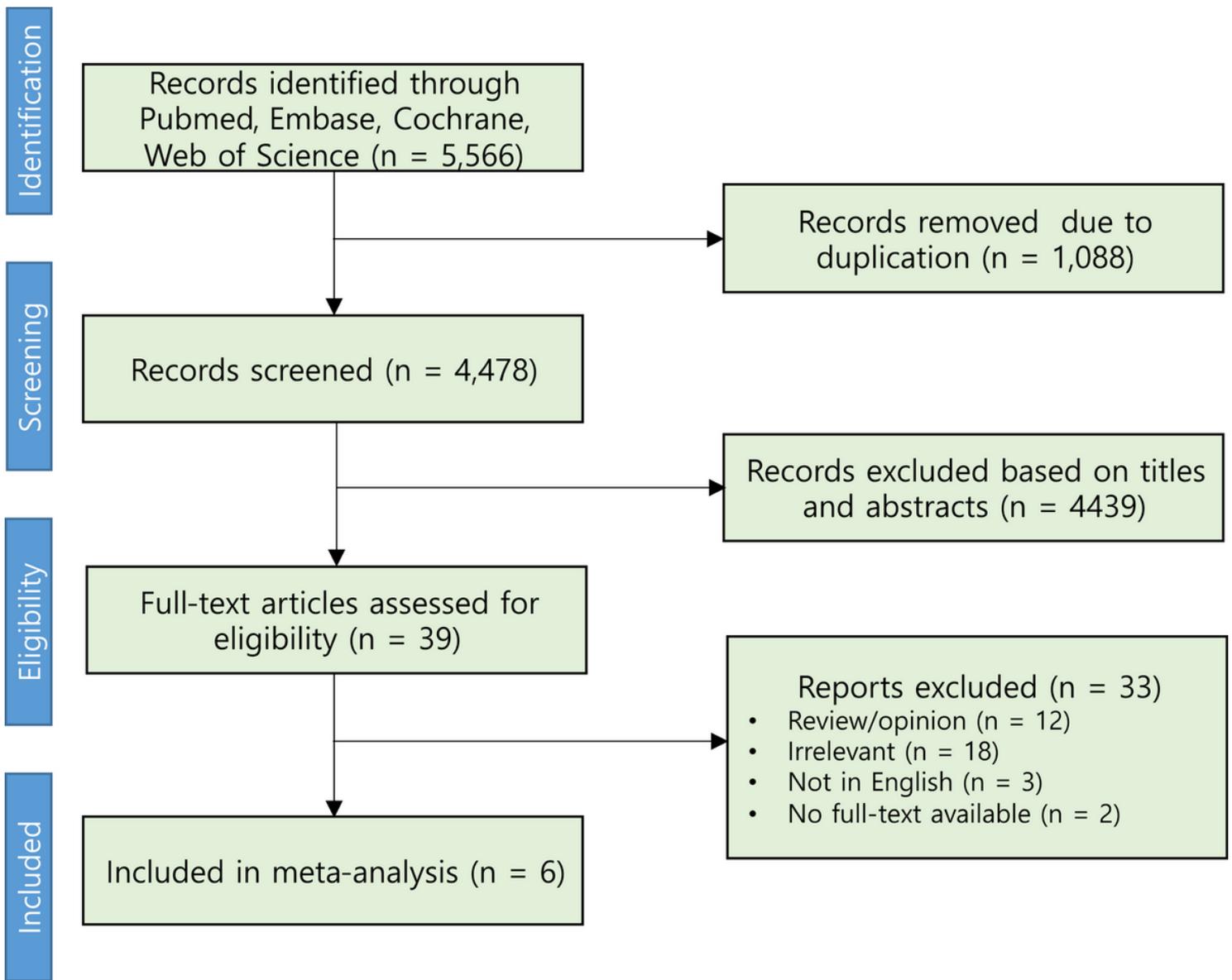


Figure 1

Flow chart of literature selection

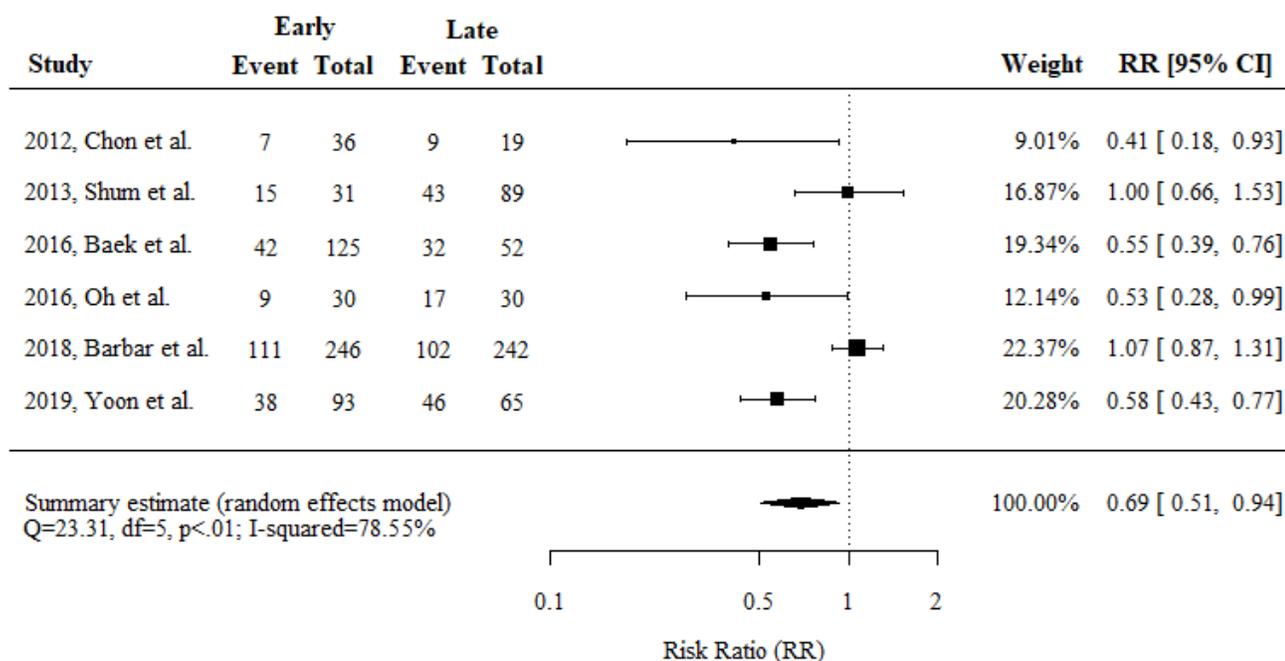


Figure 2

Meta-analysis of risk ratios for 28-day mortality in the RRT group. Higher risk ratios indicate higher 28-day mortality in the early RRT-treated group. RRT, renal replacement therapy; RR, risk ratio; CI confidence interval

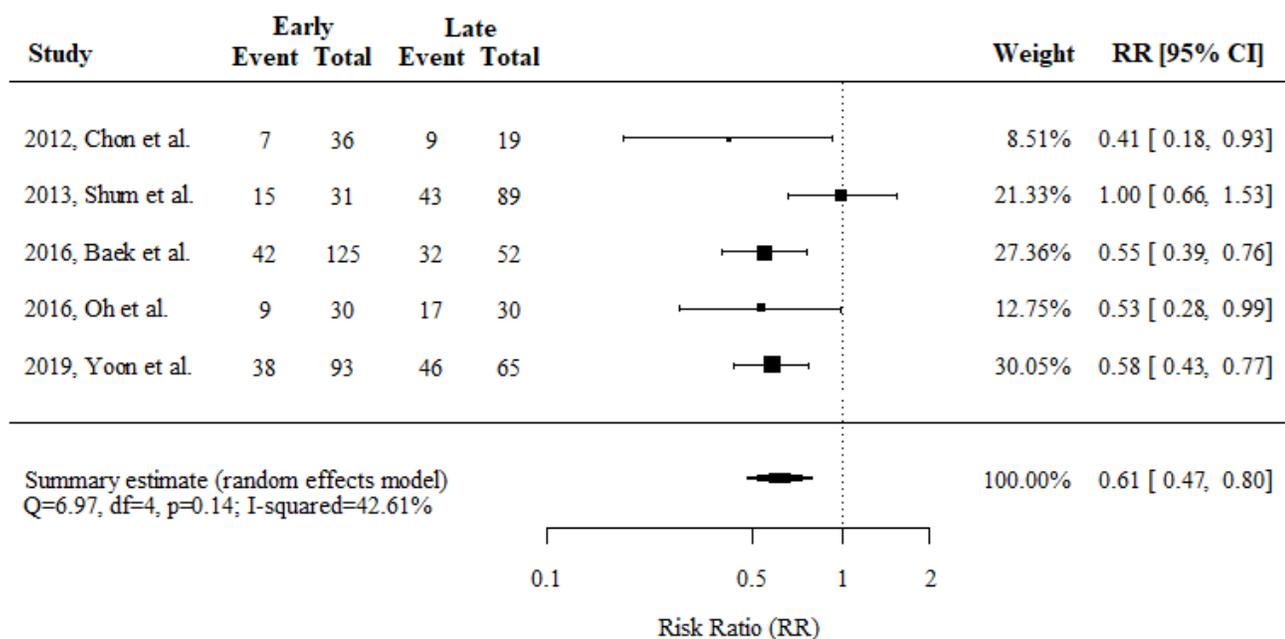


Figure 3

Meta-analysis of risk ratios for 90-day mortality in the RRT group. Higher risk ratios indicate higher 90-day mortality in the early RRT-treated group. RRT, renal replacement therapy; RR, risk ratio; CI confidence interval

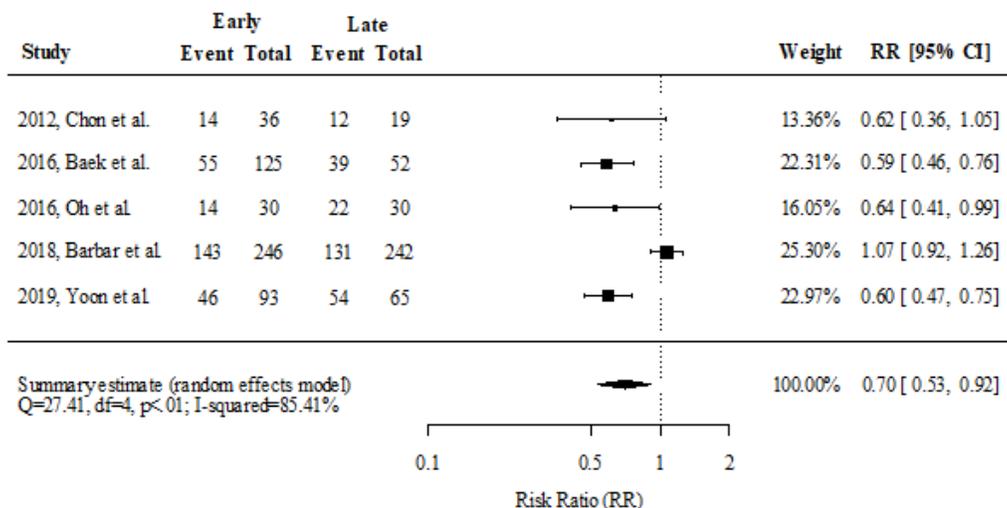


Figure 4

Meta-analysis of risk ratios for 28-day mortality in the CRRT group. Higher risk ratios indicate higher 28-day mortality in the early CRRT-treated group. CRRT, continuous renal replacement therapy; RR, risk ratio; CI confidence interval

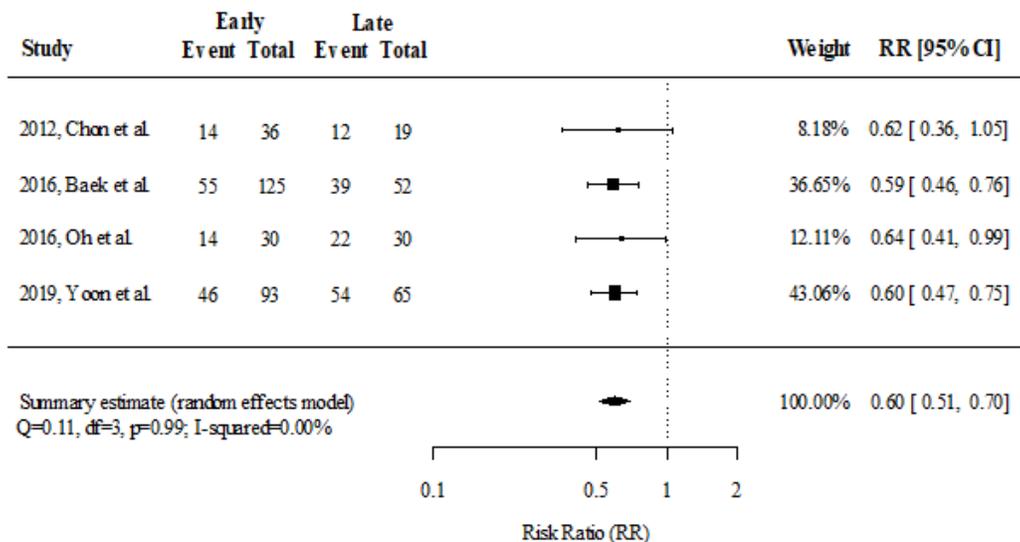


Figure 5

Meta-analysis of risk ratios for 90-day mortality in the CRRT group. Higher risk ratios indicate higher 90-day mortality in the early CRRT-treated group. CRRT, continuous renal replacement therapy; RR, risk ratio; CI confidence interval

Supplementary Files

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