Early versus late initiation of renal replacement therapy impacts mortality in septic patients with acute kidney injury: a meta-analysis

Chenglong Ge
Xiangya Hospital Central South University
Yuan Jiang
Xiangya Hospital Central South University
Qianyi Peng
Xiangya Hospital Central South University
Yuhang Ai (ayhicu1978@csu.edu.cn)
Xiangya Hospital Central South University

Research

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Abstract

Background: Acute kidney injury (AKI) is a frequent complication in septic patients and increases in-hospital mortality. Our aim was to evaluate the impact of early versus late initiation of renal replacement therapy (RRT) on clinical outcomes in septic patients with acute kidney injury (AKI).

Methods: Systematic review and meta-analysis were used in this study. We searched PubMed, EMBASE, MEDLINE and Cochrane Library.

Results: Nine studies (two randomized controlled trials (RCTs) and seven retrospective cohorts) including 1694 patients were identified for detailed evaluation. This meta-analysis suggested that early RRT initiation within 48 hours (OR 0.30; 95% CI 0.20 to 0.45; I 2 0%) in septic patients with AKI reduced 28-day mortality (odds ratio (OR) 0.56; 95% confidence interval (CI) 0.37 to 0.86; I 2 73%), but intensive care unit (ICU) length of stay (LOS) (mean difference (MD) -1.49; 95% CI -3.65 to -0.67; I 2 53%), hospital LOS (MD -3.18; 95% CI -7.35 to 0.99; I 2 41%), the duration of RRT (MD -2.05; 95%CI -6.86 to 2.76; I 2 83%) and the duration of ventilation (MD 1.99; 95%CI -2.76 to 6.75; I 2 85%) were not influenced by the timing of RRT initiation.

Conclusions: Early initiation of RRT within 48 hours in septic patients with AKI may have a beneficial impact on survival. However, this conclusion is based on heterogeneous trials of different quality and only two RCTs. Conclusive therapeutic recommendations regarding the optimal time to initiate RRT remain uncertain.

Background

Sepsis remains extremely fatal and septic shock has a mortality rate as high as 20–60% worldwide [1–6]. Acute kidney injury (AKI) is a frequent complication in septic patients and is closely related to high mortality. Acute kidney injury associated with sepsis has a distinct pathophysiology [7], and septic patients with AKI may have a different response to renal replacement therapy (RRT) than those patients without sepsis [8, 9]. RRT is known to improve the survival rate of patients with AKI in ICU, because it rectifies metabolic acidosis by removing lactate, regulating unmeasured anions and adjusting levels of phosphate and chloride [10, 11]. It is widely consentient that if there are life-threatening complications for septic patients with AKI, such as hyperkalemia, metabolic acidosis and acute pulmonary edema, RRT should be started immediately [5, 12–15].

However, considering the potential complications associated with RRT, the optimal timing of initiating RRT in septic patients with AKI remains controversial. Indirect evidence has indicated that early RRT could raise survival rate [16, 17]. Recently, some randomized controlled trials (RCTs) and cohort studies reported conflicting results [18–21]. Few meta-analyses relevant to this theme has been published in the past few years. Accordingly, we conducted a systematic review and meta-analysis to investigate whether “early” versus “late” initiation of RRT in septic patients with AKI is associated with a survival benefit.

Methods

This meta-analysis was conducted and reported according to PRISMA guidelines [22].

Search Strategy

We performed a comprehensive search of PubMed, EMBASE, MEDLINE, Cochrane Library for articles from 1985 to January 2020. The predefined key search terms included “sepsis” or “septic”, and “early” or “late” or “time”, and “renal replacement therapy” or “hemodialysis”, and “acute kidney injury” or “acute kidney failure” or “acute renal injury”. We also consulted relevant research literature at the same time.

Study Criteria

The inclusion criteria for studies included: (1) original research that related to timing of initiation of RRT in adult patients with septic AKI, (2) articles that provided exact data on mortality in septic AKI and (3) articles that reported a clear comparison of early versus late RRT initiation with a direct effect on mortality. The exclusion criteria included: (1) articles that did not report 28-day mortality, (2) studies such as comments, systemic reviews, case reports, meta-analyses, animal experimental studies etc. and (3) studies of patients who accepted RRT or with pre-existing renal disease before undergoing sepsis.

Data Extraction

Early and late RRT were defined by different criteria in original studies. The nine articles were divided into three groups according to early RRT initiation within 12 hours, within 48 hours, and unclassified. The modality of RRT was continuous renal replacement therapy (CRRT). The primary outcome was the 28-day mortality. The secondary outcomes included ICU length of stay (LOS), hospital LOS, RRT-free days and Ventilator-free days.

Data were extracted independently and the full texts of review were independently screened by two reviewers (CG and YJ) according to study criteria. The details of the selection process are shown in Fig. 1. Discrepancies were resolved between reviewers through discussion and consensus. Data extraction included the first author’s name, year of publication, study design, RRT modality, definition of early and late RRT, number of patients, number of deaths, ICU LOS, hospital LOS, RRT-free days and Ventilator-free days: details are presented in Table 1 and Table 2.

Table 1
The characteristics of studies included in the meta-analysis.

Study	Year	Study design	RRT modality	Definition of early and late RRT		Mortality at 28 days (%)		Total	OR (95%CI)	Quality score
				Early RRT	Late RRT	Early RRT	Late RRT			
Barba [20]	2018	RCT	CRRT	within 12 h after documentation of failure-stage AKI (RIFLE)*	after 48 h if renal recovery had not occurred	111/246(45.1%)	102/242(42.1%)	488	1.13 (0.79,1.61)	H
Gaudry [24]	2016	RCT	CRRT	Within 6 h after documentation of stage 3 AKI (KDIGO) **	oliguria or anuria lasted for more than 72 h	81/174 (46.6%)	78/174 (44.8%)	348	1.07 (0.70,1.63)	H
Xing [25]	2019	Retrospective cohort	CRRT	within 12 h after they met the diagnostic criteria of AKI	after 48 h if renal recovery had not occurred	9/57 (15.8%)	22/84 (26.2%)	141	0.53 (0.22,1.25)	7
Yoon [26]	2019	Retrospective cohort	CRRT	within 16.5 hours after AKI	beyond 16.5 hours after AKI	38/93 (40.7%)	46/65 (70.8%)	158	0.29 (0.15,0.56)	6
Oh [27]	2016	Retrospective cohort	CRRT	the median interval≤26.4 h between the time of EGDT enrollment and the time of CRRT initiation	the median interval>26.4 h between the time of EGDT enrollment and the time of CRRT initiation	9/30 (30%)	17/30 (56.7%)	60	0.33 (0.11,0.95)	7
Baek [28]	2017	Retrospective cohort	CRRT	The time interval from vasopressor to CRRT ≤ 24 h	The time interval from vasopressor to CRRT>24 h	42/125(33.6%)	32/52 (61.5%)	177	0.32 (0.16,0.62)	7
Shum [29]	2012	Retrospective cohort	CRRT	RIFLE Criteria (Risk)*	RIFLE Criteria (Injury or Failure) *	15/31 (48.4%)	43/89 (48.3%)	120	1.0 (0.44,2.27)	8
Chon [30]	2012	Retrospective cohort	CRRT	the time of inception of CRRT from sepsis ≤ 24 h	the time of inception of CRRT from sepsis>24 h	7/36 (19.4%)	9/19 (47.4%)	55	0.27 (0.08,0.91)	8
Carl [31]	2010	Retrospective cohort	CRRT	BUN≤100 mg/dL	BUN ≥ 100 mg/dL	44/85(52.3%)	42/62(68.3)	147	0.51 (0.26,1.01)	7

*RIFLE Criteria Failure: Increase in serum Creatinine by 3 times or urine output < 0.3 ml/kg/h × 24 h.

RIFLE Criteria Risk: Increase in serum Creatinine by 1.5 times or urine output < 0.5 ml/kg/h × 6 h.

RIFLE Criteria Injury: Increase in serum Creatinine by 2 times or urine output < 0.5 ml/kg/h × 12 h.

**KDIGO (Kidney Disease: Improving Global Outcomes) classification. EGDT early goal-directed therapy.

Quality Assessment

The assessment of study quality of RCTs was performed using Review Manager (version 5.3) risk-of-bias tool, including six sections: selection, performance, detection, attrition, reporting bias and other bias (Fig. 2). The Newcastle-Ottawa Scale (NOS) (range 0–9, with 9 indicating the highest quality) was used to evaluate the quality of cohort study (Table1). For cohort studies, stars are awarded after evaluation of the three main categories of selection, comparability and outcomes: a study can be awarded no more than one star for each numbered option within the selection and exposure categories and no more than two stars can be awarded for comparability [23].

Statistical analysis

Data were analyzed by Review Manager (version 5.3) and STATA statistical software (version 15.1). Estimation of effect was performed using a random-effects model and was summarized by forest plot, with data expressed as odds ratio (OR) with 95% CI for dichotomous outcomes and mean difference (MD) with 95% CI for continuous outcomes. A random-effects model was used to deal with data because of the significant heterogeneity between studies on this topic. Heterogeneity was assessed by the Q value and I^2 tests, and low, moderate, and high heterogeneity was represented by thresholds of < 25%, 25–75%, and > 75%, respectively [32]. $P \leq 0.05$ was considered statistically significant. Subgroup and sensitivity analyses were used to explore the potential sources of heterogeneity. Publication bias was assessed using a funnel plot. Meta regression analysis was used to assess the influence of baseline characteristics for possible sources of heterogeneity according to the following pre-defined variables: the year of publication, study design, definitions of early RRT.

Results

Description of included studies

Nine studies [20, 24–31] with a total of 1694 patients ultimately met our criteria (Table 1). These references included two RCTs [20, 24] and seven retrospective cohort studies [25–31]. The characteristics and methodological quality of all trials in the meta-analysis are shown in Table 1 and the outcomes in septic patients with AKI are shown in Table 2.

Table 2
Outcomes of studies included in the meta-analysis

Study	ICU LOS (d)		Hospital LOS (d)		RRT-free days		Ventilator-free days	
	Early	Late	Early	Late	Early	Late	Early	Late
Barba [20]	11(4–19)	10(5–19)	22(9–38)	23(10–44)	12(1–25)	16(2–28)	2(0–19)	3(0–21)
Gaudry [24]	13(9–24)	13(8–25)	28(18–51)	37(21–55)	11(1–25)	16(4–29)	4(0–21)	4(0–19)
Xing [25]	14 (11–20)	16(11–28)	26 (13–42)	28 (15–51)	NR	NR	NR	NR
Yoon [26]	NR	NR	NR	NR	NR	NR	NR	NR
Oh [27]	NR	NR	NR	NR	NR	NR	NR	NR
Baek [28]	13(5–32)	22(8–32)	NR	NR	NR	NR	NR	NR
Shum [29]	6(3–10)	7(3–15)	16(6–38)	16(8–37)	NR	NR	NR	NR
Chon [30]	12(9–27)	17(9–26)	41(21–69)	38(17–114)	14 ± 10	11.6 ± 9.4	7.5(0–20)	0(0–1)
Carl [31]	27.2 ± 39.1	29 ± 45.3	NR	NR	NR	NR	NR	NR

Assessment Of Trial Quality

Of the two included RCTs, one fulfilled all quality indicators [20], whereas the other did not perform the method of blinding for participants or describe the blinding of outcome assessment [24] (Fig. 2). The quality of seven cohort studies [25–31] were evaluated using the Newcastle-Ottawa Scale (NOS) (range 0–9, with 9 indicating the highest quality) (Table 1).

Primary Outcomes

The OR for 28-day mortality is shown in Table 3. Early RRT initiation was associated with reduced 28-day mortality compared to late initiation (pooled OR 0.56; 95%CI 0.37 to 0.86, P = 0.007) (Fig. 3). However, there was significant statistical heterogeneity (I^2=73%).

Subgroup analysis was performed according to type of study (RCTs vs cohort studies; Fig. 4). In cohort studies [25–31] there was a statistically significant decrease in mortality among patients who received early RRT (OR 0.42; 95% CI 0.30 to 0.40; I^2 21%), while mortality in the RCTs [20, 24](OR 1.1; 95% CI 0.84 to 1.45; I^2 0%) was not statistically significant.

Besides, in another subgroup analysis based on different time of starting early RRT included seven studies [20, 24–28, 30] (Fig. 5), while two of the excluded studies were not referred to time cutoffs [29, 31]. The incidence of mortality was significantly decreased by early initiation of RRT within 48 hours (OR 0.30; 95% CI 0.20 to 0.45; I^2 0%) compared to initiation within 12 hours (OR 1.01; 95% CI 0.74 to 1.38; I^2 23%).

Secondary Outcomes

Seven studies [20, 24, 25, 28–31] of the included articles described that the ICU LOS (MD -1.49 days; 95% CI -3.65 to 0.67; I^2 53%) (Table 3) was not significantly decreased in early RRT. Five [20, 24, 25, 29, 30] included articles also showed that hospital LOS (MD -3.18 days; 95% CI -7.35 to 0.99; I^2 41%) was not significantly decreased in early RRT (Table 3). There was also no statistically significant effect on the pooled MD for RRT-free days (MD -2.05 days; 95% CI -6.86 to 2.76; I^2 83%) and Ventilator-free days (MD 1.99 days; 95% CI – 2.76 to 6.75; I^2 85%) (Table 3).

Table 3
Meta-analysis of outcomes of early versus late RRT in patients

Outcomes	Studies	Study reference	patients	OR/MD (95% CI)	I^2	p
Primary outcomes						
Mortality at 28 days	9	[20, 24–31]	1694	OR 0.56 (0.37,0.86)	73%	0.007
Secondary outcomes						
ICU LOS	7	[20, 24, 25, 28–31]	1476	MD -1.49 (-3.65,0.67)	53%	0.18
Hospital LOS	5	[20, 24, 25, 29, 30]	1152	MD -3.18 (-7.35,0.99)	41%	0.13
RRT-free days	3	[20, 24, 30]	977	MD -2.05 (-6.86,2.76)	83%	0.40
Ventilator-free days	3	[20, 24, 30]	977	MD 1.99 (-2.76,6.75)	85%	0.41

Sensitivity Analysis And Publication Bias

Sensitivity analysis indicated that the meta-analysis has low sensitivity and high stability in analysis of septic patients with AKI, which is demonstrated in Fig. 6. Funnel plots were used to assess publication bias (Fig. 7), which provided no evidence of substantial publication bias in this meta-analysis.

Sources Of Heterogeneity And Meta-regression

We performed meta-regression to explore the sources of heterogeneity. The association between early RRT initiation and 28-days mortality was not influenced by year of publication (P = 0.489), study design (P = 0.056) and time of RRT initiation (P = 0.103). Therefore, meta-regression analyses with these variables could not account for the large amounts of heterogeneity observed.

Discussion

This meta-analysis of 9 unique trials compared “early” versus “late” initiation of RRT in septic patients with AKI. It suggests that a strategy of early initiation of RRT is associated with improved survival. There is insufficient evidence to conclude that ICU LOS, hospital LOS, RRT-free days and Ventilator-free days are influenced by the timing of RRT initiation.

However, there were also some passive or controversial studies on the effect of early RRT in patients with AKI, such as some review articles that suggested that it was not necessary to perform early RRT for clinicians [12, 33, 34]. They were opposed to early RRT because it could expose patients to potential risks such as thrombosis, hemorrhage, bacteremia, hypersensitivity to the extracorporeal circuit or antibiotics, clearance of trace elements and intradialytic hypotension, which could lead to added the waste of resources [35, 36]. Previous meta-analysis on this issue was not specifically focused on septic patients. Moreover, we specially excluded older studies (that is, published before 1985) because of the great advances in available technology for providing RRT and the evolution in general of interventions and technology available to support the septic patients with AKI. Accordingly, our meta-analysis is uniquely focused on how the timing of initiation of RRT impacts survival in septic patients with AKI. To explore the sources of the heterogeneity, first, we completed the subgroup analysis based on type of study and time of RRT initiation, respectively, which were statistically significant. Second, we performed sensitivity analysis, which revealed that our meta-analysis had satisfactory stability. Funnel plots indicated no publication bias in this meta-analysis. Third, meta-regression included three variables (year of publication (P = 0.489), study design (P = 0.056) and time of RRT initiation (P = 0.103)) that were not heterogenous. However, because the P value for study design (P = 0.056) was close to 0.05, we speculate that study design may be a source of heterogeneity. As for the high heterogeneity of RRT-free days and Ventilator-free days, not all the trials provided original data for the mean and standard deviation, which probably affected the heterogeneity.

Although these strengths, there are several limitations for this review. First, the number of RCTs is relatively few, so it is necessary to perform more large, multi-centered RCTs to support the present results. Second, the definition of early RRT criteria was various in the included studies, which may have result in the difference in the subsequent therapeutic results in septic patients with AKI. Third, there are some limitations to retrospective studies such as the sample size, and therefore the results may not be representative of the larger public and the risk of recall bias may be higher. Finally, we found significant statistical heterogeneity. We attribute the observed heterogeneity to study design, which we were unable to account for in sensitivity analyses.

The application of RRT in septic patients with AKI is relatively common. What’s more, the incidence is increasing. These patients have a risk of in-hospital mortality approaching 60% [5]. The therapeutic strategy to initiate RRT is a changeable intervention for these patients; however, it also means that the complexity and cost of their support has increased significantly. The current uncertainty about the optimal time to start RRT is a key knowledge gap, which almost certainly leads to wide variation in clinical practice. In addition, the issue is further complicated by the lack of consensus and a standard definition of the "early" RRT. At present, there are a number of clinical, biochemical and physiological factors that need to be considered when deciding to initiate RRT; However, there is still no consistent guidelines or rigid evidence to guide clinicians on this issue. In future randomized trials, a broad consensus on eligibility criteria and operational definitions for ‘early’ or ‘standard’ initiation of RRT in septic patients with AKI would be needed to ensure the feasibility of treatment options. Understanding ways to further optimize acute RRT is critical to improve patient outcomes, guide resource utilization, and provide reasonably standardized care.

Conclusions

In summary, our meta-analysis suggests that early initiation of RRT within 48 hours in septic patients with AKI may have a benefit on survival. However, the available evidence is based on small studies with significant differences in design and quality, and only two RCTs. Due to the lack of new evidence from more high-quality, multiple-center, large sample randomized controlled trials, conclusive therapeutic recommendations regarding the optimal time to initiate RRT remain uncertain.

Abbreviations

AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; OR: Odds ratio; CI: Confidence interval; Cr: Creatinine; h: Hours; ICU: Intensive care unit; EGDT early goal-directed therapy; KDIGO: Kidney Disease: Improving Global Outcomes; LOS: Length of stay; MD: Mean difference; NOS: Newcastle-Ottawa Scale; NR: Not reported; RCTs: Randomized controlled trials; RRT: Renal replacement therapy

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data are available for review on request.

Competing interests

The authors declare that they have no competing interests.

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Authors'contributions

CG performed the literature search, reviewed articles, completed the data analysis using the Review Manager (version 5.3) and STATA statistical software (version 12.0) and wrote the manuscript. YJ and QP reviewed the articles and provided secondary reviews during the manuscript preparation. YA designed the analysis and revised the manuscript. All the authors read and approved the final version of the manuscript.

Competing interests

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Authors' information

[1]Department of Critical Care Medicine, Xiangya Hospital, Central South University, Changsha, 410008, PR China; [2]Department of Critical Care Medicine, Xiangya Hospital, Central South University, Changsha, 410008, PR China; [3]Qianyi Peng. PhD: Department of Critical Care Medicine, Xiangya Hospital, Central South University, Changsha, 410008, PR China; [4]Yuhang Ai. PhD: Department of Critical Care Medicine, Xiangya Hospital, Central South University, Changsha, 410008, PR China.

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Figures

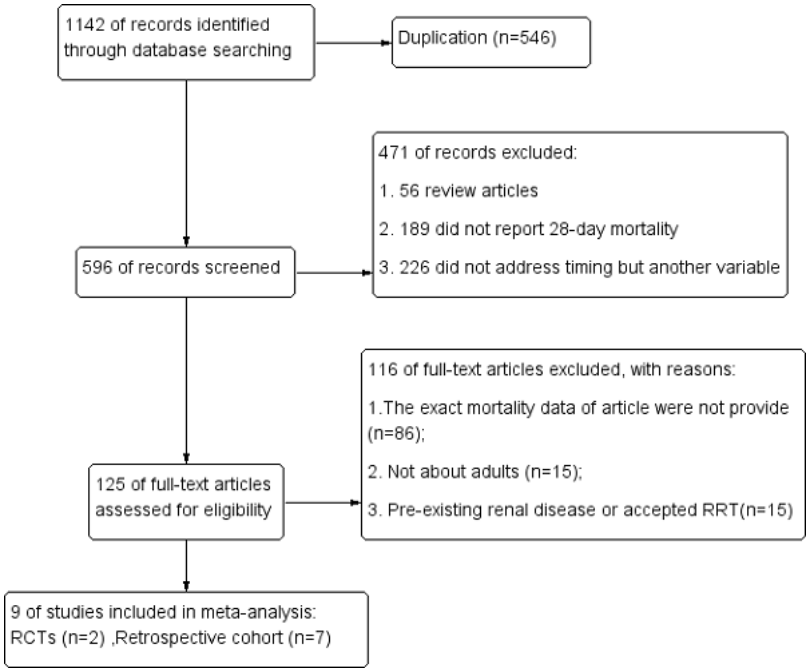

Figure 1

Study flow diagram.

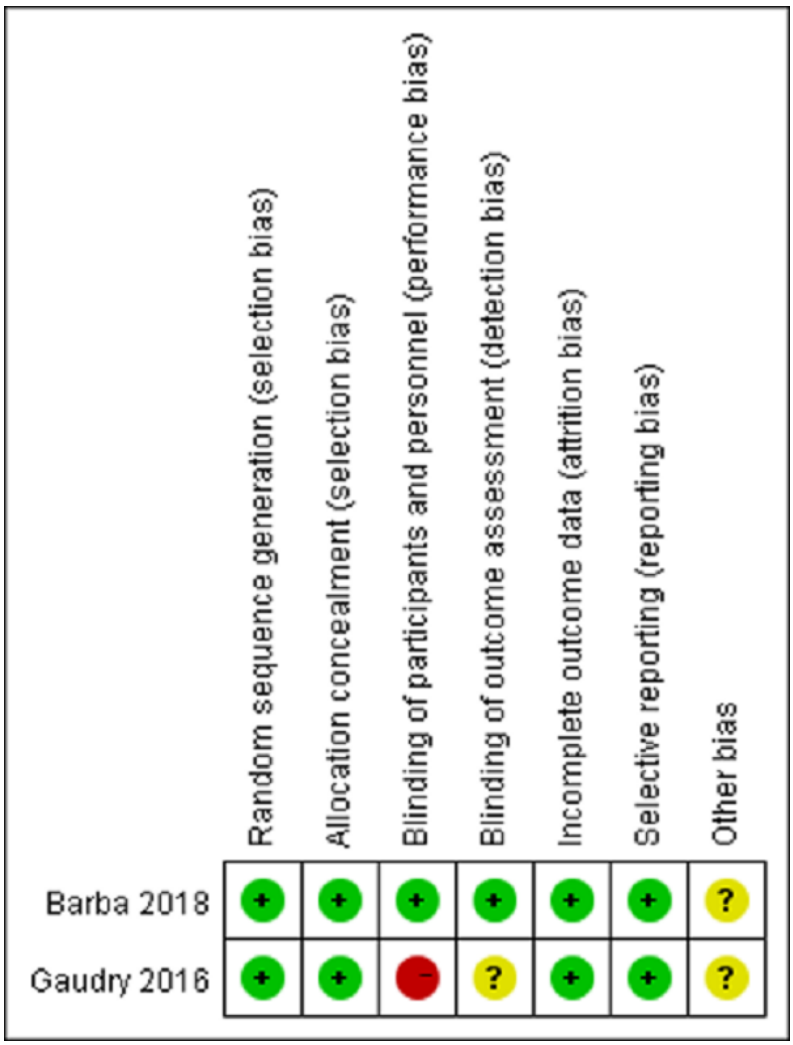

Figure 2

Risk of bias summary

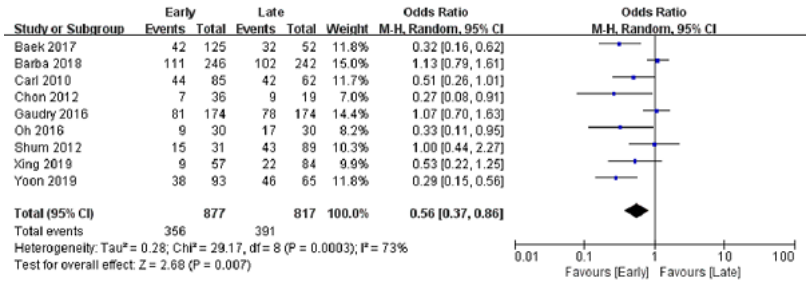

Figure 3

Forest plots of all 9 studies.

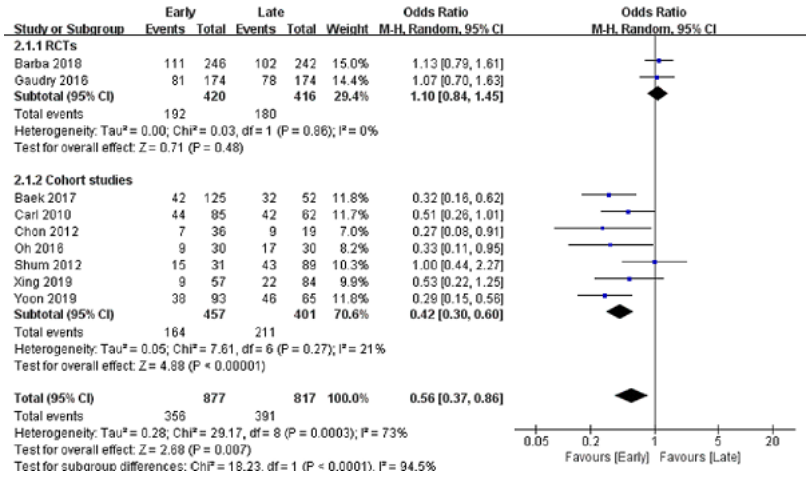

Figure 4

Subgroup analysis: the relationship between study design and mortality.

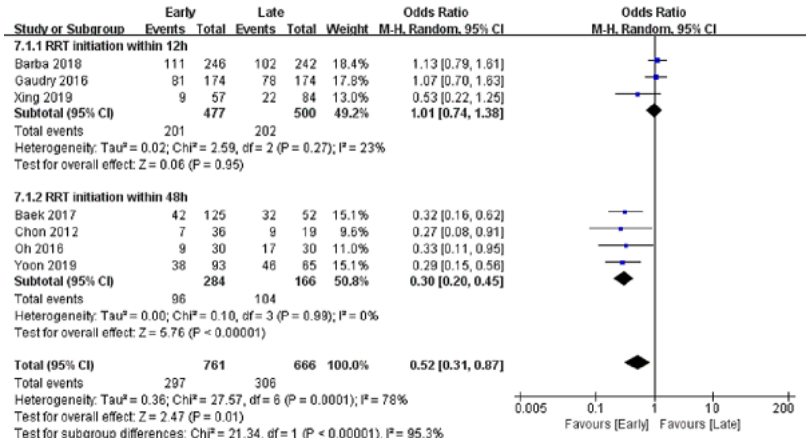

Figure 5

Subgroup analysis: the effect of the time of starting early RRT on mortality.

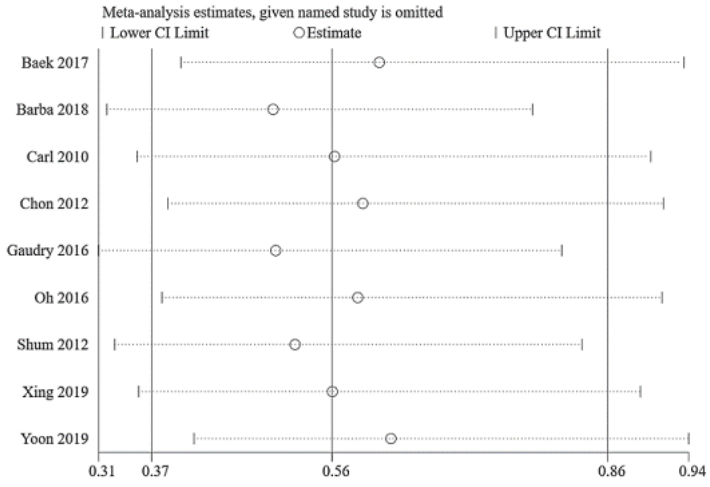

Figure 6

Sensitivity analysis shows the meta-analysis has low sensitivity and satisfactory stability.

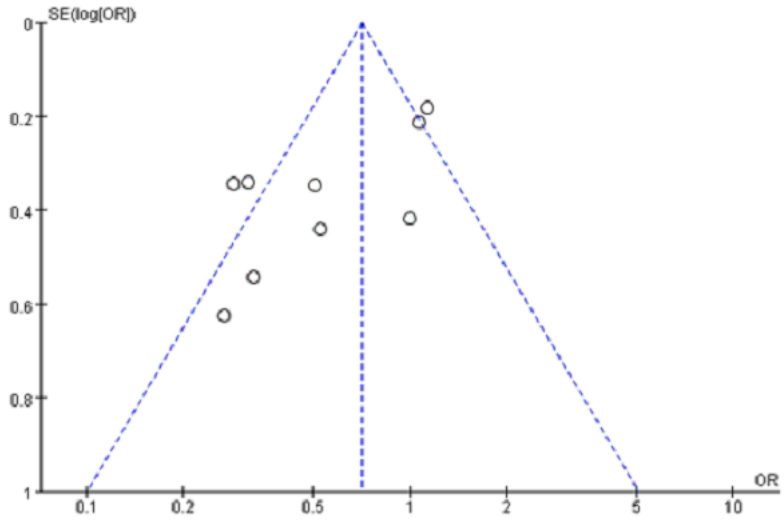

Figure 7

Funnel plot of all 9 studies.