INPLASY PROTOCOL

To cite: Xiao et al. Timing of initiation of renal replacement therapy for acute kidney injury: a meta-analysis with trial sequential analysis of randomized controlled trials. Inplasy protocol 2020120030. doi: 10.37766/inplasy2020.12.0030

Received: 04 December 2020

Published: 05 December 2020

Corresponding author:
Chuan Xiao

xc15973986196@163.com

Author Affiliation:
Guizhou Medical University

Support: **Guizhou science and technology.**

Review Stage at time of this submission: **Data extraction.**

Conflicts of interest:
None.

Timing of initiation of renal replacement therapy for acute kidney injury: a meta-analysis with trial sequential analysis of randomized controlled trials

Xiao, C[1]; Shen, F[2]; Cheng, Y[3]; Xiao, J[4].

Review question / Objective: **The objective of this study is to systematically review current evidence comparing outcomes of early versus late initiation of RRT in critically ill patients aged 18 years or older, with severe acute kidney injury.**
Condition being studied: **Acute kidney injury (AKI) is an important complication in patients admitted to the intensive care unit (ICU) where its prevalence can sometimes exceed 50% and is associated with a high risk of death or major complications and a high level of resource use1, Renal replacement therapy is often applied for patients with severe acute kidney failure who develop metabolic disorders or fluid disturbances. However, when severe acute kidney injury is not accompanied by severe complications, the benefits of renal-replacement therapy remains is highly debated. Undoubtedly, Early renal replacement therapy strategy may optimize fluid balance and hemodynamic, treat electrolyte disturbances, correct acidosis and so on, while renal replacement treatment be delayed may benefit many patients avoid this treatment and recover from acute kidney injury. What exactly would qualify as 'the optimal time' is however unclear and has not yet been tested in previous studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 December 2020 and was last updated on 05 December 2020 (registration number INPLASY2020120030).

INTRODUCTION

Review question / Objective: **XThe objective of this study is to systematically review current evidence comparing outcomes of early versus late initiation of RRT in critically ill patients aged 18 years or older, with severe acute kidney injury.**

Rationale: **Optimum timing of the initiation of dialysis therapy in acute kidney injury is not clear.**

Condition being studied: Acute kidney injury (AKI) is an important complication in patients admitted to the intensive care unit (ICU) where its prevalence can sometimes exceed 50% and is associated with a high risk of death or major complications and a high level of resource use1, Renal replacement therapy is often applied for patients with severe acute kidney failure who develop metabolic disorders or fluid disturbances, However, when severe acute kidney injury is not accompanied by severe complications, the benefits of renal-replacement therapy remains is highly debated. Undoubtedly, Early renal replacement therapy strategy may optimize fluid balance and hemodynamic, treat electrolyte disturbances, correct acidosis and so on, while renal replacement treatment be delayed may benefit many patients avoid this treatment and recover from acute kidney injury . What exactly would qualify as 'the optimal time' is however unclear and has not yet been tested in previous studies.

METHODS

Search strategy: We did an electronic search from January 1, 2010, to Oct 11, 2020, of the following databases: MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials, We also searched ClinicalTrials.gov and the International Clinical Trial Registry Platform for completed and ongoing trials. There were no language restrictions. Three investigators (XC , XJJ CYM) independently screened the titles and abstracts to ascertain whether each study met the eligibility criteria. The full texts of the identified eligible articles were then evaluated to determine whether they should be included in the analysis. Disagreements between the two reviewers resolved by consensus. In case of persistent disagreement, arbitration by a third reviewer (SF) settled the discrepancy.

Participant or population: All Study subjects were critically ill patients (aged 18 years and older), with AKI (KDIGO stage 2 or 3, or at the failure stage of RIFLE.

Intervention: Early RRT initiation strategy.In order to include all relevant trials, we did not use predefined arbitrary thresholds of RRT initiation criteria for the two groups.

Comparator: Delayed RRT initiation strategy.In order to include all relevant trials, we did not use predefined arbitrary thresholds of RRT initiation criteria for the two groups.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: 1) Randomized controlled trials (RCT s) published since Jan 1, 2010.to Oct 11, 2020. 2)All Study subjects were critically ill patients (aged 18 years and older), with AKI (KDIGO stage 2 or 3, or at the failure stage of RIFLE). 3) Excluded duplicate publications or the study lack of data on primary and secondary outcomes: mortality, survival with dependence on RRT, ICU stay, hospital length of stay (HLOS).

Information sources: We did an electronic search from January 1, 2010, to Oct 11, 2020, included the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov , the International Clinical Trial Registry Platform. There were no language restrictions.

Main outcome(s): All-cause mortality at day 28 after randomisation.

Additional outcome(s): Mortality (all-cause up to day 60 , 90, in hospital and in ICU),length of hospital stays, length of ICU stays, 28-day RRT-free , 28-day ventilator-free ,28-day vasoactive agents-free, renal replacement therapy dependence up to day 28, day 60 and day 90. the rate of total adverse events, and hyperkalaemia, hypotension, Arrhythmia, Bleeding.

Data management: We performed meta-analysis when more than one trial was included and outcomes with comparable methods in similar population. We used the statistical software Review Manager 5 provided by Cochrane and the TSA software for the meta-analysis.

Quality assessment / Risk of bias analysis: At least two review authors (XC, CYM or XJJ) independently evaluated the methodological quality of each included trial and assessed the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions included the following risk of bias domains9, 10: random sequence generation, blinding of participants, personnel and outcome assessors, incomplete outcome data, allocation concealment, selective outcome reporting, other potential sources of bias. Based on overall risk of bias, the included trials and each outcome were judged to be of low risk of bias if we judged as low risk of bias in all bias domains. To provide a summary assessment of the risk of bias, we prepared "Risk of bias graph "and "Risk of bias summary figure". Any disagreements concerning assess the risk of bias were negotiated or consulted with a third review author (SF) if necessary.

Strategy of data synthesis: We performed meta-analysis when more than one trial was included and outcomes with comparable methods in similar population. We used the statistical software Review Manager 5 provided by Cochrane and the TSA software for the meta-analysis (Review Manager 5.3; TSA 0.9.5.10 Beta). Assessment of significance set $P<0.05$ as statistical significance. Assessment of heterogeneity: using the I^2 statistic. and using chi-square test with significance set at $P <= 0.10$. As large clinical heterogeneity and statistical heterogeneity were anticipated, we adopted a random-effects model.

Subgroup analysis: Subgroup analyses were conducted to explore eventual heterogeneity based on following characteristics: Study Design, Patient Population, Modality of RRT, Sample size, Creatinine Difference, UO Difference, portion of patients with sepsis.

Sensibility analysis: Removed individual trials at a time, removed the sample size of trail less than 100 patients, removed trials at non-low of bias in each domain.In addition, To evaluate the possible impact of missing data on mortality up to 28, we performed the two following analyses:1. 'best-worst-case' scenario: Assuming that all patients with missing outcomes in the early RRT group was alive; and all those with missing outcomes in the delayed RRT group were dead.2. 'worst-best-case' scenario: assuming that all patients with missing outcomes in the early RRT were dead; and all those with missing outcomes in the delayed RRT group were alive.

Language: There was no language limitations.

Country(ies) involved: China.

Keywords: Acute kidney injury, Renal replacement therapy, Randomized-controlled trials.

Contributions of each author:
Author 1 - Chuan Xiao.
Author 2 - Feng Shen.
Author 3 - Yumei Cheng.
Author 4 - Jingjing Xiao.