BMJ Open

The effect of restrictive fluid resuscitation on severe acute kidney injury in septic shock: A systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086367
Article Type:	Original research
Date Submitted by the Author:	14-Mar-2024
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Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Acute renal failure < NEPHROLOGY, Mortality

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The effect of restrictive fluid resuscitation on severe acute kidney injury in septic shock: A systematic review and meta-analysis

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Abstract

Objectives: Septic shock is a current clinical emergency that has high mortality and multiple complications. A new restrictive fluid resuscitation therapy has been applied, and its influence on patients' renal function remains unclear. The purpose of this study is to evaluate the influence of restrictive fluid resuscitation on incidence of severe acute kidney injury(AKI) in adult patients with septic shock compared with usual care.

Methods: Randomized controlled trials(RCT) were retrieved from PubMed, Embase, Web of Science and Cochrane Library from the database inception until 28 April 2023. Studies which were conducted on adult patients who were diagnosed as septic shock and received restrictive fluid resuscitation as a test group of the research, were elected. Primary outcome was the incidence of severe acute kidney injury, which was defined as the acute kidney injury network (AKIN) score 2 to 3 or Kidney Disease Improving Global Outcomes (KDIGO) stage of 2 and 3. Secondary outcomes were clinical outcomes including overall mortality, ICU LOS, the incidence of worse AKI, and duration of ventilation. Sensitivity and subgroup analyses, plus trial sequential analysis (TSA), were performed.

Results: 5 trials (1943 participants) were included in the meta-analysis. There was a significant difference in the incidence of severe AKI (R 0.89, 95%CI 0.80 to 0.99, P=0.03; I^2=0%) and the duration of mechanical ventilation (Mean Difference -32.06,95%CI -59.04 to -5.07; P=0.02; I^2=75%) between patients receiving restrictive fluid resuscitation and patients receiving liberal fluid resuscitation. TSA showed that the diversity-adjusted required information size(RIS) was 14876.

Conclusions: Fluid restriction strategy is concerned with less incidence of severe acute kidney injury in patients with septic shock, and decrease in their duration of mechanical ventilation as well. More randomized clinical trials need to be conducted to confirm the association between restrictive fluid resuscitation therapy and better prognosis, thus less complications of septic shock.

Trial registration

This study was retrospectively registered at the PROSPERO (International prospective register of systematic reviews) website on 29 July 2023 and the ID was CRD42023449239.

Keywords: Septic shock, Restrictive fluid resuscitation, Acute kidney injury, Mortality

Strengths and limitations of this study

- We performed a comprehensive search and had an explicit standard of studies inclusion.
- The aim of this study was specific and up-to-date and it focused on a topic (severe AKI in septic shock) that few researchers had ventured into.

- Quantities of trials we could include may be insufficient. Due to lack of data and corresponding issue, some latest studies were not able to be included. We didn't include unpublished data or data reported in abstract form, which may lead to publication bias.
- The risk of bias of the extraction of data existed, and may influence the results of the analyses. The heterogeneity issue was also worth concerning.

Introduction

Septic shock is defined as a subset of sepsis in which potential circulatory, cellular, and metabolic damages are serious and profound enough to increase the risk of mortality. [1] It is a common clinical emergency characterized by refractory hypotension, hyperlactatemia and organ dysfunction, which occurs in more than 230,000 US patients each year, leading to over 40000 deaths annually, [2,3] and affecting millions of people around the world each year. [4] AKI is a common complication in critical ill patients with sepsis and/or septic shock. [5,6] When septic shock and AKI are present simultaneously, the mortality rate is up to nearly 50%. [7] And patients with severe AKI have a high risk of stabilizing the situation of chronic

kidney disease (CKD) or progress to complete organ failure and compulsive dialysis requirement. [8,9] This would cause serious health and financial burden on the patients. When it comes to septic shock, intravenous fluid resuscitation is a very common therapy in the initial treatment. It aims to increase depleted or functionally reduced intravenous volume that occurs in sepsis owing to a vasodilated vascular network. Initial fluid therapy can augment macrovascular perfusion and microvascular perfusion and counter organ hypo-perfusion. [1,10] And AKI under the circumstance of vascular changes in septic shock is more related to pre-renal factors instead of post-renal or intra-renal, specifically due to micro-vascular abnormalities sand tubular stress. [3] Therefore correction of intravascular hypovolemia is a key component of the prevention and management of AKI in septic shock as well.

But in the case of increased endothelial cell permeability, excessive infusion can exacerbate organ dysfunction. [11] Excessive fluid administration is believed to be associated with development and progression of AKI, so individualized fluid therapy has been taken into consideration, taking into account patients' characteristics, origin

of patients' kidney dysfunction and risks and benefits of fluids. Therefore, this complex situation attached great importance to the choice of fluid resuscitation. A new strategy called restrictive fluid strategy , which is a resuscitating therapy of lower volumes of fluid and earlier initiation of vasopressor agents, are to be taken into consideration. But there is still insufficient evidence to make a recommendation on the use of restrictive or liberal fluid strategies in patients with septic shock who still have sighs of hypo-perfusion and volume depletion after initial resuscitation. [10] A resent pilot multicenter, randomized, controlled trial of critically ill patients with AKI proved that a restrictive fluid management regimen was feasible. [12] Although whether restrictive fluid therapy has a positive impact on septic patients' kidney function is not supported by strong evidence, it is commonly believed that fluid overload has deleterious impact on renal function balance.

The impact restrictive fluid resuscitation therapy has on the incidence of severe AKI may lay out some priority. When combined with severe kidney dysfunction, the mortality and ICU length of stay of patients with higher AKIN score all rise significantly comparing to patients with lower AKIN score, whether the patients had

sepsis or not. [13] Therefore, in this meta-analysis, we defined severe AKI as acute kidney injury network (AKIN) [14] score 2 to 3 or Kidney Disease Improving Global Outcomes (KDIGO) [15] stage of 2 and 3 [16], which is a much more serious and emergent situation of the kidney function of the patients that needs urgent recognition and treatment.

As intravenous fluid and vasopressor application both have an impact on the patients' organ and tissue perfusion, the renal situation should be taken into consideration. This meta-analysis is conducted in the aim of investigating the effect of the restrictive fluid resuscitation strategy on the occurrence of severe acute kidney injury in adult patients with septic shock.

Materials and methods

This study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement methodology [17], a systematic review and meta-analysis of randomized clinical trials. The study was registered at the PROSPERO (International prospective register of systematic reviews) website and the ID was CRD42023449239.

Search strategy and selection of studies

A literature search of PubMed, Web of science, Embase and Cochrane library was undertaken to identify randomized clinical trials. The searches were last updated on 28 April 2023. The search terms used were “acute kidney injury” or “acute kidney failure” or “acute renal failure” or “continuous renal replacement therapy” or “blood purification therapy” or “mortality”, and “restrictive fluid” or “resuscitation”. The search and reviewing of all the articles were conducted by two reviewers independently. When encountered disagreements, a third reviewer would provide a suggestion.

Title and abstract screening was conducted for all relevant studies and potentially relevant records were thoroughly read. The inclusion criterions were as follows: 1) the research was limited to randomized clinical trials only, 2) studies conducted on adult patients(≥18 years) who were diagnosed as septic shock, 3) trials where the intervention assessed was restrictive fluid resuscitation therapy or conservative fluid strategy versus liberal or conventional fluid resuscitation, 4)studies that contained the data of numbers of patients who countered AKI, or the mortality. Trials with the

following features were excluded: 1) studies enrolling pregnant patients, 2) studies in which most patients had systematic inflammatory response syndrome secondary to other causes such as burn or pancreatitis without a clear sepsis subgroup, 3) studies that focused on patients undergoing elective surgery, or the therapy was carried out during perioperative period [18,19], 4) studies that were narrated in other languages rather than English. No date, publication status, or predefined outcome restriction were applied.

Data extraction and Synthesis

Data including primary outcome were extracted by two reviewers. If there were disagreements, a discussion was performed with another reviewer.

Titles and abstract of all reports identified in the literature searches were screened for further review. The data collected form each study included 1) general information (author, year, study design), 2) characteristics of the participants (including gender, age, inclusion and exclusion criteria, initial places where they stayed before admitted into ICU and randomization, and the diagnosis criterions and diagnosing time point of septic shock), 3) outcomes, with primary outcome

determined as incidence of severe AKI (with clear clarification of numbers of patients of AKIN score 2 and 3, or KDIGO stage 2 and 3) and secondary outcomes as clinical outcomes including overall mortality (when there was more than one indicator concerning with the mortality of all participants at different times, the mortality of the longest period would be prioritized for inclusion in the meta-analysis), ICU LOS, the incidence of worse AKI (defined as higher stages of KDIGO criterion or higher scores of AKIN), and duration of ventilation.

When countering missing data, the author tent to contact authors of the relevant studies. The reference lists of included randomized clinical trials were reviewed for additional trials meeting eligibility criteria.

Dichotomous variables were expressed as counts and proportions. Means and standard deviations (SDs) were used to describe normally distributed continuous variables. Because the ICU length of stay and ventilation time were not normally distributed, all studies involving the data reported the ICU LOS and duration of ventilation by using the median and the first and third quartiles. We estimated the

sample mean and standard deviation (SD) value based on the method of mean variance estimation presented by the Hong Kong Baptist University. [20,21,22,23]

Study quality and risk of bias assessment

The risk of bias was assessed for each outcome in all included studies using the Cochrane Systematic Review Handbook for randomized clinical trials. The 5 studies were assessed as being at low, uncertain or high risk of bias for each of 6 domains. Two reviewers assessed study quality independently. If there were disagreements, a discussion was performed with another reviewer. 6 aspects were performed for assessing the risk of bias, including allocation concealment, random sequence generation, blinding, incomplete outcome data, selective reporting and other bias.

Outcome measures

The primary outcome was the incidence of severe AKI of all participants. Key secondary outcomes were all-cause mortality at the latest time of follow-up, ICU LOS, duration of ventilation and the full amount of patients developing worse AKI comparing to the situation of their first admission into the hospital.

Analysis

Review Manager((RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.) software was used to carry out the meta-analysis using a random effects model for outcomes for which two or more randomized studies were available. The results of outcomes were reported in the form of narrative and graphs. We used Risk Ratio(RR) with 95%CI for dichotomous outcomes (incidence of AKI, incidence of worse AKI, mortality) and Mean Difference(MD) with 95%CI for continuous outcomes (ICU LOS, duration of ventilation) to estimate the pooled effects. In all analyses, $P<0.05$ was considered significant, and statistically significant.

For key outcomes, we assessed the quality of evidence using the Grades of Recommendation, Assessment, Development and Evaluation(GRADE) approach. [24]

The heterogeneity of these 5 studies was measured by the I^2 which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates that no heterogeneity is observed, and larger values of the I^2 means more heterogeneity of the studies. [25]

A sensitivity analysis was performed by removing one study at a time to determine whether a specific trial had a higher contribution to the heterogeneity. Simultaneously we tested the analysis by including high-quality researches only to see if the results changed utterly. Subgroup analysis was carried out to see if the following factors contributed to the result: enrolling patients with an average age ≥ 70 years or <70 years, places where the patients were admitted from(the emergency department (ED) only, or places including ED, hospital wards, the operation room (OR), and other ICU).

A trial sequential analysis (TSA) was performed to estimate the optimal sample size to reach a plausible conclusion on the research. We used Trial Sequential Analysis (TSA) [Computer program]. Version 0.9.5.10 Beta. The Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital – Rigshospitalet, 2021. Statistical significance was set at a P-value of 0.05.

Results

The search was conducted up to 28 April 2023. And the process of the search of literature is summarized and presented in **Figure 1**. A total of 6142 studies were retrieved from 4 databases and screened title and abstract for potential relevant researches. 1621 of records were removed for duplication first. 4441 records were identified as ineligible or irrelevant, leaving 80 records for full-text review. 5 studies met criteria for inclusion and were included in the quality assessment. At the end, all 5 randomized clinical trials were included into this meta-analysis covering 1943 participants. Details of the selection process were shown in **Figure 1**.

Description of included randomized trials

Sample sizes ranged from 30 to 1554. Two studies took place in the United State of America, one in Denmark, one in Australia and New Zealand. And one study took place in worldwide. All trials were conducted on adult patients and no pregnant patients were included. All 5 studies evaluated patients with septic shock. Further characteristics of the 5 chosen RCTs were summed up in **Table 1**. No heterogeneity was observed in these RCTs.

Methodological quality and risk if bias

The overall quality of included RCTs was shown in **Figure 2**. The use of random sequence generation and allocation concealment and the risk of reporting bias were unclear in a number of studies. Confounding by indication and time-dependent exposure might have biased the studies. [26]

Assessment of the risk of bias was summarized in **Figure 2**. Among the 5 RCTs, none of the trials were double blinded. The allocation may be blinded for the statistician. But it was obviously impossible to blind both patients and caregivers in the medical intervention of the trials, we proposed that the outcomes may not be influenced by a lack of blinding. One trial was classified as having an unclear risk of bias in selection reporting.

The incidence of severe AKI

The depiction of AKI differed in 5 RCTs. But they could all come down to the criterion of AKIN score 2 and 3 or KDIGO stage 2 and 3. Some defined patients who met the KDIGO stage of 1-3 as AKI [27], or modified the classification into stage 2 or higher, both with higher stages indicating more severe kidney injury [26]. Some chose to reflect the patients' renal situation by the patients' peak AKIN score [28].

One study reported numbers of worsening AKI, which was defined as worsening of the KDIGO stage (plasma creatinine criteria or use of renal replacement therapy) [29]. The exact number of patients' of KDIGO stage 2 and 3 was not available neither in the article nor the supplement appendix. We extracted the numbers of patients receiving continuous renal-replacement therapy (CRRT) treatment according to the information this article provided in their supplement appendix, which met the diagnostic criteria for KDIGO stage 3 or AKIN score 3. In the study conducted by Corl et al. in 2019 [30], serious AKI was narrated as doubling in the triage creatinine within 72 hours, which could be considered as KDIGO stage 2.

A total of 1907 patients were analyzed for renal function. 348 of the 942 patients analyzed in the restrictive fluid resuscitation group (36.9%) and 401 of the 965 patients analyzed in the liberal fluid resuscitation group (41.6%) were diagnosed severe AKI or evaluated as KDIGO score of 2 and 3 or reached AKIN score 2 and 3 during the follow-up of the studies (RR 0.89, 95% CI 0.80 to 0.99, P=0.03; I^2=0%; P=0.81). Obviously there was a significant difference in the incidence of acute kidney injury between patients receiving a restrictive or conservative fluid

resuscitation strategy and those who received a liberal fluid resuscitation strategy or usual care therapy. The process was shown in the forest plot in **Figure 3**.

Second outcomes

Mortality

Data on all-cause mortality of the participants were available in all 5 RCTs. A total of 1930 patients were tracked down for their clinical ending at most protracted time point, including 90-day mortality in 4 RCTs [25,27,28,26] and 60-day mortality in one study [30]. We found no significant difference in the mortality between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (RR 0.99, 95% CI 0.89 to 1.10; P=0.83; I^2=0%; P=0.88). The result of the I^2 evaluation indicated that there was no heterogeneity observed. Specific data was reported by **Supplement Figure 1** in supplementary appendix.

ICU length of stay

Five RCTs reported the patients' length of stay in ICU, of which 2 were measured in hours [28,30] and 3 were measured in days [26,29,27]. All data was extracted in the form of median and IQR and was transformed into value of mean and SD by the

method proposed by the Hong Kong Baptist University. The result was shown in **Supplement Figure 2**, obviously no heterogeneity was detected in the trial neither (Mean Difference -0.29,95%CI -0.75 to 0.18; P=0.23; I^2=0%).

Incidence of worse AKI

Data on the incidence of worse AKI were available in 2 RCTs. We analyzed the full amount of patients developing worse AKI comparing to the situation of their first admission into the hospital. It was narrated as worse situation of AKI in patients who already suffered from AKI, [28,29] (according to the KDIGO criteria, higher stage means worse kidney function situation), and for patients without AKI at baseline, development of AKI after randomization was regarded as worsening of AKI. The result was shown in **Supplement Figure 3**. No significant difference was found in the incidence of worse AKI between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (RR 0.80, 95% CI 0.45 to 1.44; P=0.46; I^2=33%). Low heterogeneity was detected in the trial.

Duration of ventilation

2 RCTs reported the patients' mechanical ventilation hours [28,30]. All data was extracted in the form of median and IQR and was transformed into value of mean and SD by the method proposed by the Hong Kong Baptist University. The result was shown in **Figure 4**. There was a significant statistical difference in the duration of ventilation of patients between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (Mean Difference -32.06,95%CI -59.04 to -5.07; P=0.02; I^2=75%). High heterogeneity was detected in the trial.

Sensitivity analysis

In the sensitivity analysis, we removed the studies individually to see if any of them had a larger impact on the result. And when trial conducted by Meyhoff et al. [26] or Semler et al. [27] was removed, the result reversed and had no statistical meaning. This indicated that these two trials took a large position in the analysis.

Subgroup analysis

All five RCTs concluded the participants' median age. We calculated the average age and then divided the studies into two divisions according to the criterion(<70 year versus ≥70 years). The role the initial places where the patients were admitted

from played was investigated as well. Most patients were extracted from the emergency department (ED) of the hospital. [28,29] The rest participants were admitted into the ICU from OR, hospital wards or other ICUs, especially in multicenter trials. [26,27,29] Simultaneously we analyzed whether these factors had an impact on the results of the incidence of severe AKI and the mortality of the patients.

Results showed that there was a significant difference in the incidence of severe AKI between patients receiving restrictive fluid resuscitation in the subgroup analyzing the factor of age above 70 (RR 0.88, 95%CI 0.79 to 0.99; P=0.04; I^2=0%) and the multiple initial places where the patients were admitted from (RR 0.88, 95%CI 0.79 to 0.99, P=0.03; I^2=0%) (**Supplement Figure 4&5**). This led to the indication that restrictive fluid resuscitation therapy could make an impact on the kidney function of patients over 70 years old. And when patients were admitted from not only the ED, but also the OR, hospital wards and other ICUs, they were more likely to benefit from restrictive fluid resuscitation strategy.

Simultaneously, these two factors above didn't have a connection with the mortality of the patients. No significant difference was found in the subgroup analysis. And no significant heterogeneity was detected. (**Supplement Figure 6&7**)

Trial Sequential Analysis

We conducted trial sequential analysis (TSA) to calculate the optimal required information size [31,32] (meta-analysis sample size) for our meta-analysis based on a baseline incidence rate of 45% in the control group [33], a relative risk reduction of 10%, 80% of power and a type I error of 5%. TSA showed that the diversity-adjusted RIS was 14876 which was more than that in our study (n=1943). Trial sequential adjusted 95% CI of RR was 0.77 to 1.05 in the fixed effects model, and 0.76 to 1.04 in the random effects model. The results were distinctly shown in **Supplement Figure 8**. The cumulative Z-curve surpassed the conventional boundary for benefit, but it did not touch the trial sequential monitoring boundary for benefit or harm. This indicated that more clinical trials need to be conducted to testify the accuracy of the meta-analysis.

Discussion

Occurrence of AKI remains one of the major causes of mortality in septic shock. This study focused on the influence of the up-to-date restrictive fluid resuscitation therapy on the incidence of severe AKI of patients with septic shock. The treatment strategy connects closely with the prognosis. No previous researches focused on the connection between the fluid therapy and the incidence of severe AKI in septic shock. And in this study we found that the traditional fluid volume may be suitable for most patients, but it still can be improved for certain patients, especially the elderly ones. We provided a new evidence for the need of more individual and specialized fluid resuscitation therapy for patients with septic shock.

The manifestations of renal dysfunction are an important part of sepsis shock. Kidney injuries may contribute to long-term effects such as secondary episodes of sepsis and multiple organ dysfunction syndrome(MODS). [34] It is of vital significance that we determine the optimal fluid resuscitation strategy and the volume of intravenous fluid for critically ill patients. This meta-analysis has proved that adapting restrictive or conservative fluid resuscitation strategy on patients with septic shock has an important connection with less incidence of severe acute kidney injury, indicating

that it is associated with less degeneration of patients' renal function. And subgroup analyses also proved that restrictive fluid resuscitation therapy may have an impact on the recovery of kidney function of patients over 70 years-old especially. When patients were admitted into the ICU from other places such as the OR and hospital wards rather than only ED, adapting restrictive fluid resuscitation strategy on them may be more suitable. It certainly provided more data on this topic.

Previous studies [29,35,36] proposed that it may benefit the patients' renal function, by the strict condition that optimal kinds of fluid and volumes were applied. Our study arrived in the conclusion that lays with this finding. Simultaneously, we found that restriction on fluid volume is associated with decrease in patients' duration of mechanical ventilation. This indicated benefit of the participants' pulmonary function. Less hours of mechanical ventilation on the patients not only induces less complications like ventilator-associated pneumonia (VAP) [37], but also has economic benefits. The general economic assessment was not taken into consideration, which future trials should incorporate.

For the sake of patients' safety and to promote the stabilization of patients' vital signs, caregivers all adapted an initial treatment before randomization and admission into the ICU or emergency department. The treatments aimed to delay the progression of the disease. And all patients included into the RCTs had undergone a similar initial resuscitation treatment. Three trials included in this analysis followed the surviving sepsis campaign bundle which was updated in 2018 [38], and gave their participants an initial fluid volume of 30ml/kg [26,29,30]. The other two didn't mention their initial resuscitation fluid volume. So the amount of resuscitation fluid can be recognized as sufficient. In all 5 RCTs, 4 of which applied norepinephrine, or to say norepinephrine [26,27,28,29], and one was unclear [30]. This may attribute to the very little heterogeneity measured by the I^2 trial.

Fluid resuscitation need to be sufficient, but must be in a controlled fashion and be carried out under dynamic assessment monitoring of patients' volume situation [39]. Volumes of intravenous resuscitation fluids directly ameliorate the tissue and organ perfusion, along with vasopressors, the treatment hold a profound meaning for the safety of organs and the resuscitating process. However, too rapid and aggressive

fluid resuscitation strategy could potentially burden cardiac and renal function, creating an underlying danger to the precarious physical condition of patients with septic shock. It is of vital importance to maintain a sufficient resuscitation fluids treatment and restore the patients' tissue perfusion and circulation volume, but the pace of providing intravenous fluids in the beginning time should not be neglected. Therefore, it holds great necessity to conduct more targeted clinical trials to evaluate a modified and optimal pace to provide intravenous resuscitation fluids for patients with septic shock.

Subgroup analysis also showed that the influence of restrictive fluid resuscitation strategy was especially obvious on patients with an elderly age of over 70. This may be for the reason that the aged have poor cardiopulmonary function and a narrow volume window. In the presence of septic shock, it is likely that vasoplegia plays an important role in the volume responsiveness assessment. And elder patients' vascular wall elasticity decreases, leading to a decrease in their ability to respond to variety in circulating volume. So more RCTs and cohort studies need to be performed in the territory of vasoactive agents in medicine care of patients with septic shock. When

patients are admitted from not only the ED, but also other places such as the OR and hospital wards, they generally possess longer hospital stay period and more complicated symptoms. Restriction on their resuscitation fluids may be beneficial for their renal function.

Through the study, few evidence was found to definite that the fluid restriction strategy has any influence on the patients' mortality and ICU LOS. This may be because the original infection differed among all the participants, leading to a much complicated subject to compare the ending of all patients. And ICU LOS is a multifactorial indicator and is very dependent on the patients' condition. Most participants in the studies relied on life-support instruments, exclusively available in the ICU early stages of treatment.

The sensitivity analysis indicated that the trial conducted by Meyhoff et al. [26] and Semler et al. [27] took a large position in the analysis. When one of these two trials was removed individually, the result reversed and had no statistical meaning. But no distinct change in the heterogeneity was found. This phenomenon has a lot to do with their numbers of participants.

Conclusion

Fluid restriction strategy is concerned with less incidence of severe acute kidney injury in patients with septic shock, and decrease in their duration of mechanical ventilation as well. The restrictive fluid resuscitation therapy works on reducing the incidence of severe AKI of elderly patients with age over 70 years-old especially. More randomized clinical trials need to be conducted to confirm the association between restrictive fluid resuscitation therapy and better prognosis, thus less complications of septic shock.

List of abbreviations

AKI: Acute kidney injury; RCT: randomized controlled trial; ICU: Intensive care unit; TSA: trial sequential analysis; LOS: length of stay; RRT: renal-replacement therapy; RR: relative risk; CI: confidence interval; SD: standard deviation; MD: mean difference; ED: emergency department; OR: operation room; KDIGO: kidney disease improving global outcomes; RIS: required information size; MODS: multiple organ dysfunction syndrome

Declarations

Ethics approval and consent to participate

No ethics approval was mandatory for this is a systematic review and meta-analysis, no data was withdrawn directly from patients. We only calculated and synthesized data in published studies.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

This work is partially supported by grants from the National Natural Science Foundations of China (81501705, 82272211), grants from the Scientific Research Foundation of Graduate School of Southeast University (YBPY1604), grants from the

Jiangsu Provincial Medical Youth Talent (QNRC2016808), Jiangsu Province's Key Provincial Talents Program (ZDRCA2016082).

Authors' contributions

JYX conceived the study. XEC performed the analysis, synthesis and interpretation of data and wrote the first draft of the manuscript. The search and reviewing of all the articles and the assessment of the studies' quality were conducted by two reviewers (XEC and XTC) independently. When encountered disagreements, a third reviewer (WTL) would provide a suggestion. YJZ and MKY contributed to the progress of the trial sequential analysis. JYX was responsible for designing and the coordination of the study, and critical revision of the manuscript for important intellectual content. All authors read and approved the final version. XEC and JYX are the guarantors.

Acknowledgements

We are sincerely grateful to the investigators and clinical trials group of all the trials included in this study for providing access to their trial data.

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Table 1. Characteristics of included studies

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Meyhoff,2022	Denmark & Norway & Sweden & Switzerland & Italy & Czech Republic & United Kingdom & Belgium & Finland	31	1554	1798(500 to 4366) after 90 days	3811(1861 to 6762) after 90 days	death within 90 days after randomization	1.suspected or confirmed infection, a plasma lactate level of 2 mmol per liter (18 mg per deciliter) or higher, receipt of ongoing infusion of a vasopressor or inotropic agent, and receipt of at least 1 liter of intravenous fluids in the 24 hours before screening.13 Patients were included if the onset of shock had been within 12 hours before screening	a new episode of severe acute kidney injury, as defined by a modified Kidney Disease: Improving Global Outcomes (KDIGO) stage of 3 on a scale ranging from 1 to 3, with higher stages indicating more severe kidney injury, and the use of a modified classification because urinary output data might not have been available from all patients
Macdonald,2018	Australia & New Zealand	8	99	2387(1750 to 2750),30(32 to 39)ml/kg from presentation to 6h	3000(2250 to 3900),43(35 to 50)ml/kg from presentation to 6h	total fluid administered within 6hrs of randomization	1.Suspected infection AND 2. Systolic blood pressure (SBP) <100mmHg, despite 1000ml intravenous isotonic crystalloid administered over not more than 60 minutes AND 3.Study intervention can be administered within 2 hours of inclusion criteria being met	the Acute Kidney Injury Network (AKIN) criteria based upon creatinine data. Baseline serum creatinine was defined as a stable serum creatinine recorded in the 12 months pre-randomization, or a convalescent creatinine up to 3 months post-randomization. Where no baseline creatinine was available this was estimated using the MDRD formula assuming GFR 75ml/min/1.73m^2

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Hjortrup,2016	Denmark	9	151	500(0 to 2500) for the first 5 days, 500(0 to 3250) during ICU stay after randomization	2000(1000 to 4100) for the first 5 days, 2200(1000 to 4750) during ICU after randomization	the amount of resuscitation fluid in the first 5 days after randomization and during the entire ICU stay	1.adults in ICU(≥18years) 2.Sepsis defined as at least 2 of 4 SIRS criteria fulfilled within 24 hours according to Society of Critical Care Medicine/American College of Chest Physicians (SCCM/ACCP)2:1)CORE TEMPERATURE >38°C or <36°C. (Core temperature is rectal, urinary bladder, central line, or tympanic). If oral, inguinal or axillary temperatures are used, add 0.5°C to the measured value. Hypothermia <36°C must be confirmed by core temperature. Use the most deranged value recorded in the 24 hours before randomization. 2)HEART RATE >90 beats/minute. If patient has an atrial arrhythmia, record the ventricular rate. If patients have a known medical condition or are receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they must meet two of the remaining three SIRS criteria. Use the most deranged value recorded in the 24 hours before randomization. 3)MECHANICAL VENTILATION for an acute process or respiratory rate > 20 breaths per minute or a $PaCO_2$ < 4.3 kPa (32 mmHg). Use the most deranged respiratory rate or $PaCO_2$ recorded in the 24 hours before randomization. 4)WHITE BLOOD CELL COUNT of >12 x 10^9/l or < 4 x 10^9/l. Use the most deranged value recorded in the 24 hours before randomization. 3.Suspected or confirmed site of infection OR positive blood culture 4.Suspected or confirmed circulatory impairment (hypotension/hypo-perfusion/hypovolemia) for no more than 12 hours including the hours preceding ICU admission. Circulatory impairment defined as at least one of the following: Systolic blood pressure < 90 mmHg, heart rate > 140 beats/min, lactate ≥ 4 mmol/l, OR use of vasopressors. 5.At least 30 ml/kg ideal bodyweight fluid (colloids, crystalloids or	the KDIGO criteria (values of plasma creatinine were assessed in ICU and the use of renal replacement therapy in the 90 days after randomization; the urinary output criteria were not assessed). For patients without AKI at baseline, development of AKI after randomization was regarded as worsening of AKI.

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
							blood products) given in the last 6 hours 6.Shock defined as ongoing infusion of noradrenaline (any dose) to maintain blood pressure	
Corl,2019	America	2	109	(mean ± sd)47.1±22.3ml/kg of total resuscitation IV fluid	(mean ± sd)61.1±32.0ml/kg of total resuscitation IV fluid	30-day all-cause mortality	1. Patients with severe sepsis or septic shock, as defined by the Sepsis 2 International Consensus definitions: Temperature >38°C or <36°C, heart rate of >90/min, respiratory rate of >20/min or PaCO2 <32 mmHg, white blood cell count > 12000/mm3 or <4000/mm3 or >10% immature bands, with known or suspected infection at the time of enrollment. The worst value for each variable is used obtained between triage time zero and enrollment. 2. Since over 12% of patients ultimately diagnosed with sepsis do not meet SIRS criteria, SIRS negative patients may be enrolled if the treating attending physician clinically diagnoses severe sepsis or septic shock. 3. Severe sepsis or septic shock is defined as refractory hypotension or a lactic acid >4 mmol/L. Refractory hypotension is a systolic blood pressure (SBP) <90 mmHg or a mean arterial pressure (MAP) <65 mmHg for 15 minutes, following 1000 mL of IV fluid, or any blood pressure maintained by vasopressor administration	doubling in the triage creatinine from the first recorded value during the study period
Semler,2019	America	1	30	mean of fluid from IV boluses of 300(560) in the 3 days after enrollment	mean of fluid from IV boluses of 733(1083) in the 3 days after enrollment	mean daily fluid balance(phase II) and ICU-free days(phase II)	adults (age >18 years) admitted to the medical ICU at Vander- bilt University Medical Center who met 2 or more criteria for systemic inflammatory response syndrome, were receiving antimicrobial therapy, and met criteria either for shock (defined as a mean arterial pressure <60 mmHg or vasopressor receipt) or respiratory insufficiency (defined as receipt of invasive or noninvasive mechanical ventilation or an arterial oxygen saturation <97% while receiving a fraction of inspired oxygen [FiO2] ≥30%)	the KDIGO criteria

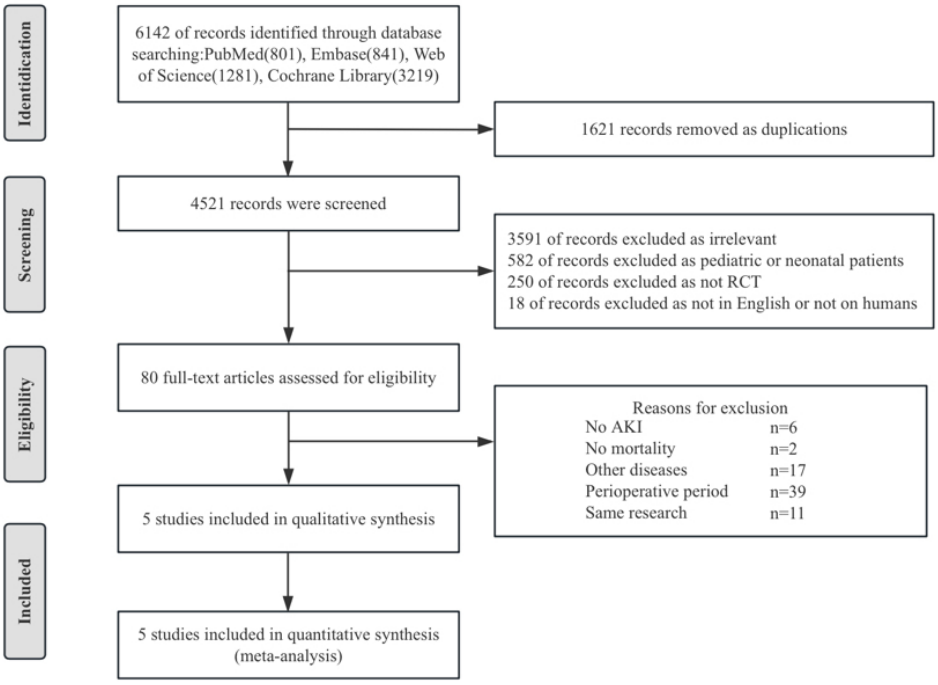


Figure 1. The process of literature search.

146x109mm (150 x 150 DPI)

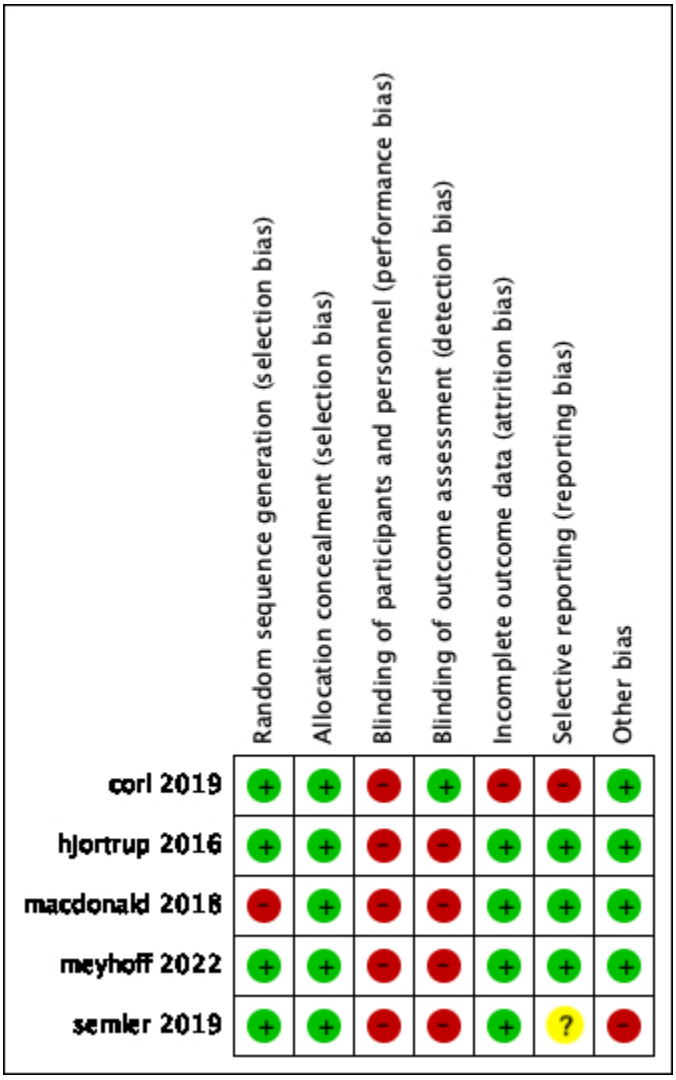


Figure 2. Risk of bias summary for each included study. Red(-)indicates high risk of bias; yellow(?) indicates unclear risk of bias; green(+) indicates low risk of bias.

118x188mm (72 x 72 DPI)

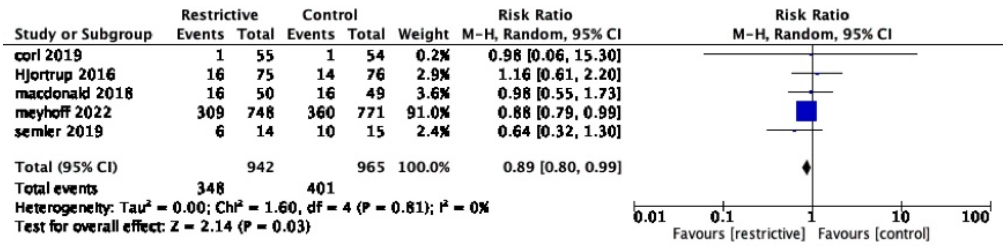


Figure 3. Forest plot for primary outcome of the incidence of severe AKI. It illustrates the result of restrictive or conservative fluid resuscitation strategy versus liberal fluid resuscitation or usual care strategy.

146x36mm (150 x 150 DPI)

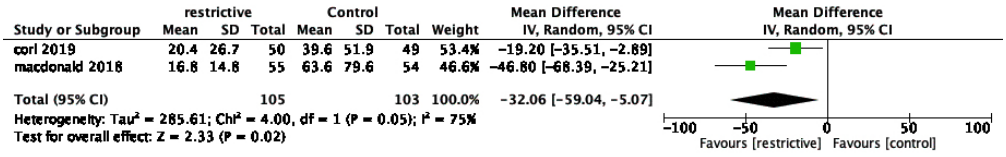


Figure 4. Forest plot for second outcome of the duration of ventilation. It shows the result of restrictive fluid resuscitation strategy versus liberal fluid resuscitation strategy on the duration of ventilation of patients with septic shock.

323x50mm (72 x 72 DPI)

Supplementary appendix

This supplementary appendix provides:

1. Search equation via PubMed, Embase, Web of Science, and Cochrane Library

2. PRISMA checklist

3. Other supplementary Figures

4. Summary of contextual factor data

5. List of citation of excluded potential studies and the reasons to rule out them

6. The GRADE results

7. specific resuscitation therapy of restrictive or conservative resuscitation strategy

8. specific resuscitation therapy of liberal resuscitation strategy or usual care

1. Search equation via PubMed, EMBASE, Medline, and Cochrane Library

Search strategies for the different databases ran on **April 28,2023**

PubMed (801)

Search: ("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal replacement therapy" OR "blood purification therapy" OR "mortality") AND ("restrictive fluid" OR "resuscitation")

Filters: Randomized Controlled Trial, Humans

Embase (841)

("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal replacement therapy" OR "blood purification therapy" OR "mortality") AND ("restrictive" AND "fluid" AND "resuscitation")

Web of Science (1281)

(TS=("restrictive fluid") OR TS=("resuscitation")) AND TS=(("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal

replacement therapy" OR "blood purification therapy" OR "mortality"))

Filters: English +Clinical Trial +Humans

Cochrane Library (3219)

restrictive fluid OR resuscitation in All Text AND acute kidney injury OR acute kidney failure OR acute renal failure OR continuous renal replacement therapy OR blood purification therapy OR mortality in All Text - in Trials (Word variations have been searched)

The total amount of the studies are 6142, in which the duplication number is 1621, leading 4521 records to be screened.

2. PRISMA checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Yes, as supplementary appendix subheading 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg. 9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg.8, supplementary appendix subheading 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary appendix subheading 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg.8, Supplementary appendix subheading 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg.9-10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg.11-12
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg.12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Table 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg.12-14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg.12-14
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg.13
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Supplementary appendix 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg.13
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure1, Pg.14-15
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary appendix 5
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pg.15-16, Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pg.16-19, Figure 3-4, Supplement Figure 1-7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg.13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg.16-19, Figure 3-4, Supplement Figure 1-7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg.20-21, Supplement Figure 1-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg.20
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplementary appendix 6
DISCUSSION			

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg.22-29
	23b	Discuss any limitations of the evidence included in the review.	Pg.28
	23c	Discuss any limitations of the review processes used.	Pg.28
	23d	Discuss implications of the results for practice, policy, and future research.	Pg.29-32
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg.4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg.4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg.31
Competing interests	26	Declare any competing interests of review authors.	Pg.32
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA checklist for abstract

PRISMA 2020 for Abstracts Checklist

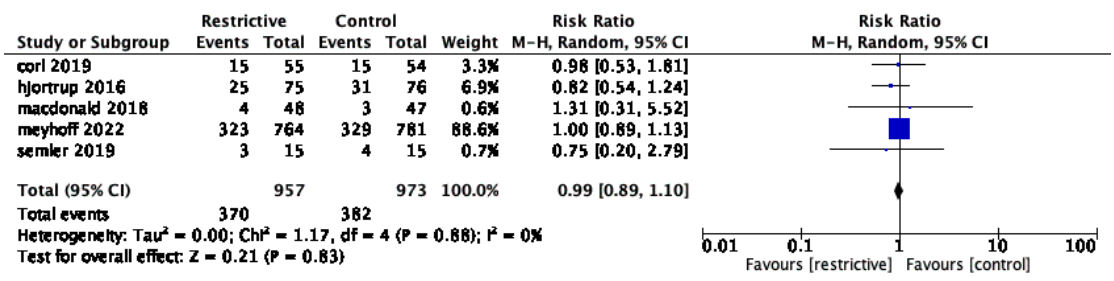
Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

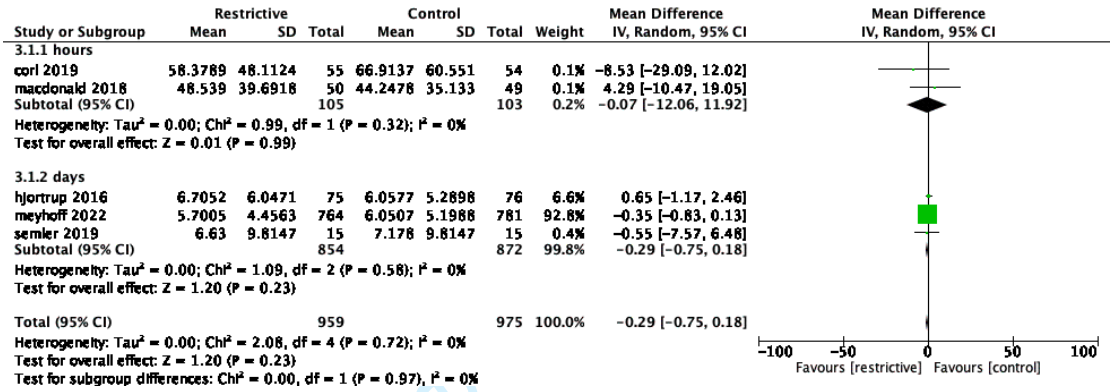
For more information, visit: http://www.prisma-statement.org/

3. Other supplementary Figures

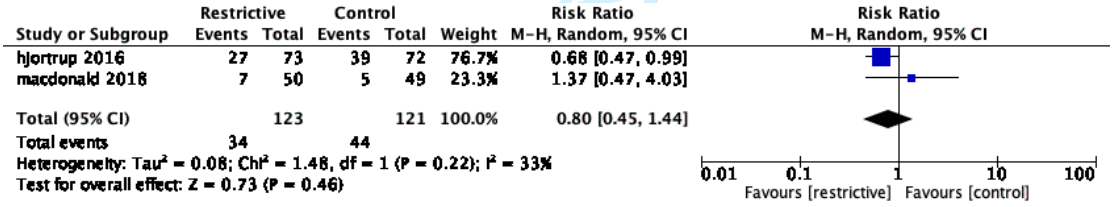
Supplement Figure 1. Forest plot for mortality at most protracted time point available



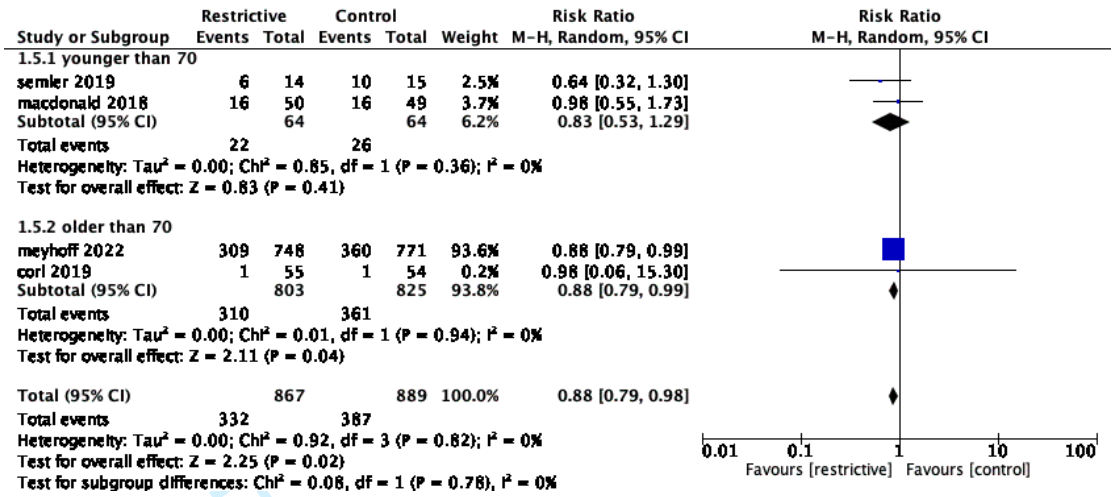
Supplement Figure 2. Forest plot for the ICU length of stay(LOS). The result was compared in two measurements, one in hours and one in days.



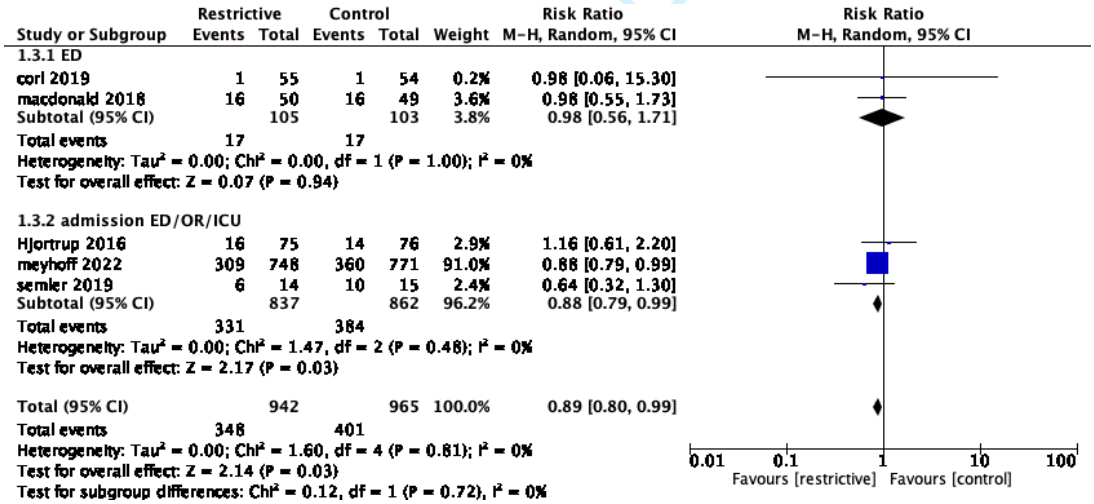
Supplement Figure 3. Forest plot for the incidence of worse AKI.



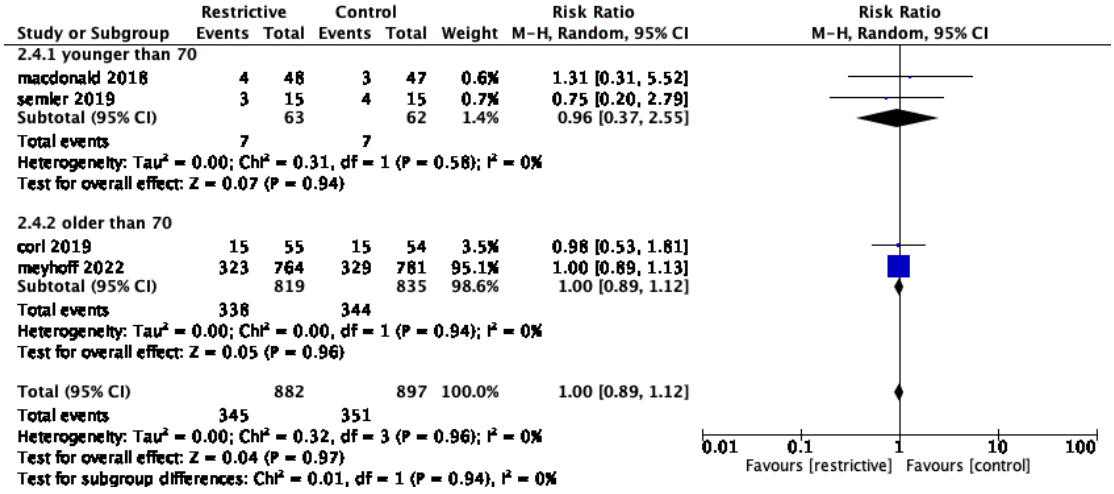
Supplement Figure 4. Forest plot for subgroup analysis on the influence of age on severe AKI. The result was focused on the influence of the factor of age on the incidence of severe AKI in patients in 2 group.



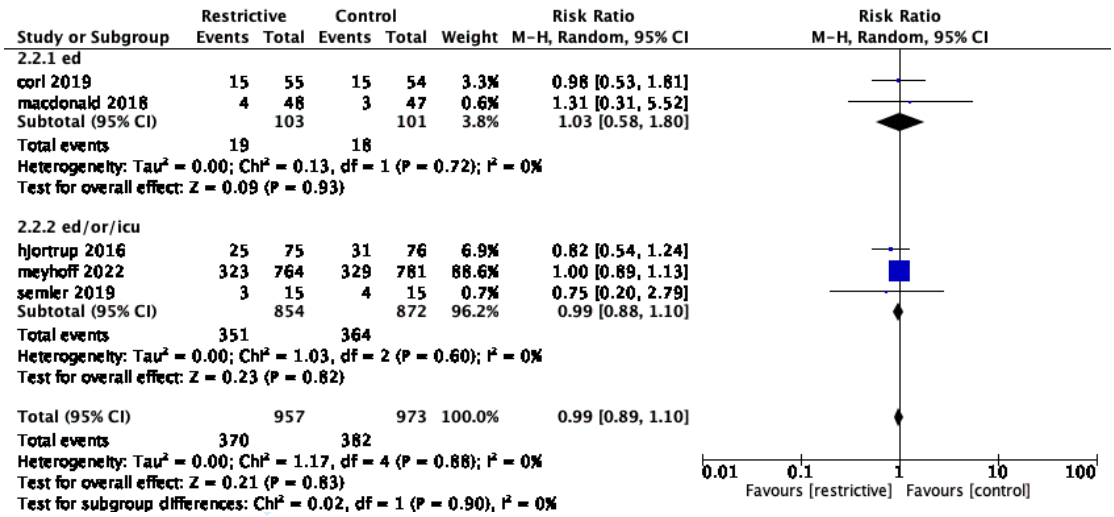
Supplemental Figure 5. Forest plot for the influence of initial places the patients were admitted into on severe AKI. This figure showed the results of the subgroup analysis on the influence of the initial places where the patients stayed before admitted into the ICU before randomization, which was focused on the incidence of severe AKI in patients in 2 group.



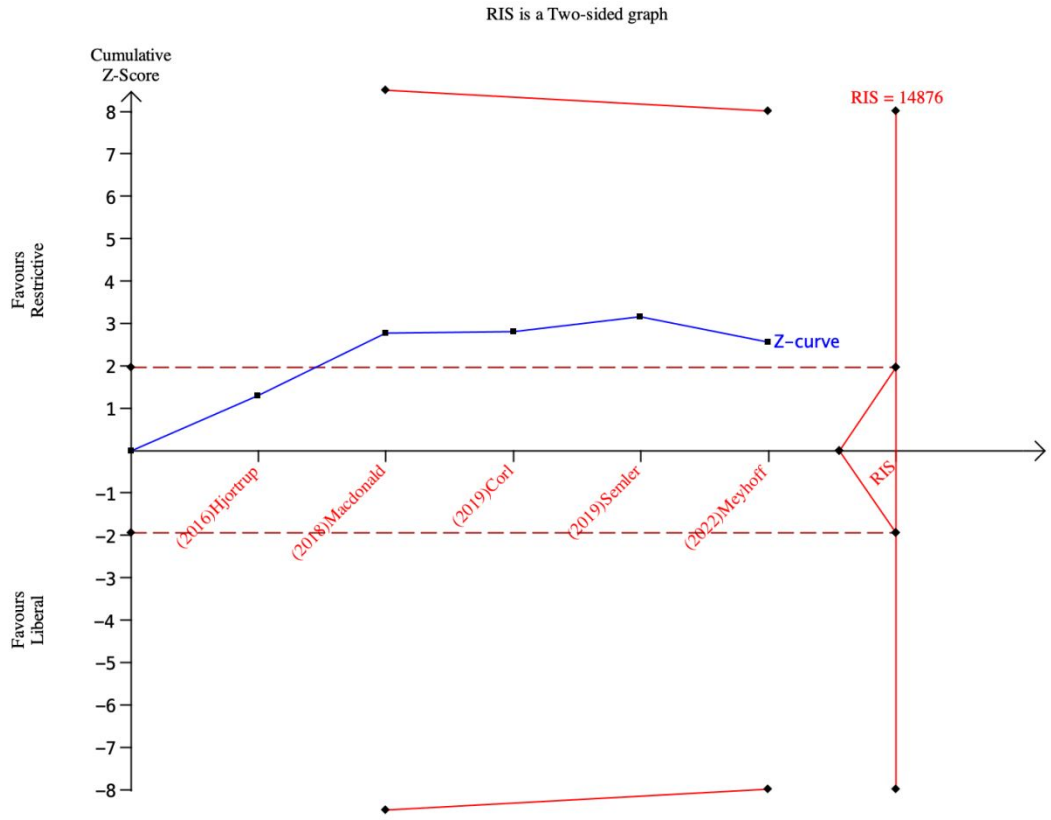
Supplement Figure 6. Forest plot for subgroup analysis on the influence of age on mortality. The result was focused on the influence of the factor of age on mortality of patients.



Supplemental Figure 7. Forest plot for the influence of initial places the patients were admitted into on mortality. This figure showed the results of the subgroup analysis on the influence of the initial places where the patients stayed before admitted into the ICU before randomization, which was focused on the mortality in patients in 2 group



Supplement Figure 8. Trial sequential analysis. TSA showed that the diversity-adjusted required information size(RIS) was 14876. The Z-curve didn't surpass the TSA boundary, indicating the result may conduct a type I error. More clinical trials are encouraged.



4. Summary of contextual factor data

For analysis of the effects of restrictive fluid resuscitation therapy on patients with septic shock, 5 randomized controlled trials were included into this meta-analysis.

The studies contained a total amount of 1943 participants.

Meyhoff et al (2022) enrolled 1554 patients. During the 90-day trial in the ICU, excluding fluids administered with medication and nutrition, the restrictive-fluid group received a median of 1798 ml of intravenous fluid (interquartile range, 500 to 4366); the standard-fluid group received a median of 3811 ml (interquartile range, 1861 to 6762). Sever acute kidney injury was defined as stage 3 on a modified Kidney Disease: Improving Global Outcomes (KDIGO). The incidence of severe AKI was 173 out of 750 (23.1%) in restrictive-fluid group and 189 out of 772 (24.5%).

Macdonald et al (2018) enrolled 99 patients. Median volumes administered from ED arrival to 6 h post randomization were 2387 ml (30 ml/kg) in the restricted volume arm, and 3000 ml (43 ml/kg) in the usual care arm ($p<0.001$). At 24 h respective median cumulative volumes were 3543 ml (40 ml/kg) and 4250 ml (61 ml/ kg), $p=0.005$. The new incidence of AKI was defined as worse AKI according to the changes in patients' peak acute kidney injury network (AKIN) score to day 7. The number was 7 out of 50 (14%) in restricted volume group and 5 out of 49 (10%) in usual care group.

Hjortrup et al (2016) enrolled 151 patients. During ICU stay after randomization, excluding fluids administered with medication and nutrition, the fluid restriction group received a median of 500 ml of intravenous fluid (interquartile range, 0 to 3250); the standard-fluid group received a median of 2200 ml (interquartile range,

1000 to 4750), p<0.001. Worsening acute kidney injury (AKI) was defined as worsening of the KDIGO stage (plasma creatinine criteria or use of renal replacement therapy). The number of worsening of AKI in patients was 27 out of 73 (37%) in fluid restriction group and 39 out of 72 (54%) in standard care group, p=0.03.

Corl et al (2019) enrolled 109 patients. During the first 72 hours of care, the restrictive group received significantly less resuscitative IV fluid than the usual care group (47.1 vs 61.1mL/kg; p = 0.01). Acute kidney injury defined as a doubling in the triage creatinine. The number of AKI was 1 out of 55 (1.8%) in restrictive fluid group and 1 out of 54 (1.9%) in standard care group, p>0.99.

Semler et al (2019) enrolled 30 patients. Over the course of the trial, patients in the usual care group received a mean volume of fluid from IV boluses of 733 (1083) compared with 300 (560) in the conservative fluid management group (P=0.30). Severe acute kidney injury defined as was defined as stage 3 on a modified Kidney Disease: Improving Global Outcomes (KDIGO). The number of AKI was 3 out of 14 (21.4%) in conservative group and 6 out of 15 (40.0%) in usual care group.

5. List of citation of excluded potential studies and the reasons to rule out them

5.1No AKI

1)No data on the numbers of AKI patients was found in the following article. Communication with the corresponding author didn't provide enough information in time.

[1] National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network; Shapiro NI, Douglas IS, Brower RG, Brown SM, Exline MC, Ginde AA, Gong MN, Grissom CK, Hayden D, Hough CL, Huang W, Iwashyna TJ, Jones AE, Khan A, Lai P, Liu KD, Miller CD, Oldmixon K, Park PK, Rice TW, Ringwood N, Semler MW, Steingrub JS, Talmor D, Thompson BT, Yealy DM, Self WH. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension. N Engl J Med. 2023 Feb 9;388(6):499-510. doi: 10.1056/NEJMoa2212663. Epub 2023 Jan 21. PMID: 36688507.

2) The following were titles and accession numbers of the trial protocol we found in the literature search. The titles and abstracts convinced us the trials were focused on the topic concerning our study, but neither full-text nor information about AKI could be retrieved. The protocol containing their outcomes didn't included indicators about AKI neither.

[2] ACTRN12616000006448. Restricted Fluid Resuscitation in Sepsis-associated Hypotension (REFRESH) Trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12616000006448 2016; null(null): null.

[3] ChiCTR-INR-17011928. Controlled Fluid Resuscitation Strategy in Sepsis

Patient. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-INR-17011928 2017; null(null): null.

[4] NCT03137446. Restrictive Intravenous Fluids Trial in Sepsis. https://clinicaltrials.gov/show/NCT03137446 2017; null(null): null.

3) No data on AKI was found in these articles' full text.

[5] Douglas IS, Alapat PM, Corl KA, Exline MC, Forni LG, Holder AL, Kaufman DA, Khan A, Levy MM, Martin GS, et al. Fluid response evaluation in sepsis hypotension and shock: a randomized clinical trial. Chest. 2020;158(4):1431–45.

[6] Corl K, Prodroumo M, Marks S, Delcompare C, Palmasciano A, Merchant R, Levy M. The restrictive intravenous fluid trail in severe sepsis and septic shock (RIFTS): a pilot study. Intensive care medicine experimental, 2018, 6(Supplement 2) ESICM LIVES 2018. ICMx 6 (Suppl 2), 40 (2018). doi:10.1186/s40635-018-0201-**5.2 No mortality**

No data on mortality of patients was mentioned in the following articles, or in the outcomes planned in the trial protocol.

[7] Aung NM, Kaung M, Kyi TT, Kyaw MP, Min M, Htet ZW, Anstey NM, Kyi MM, Hanson J. The Safety of a Conservative Fluid Replacement Strategy in Adults Hospitalised with Malaria. PLoS One. 2015 Nov 18;10(11):e0143062. doi: 10.1371/journal.pone.0143062. PMID: 26581060; PMCID: PMC4651424.

[8] Hjortrup PB, Haase N, Wetterslev J, Lange T, Bundgaard H, Rasmussen BS, Dey

N, Wilkman E, Christensen L, Lodahl D, Bestle M, Perner A. Effects of fluid restriction on measures of circulatory efficacy in adults with septic shock. Acta Anaesthesiol Scand. 2017 Apr;61(4):390-398. doi: 10.1111/aas.12862. Epub 2017 Feb 1. PMID: 28150304.

5.3 Not septic shock

The trial was not conducted on patients with septic shock, only patients with severe sepsis.

[9] Jessen MK, Andersen LW, Thomsen MH, Kristensen P, Hayeri W, Hassel RE, Messerschmidt TG, Sølling CG, Perner A, Petersen JAK, Kirkegaard H. Restrictive fluids versus standard care in adults with sepsis in the emergency department (REFACED): A multicenter, randomized feasibility trial. Acad Emerg Med. 2022 Oct;29(10):1172-1184. doi: 10.1111/acem.14546. Epub 2022 Aug 5. PMID: 35652491; PMCID: PMC9804491.

5.4 Perioperative period

The trials were conducted on patients undergoing elective surgery, and the fluid therapy was performed during the perioperative period.

[10] Healy MA, McCahill LE, Chung M, Berri R, Ito H, Obi SH, Wong SL, Hendren S, Kwon D. Intraoperative Fluid Resuscitation Strategies in Pancreatectomy: Results from 38 Hospitals in Michigan. Ann Surg Oncol. 2016 Sep;23(9):3047-55. doi: 10.1245/s10434-016-5235-y. Epub 2016 Apr 26. PMID: 27116681.

[11] Alimian M, Mohseni M, Moradi Moghadam O, Seyed Siamdoust SA, Moazzami J. Effects of Liberal Versus Restrictive Fluid Therapy on Renal Function Indices in Laparoscopic Bariatric Surgery. Anesth Pain Med. 2020 Oct 20;10(5):e95378. doi: 10.5812/aapm.95378. PMID: 34150556; PMCID: PMC8207848.

[12] Behman R, Hanna S, Coburn N, Law C, Cyr DP, Truong J, Lam-McCulloch J, McHardy P, Sawyer J, Idestrup C, Karanicolas PJ. Impact of fluid resuscitation on major adverse events following pancreaticoduodenectomy. Am J Surg. 2015 Nov;210(5):896-903. doi: 10.1016/j.amjsurg.2015.04.020. Epub 2015 Jul 17. PMID: 26255229.

[13] R. Dahal, R.S. Bhandari, P.J. Lakhey, Restrictive versus Liberal Fluid Therapy in Patients Undergoing Pancreaticoduodenectomy, HPB, Volume 24, Supplement 1, 2022, Page S260, ISSN 1365-182X, https://doi.org/10.1016/j.hpb.2022.05.546. (https://www.sciencedirect.com/science/article/pii/S1365182X22006815)

[14] Diaper J, Schiffer E, Barcelos GK, Luise S, Schorer R, Ellenberger C, Licker M. Goal-directed hemodynamic therapy versus restrictive normovolemic therapy in major open abdominal surgery: A randomized controlled trial. Surgery. 2021 May;169(5):1164-1174. doi: 10.1016/j.surg.2020.09.035. Epub 2020 Nov 2. PMID: 33143931.

[15] Futier E, Constantin JM, Petit A, Chanques G, Kwiatkowski F, Flamein R, Slim K, Sapin V, Jaber S, Bazin JE. Conservative vs restrictive individualized goal-

directed fluid replacement strategy in major abdominal surgery: A prospective randomized trial. Arch Surg. 2010 Dec;145(12):1193-200. doi: 10.1001/archsurg.2010.275. PMID: 21173294.

[16] Grant F, Brennan MF, Allen PJ, DeMatteo RP, Kingham TP, D'Angelica M, Fischer ME, Gonen M, Zhang H, Jarnagin WR. Prospective Randomized Controlled Trial of Liberal Vs Restricted Perioperative Fluid Management in Patients Undergoing Pancreatectomy. Ann Surg. 2016 Oct;264(4):591-8. doi: 10.1097/SLA.0000000000001846. Erratum in: Ann Surg. 2018 Mar;267(3):e61. PMID: 27355261; PMCID: PMC5017901.

[17] Guan Z, Gao Y, Qiao Q, Wang Q, Liu J. Effects of intraoperative goal-directed fluid therapy and restrictive fluid therapy combined with enhanced recovery after surgery protocol on complications after thoracoscopic lobectomy in high-risk patients: study protocol for a prospective randomized controlled trial. Trials. 2021 Jan 7;22(1):36. doi: 10.1186/s13063-020-04983-y. PMID: 33413593; PMCID: PMC7792083.

[18] Hendrix RJ, Damle A, Williams C, Harris A, Spanakis S, Lambert DH, Lambert LA. Restrictive Intraoperative Fluid Therapy is Associated with Decreased Morbidity and Length of Stay Following Hyperthermic Intraperitoneal Chemoperfusion. Ann Surg Oncol. 2019 Feb;26(2):490-496. doi: 10.1245/s10434-018-07092-y. Epub 2018 Dec 4. PMID: 30515670.

[19] Sahmeddini MA, Janatmakan F, Khosravi MB, Ghaffaripour S, Eghbal MH,

Nickeghbalian S, Malek-Hosseini SA. Restricted Crystalloid Fluid Therapy during Orthotopic Liver Transplant Surgery and its Effect on Respiratory and Renal Insufficiency in the Early Post-operative Period: A Randomized Clinical Trial. Int J Organ Transplant Med. 2014;5(3):113-9. PMID: 25184031; PMCID: PMC4149738.

[20] ISRCTN52446152 . Fluid restriction following open aortic aneurysm surgery. https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN52446152 2010; null(null): null.

[21] Jie HY, Ye JL, Zhou HH, Li YX. Perioperative restricted fluid therapy preserves immunological function in patients with colorectal cancer. World J Gastroenterol. 2014 Nov 14;20(42):15852-9. doi: 10.3748/wjg.v20.i42.15852. PMID: 25400472; PMCID: PMC4229553.

[22] Li M, Peng M. Prospective comparison of the effects of intraoperative goal-directed fluid therapy and restrictive fluid therapy on complications in thoracoscopic lobectomy. J Int Med Res. 2021 Dec;49(12):3000605211062787. doi: 10.1177/03000605211062787. PMID: 34918965; PMCID: PMC8728787.

[23] Luo J, Xue J, Liu J, Liu B, Liu L, Chen G. Goal-directed fluid restriction during brain surgery: a prospective randomized controlled trial. Ann Intensive Care. 2017 Dec;7(1):16. doi: 10.1186/s13613-017-0239-8. Epub 2017 Feb 16. PMID: 28211020; PMCID: PMC5313491.

[24] Mahmooth Z, Jajja MR, Maxwell D, Ferez-Pinzon A, Sarmiento JM. Ultrarestrictive intraoperative intravenous fluids during pancreatoduodenectomy is

not associated with an increase in post-operative acute kidney injury. Am J Surg. 2020 Aug;220(2):264-269. doi: 10.1016/j.amjsurg.2020.03.021. Epub 2020 Mar 23. PMID: 32234242.

[25] Mintz Y, Weiss YG, Rivkind AI. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2004 Aug;240(2):386; author reply 386-8. doi: 10.1097/01.sla.0000134633.10987.87. PMID: 15273568; PMCID: PMC1356423.

[26] Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, Christophi C, Leslie K, McGuinness S, Parke R, Serpell J, Chan MTV, Painter T, McCluskey S, Minto G, Wallace S; Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. N Engl J Med. 2018 Jun 14;378(24):2263-2274. doi: 10.1056/NEJMoa1801601. Epub 2018 May 9. PMID: 29742967.

[27] NCT00854386. Effect of Intraoperative Fluid Restriction on Postoperative Outcomes in Video-assisted Thoracic Surgery (VATS). https://clinicaltrials.gov/show/NCT00854386 2009; null(null): null.

[28] NCT00905502 . Intraoperative Fluid Management in Laparoscopic Bariatric Surgery. https://clinicaltrials.gov/show/NCT00905502 2009; null(null): null.

[29] NCT01399814 . Restricted Intravenous Fluid Regime Effects on Immunological

Indicators of Elderly Patients Operated for Abdominal Cancer. https://clinicaltrials.gov/show/NCT01399814 2011; null(null): null.

[30] NCT01563991 . Impact of Perioperative Intravenous Fluid Utilization on Postoperative Outcomes. https://clinicaltrials.gov/show/NCT01563991 2012; null(null): null.

[31] NCT02113358 . Comparison of Stroke Volume Variation-guided Normovolemic and Restrictive Fluid Management During Craniotomy: a Randomized Controlled Trial. https://clinicaltrials.gov/show/NCT02113358 2014; null(null): null.

[32] NCT02135146 . Evaluating Fluid Strategies in Thoracic Surgery Patients Utilizing a Goal Directed Approach. https://clinicaltrials.gov/show/NCT02135146 2014; null(null): null.

[33] NCT03519165 . Restrictive or Individualized Goal-Directed Fluid Replacement Strategy in Ovarian Cancer Cytoreductive Surgery. https://clinicaltrials.gov/show/NCT03519165 2016; null(null): null.

[34] Brandstrup B, Svendsen PE, Rasmussen M, Belhage B, Rodt SÅ, Hansen B, Møller DR, Lundbech LB, Andersen N, Berg V, Thomassen N, Andersen ST, Simonsen L. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? Br J Anaesth. 2012 Aug;109(2):191-9. doi: 10.1093/bja/aes163. Epub 2012 Jun 17. PMID: 22710266.

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6. The GRADE results

Author(s):
Question: Restrictive fluid resuscitation compared to liberal fluid resuscitation for septic shock
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	restrictive fluid resuscitation	liberal fluid resuscitation	Relative (95% CI)	Absolute (95% CI)		
incidence of severe AKI												
5	randomised trials	serious[a]	not serious	not serious	serious[b]	none	348/942 (36.9%)	401/965 (41.6%)	**RR 0.89** (0.80 to 0.99)	**46 fewer per 1,000** (from 83 fewer to 4 fewer)	⨁◯◯◯ Low	
mortality												
5	randomised trials	serious[a]	not serious	not serious	serious[b]	none	370/957 (38.7%)	382/973 (39.3%)	**RR 0.99** (0.89 to 1.10)	**4 fewer per 1,000** (from 43 fewer to 39 more)	⨁◯◯◯ Low	
ICU LOS												
5	randomised trials	serious[a]	not serious	not serious	serious[b]	none	959	975	-	MD **0.29 lower** (0.75 lower to 0.18 higher)	⨁◯◯◯ Low	
incidence of worse AKI												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	34/123 (27.6%)	44/121 (36.4%)	**RR 0.80** (0.45 to 1.44)	**73 fewer per 1,000** (from 200 fewer to 160 more)	⨁⨁⨁◯ Moderate	
duration of ventilation												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	105	103	-	MD **32.06 lower** (59.04 lower to 5.07 lower)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Blinding of participants and personnel(performance bias) and blinding of outcome assessment(detection bias) of all 5 trials were serious.
b. The variation between the numbers of participants in the trials was considerable.

7. specific resuscitation therapy of restrictive or conservative resuscitation strategy

1)Meyhoff, 2022

5)Semler, 2019

Conservative Fluid Management Protocol Part 1: “SHOCK”

Patients who had experienced a MAP < 60 mmHg or vasopressor use in the prior 12 hours were considered to be in shock. For patients more than 12 hours from admission to the study ICU and in shock, fluid boluses were NOT administered except as directed by the protocol for the indications of oliguria and worsening shock. MAP 60 – 80 mmHg was maintained using addition of or titration of vasopressors.

Oliguria: If a patient in shock experienced a urine output of less than 30 mL/h for at

least 6 hours, a fluid bolus of 500 mL of crystalloid was administered over 30 minutes. If urine output was more than 30 mL/h in the following two hours, the patient returned to the study protocol of fluid restriction and vasopressor titration and did not receive further fluid boluses at that time. If urine output was less than 30 mL/h in the following two hours, a fluid bolus of an additional 1,000 mL of crystalloid was administered after which the patient returned to the study protocol of fluid restriction and vasopressor titration. If a patient previously treated with a fluid bolus for oliguria experienced another 6 hour period of oliguria, the fluid boluses were repeated as per the protocol to a maximum of 3 L of crystalloid administered in fluid boluses on a given study day. In a patient who experiences urine output < 30 mL/h for 24 hours, the protocol was held until urine output ≥ 30 mL/h for 6 consecutive hours and then resumed. In a patient who was started on renal replacement therapy, the protocol was held until the study day following the final episode of renal replacement therapy.

Worsening Shock: If a patient in shock experienced increasing vasopressor requirements, the administration of IV fluid boluses and vasopressor administration was dictated by the study protocol. For patients requiring less than 10 mcg/min of norepinephrine (or equivalent), fluid boluses were not administered. For patients whose norepinephrine rate was greater than or equal to 10 mcg/min and whose rate had increased by more than 5 mcg/min in the prior six hours, a fluid bolus of 500 mL of crystalloid was administered over 30 minutes and then fluid restriction and vasopressor titration through the protocol was resumed. For patients whose

norepinephrine dose was greater than or equal to 20 mcg/min and whose vasopressor requirement had increased more than 10 mcg/min in the last 6 hours, a fluid bolus of 500 mL over 30 minutes was administered and then fluid restriction and vasopressor titration through the protocol was resumed. If a patient who had previously received a fluid bolus for worsening shock again met criteria by vasopressor increase over another 6 hour period, another fluid bolus was administered in accordance with the study protocol to a maximum of 3 L of IV fluid bolus intake on a given study day. In patients whose vasopressor requirement equaled or exceeded 60 mcg/min or had increased more than 20 mcg/min in the last 6 hours, the protocol was held until the patient's mean arterial pressure was stable in the goal range for six hours without addition of or increased dose of vasopressors.

Fluid Bolus Administration: In patients on study in shock, fluid boluses were only administered as directed by the study protocol for oliguria or worsening shock. When a fluid bolus was indicated in accordance with the protocol, the fluid bolus volume was determined by the protocol and the type of crystalloid to be administered was determined by the treating clinician. Fluid boluses were administered over 30 minutes and vital signs and urine output were measured and recorded before and after each fluid bolus. The maximum volume of fluid which was given in the form of protocol-directed fluid boluses on a given study day was 3 L. If a fluid bolus was indicated by the study protocol but the treating clinicians felt administering a fluid bolus would be unsafe, the fluid bolus was NOT administered.

Acute Event: If a patient experienced a cardiac arrest, post-intubation hypotension, or hemodynamically significant bleeding, the nurse notified the clinical team and study staff and the protocol was held until the mean arterial pressure was in the goal range for 6 consecutive hours without addition of or increased dose of vasopressors.

Resolution of Shock: If a patient who had been in shock achieved MAP ≥ 60 mmHg for 12 hours without the use of vasopressors, the protocol transitioned to "**NOT in SHOCK**".

Conservative Fluid Management Protocol Part 2: "NOT in SHOCK"

Patients who had not experienced a MAP < 60 mmHg or vasopressor use in the prior 12 hours were considered not to be in shock. For patients who had been in the study ICU for more than 12 hours and who were not in shock, (1) fluid boluses were not administered except as directed by the protocol for oliguria and (2) a fluid balance of total output greater than total input was targeted for each 24 hour period utilizing a diuretic infusion if necessary.

Oliguria: If a patient not in shock experienced a urine output of less than 30 mL/h for 6 hours, the diuretic infusion was discontinued and a fluid bolus of 500 mL of crystalloid was administered over 30 minutes. If urine output was more than 30 mL/h in the following two hours, no further fluid was administered and the diuretic infusion was restarted after urine output was more than 30 mL/h for 6 hours. If urine output was less than 30 mL/h in the following two hours, a fluid bolus of 1000 mL of crystalloid was administered and the diuretic infusion was restarted after the urine

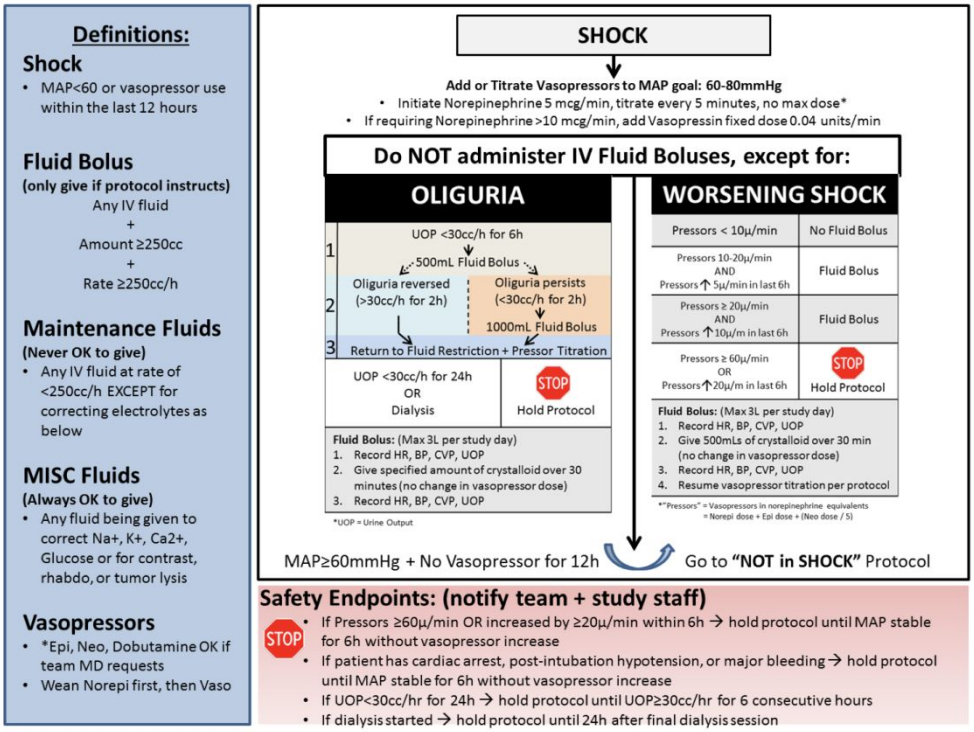
output was more than 30 mL/h for 6 hours. If, after receiving a fluid bolus, a patient again experienced urine output of less than 30 mL/h for 6 hours, the protocol was repeated up to a maximum of 3 L of intravenous fluid boluses directed by the protocol on a given study day. In a patient who experienced urine output < 30 mL/h for 24 hours, the protocol was held until urine output ≥ 30 mL/h for 6 consecutive hours and then was resumed. In a patient who was started on renal replacement therapy, the protocol was held until the study day following the final episode of renal replacement therapy.

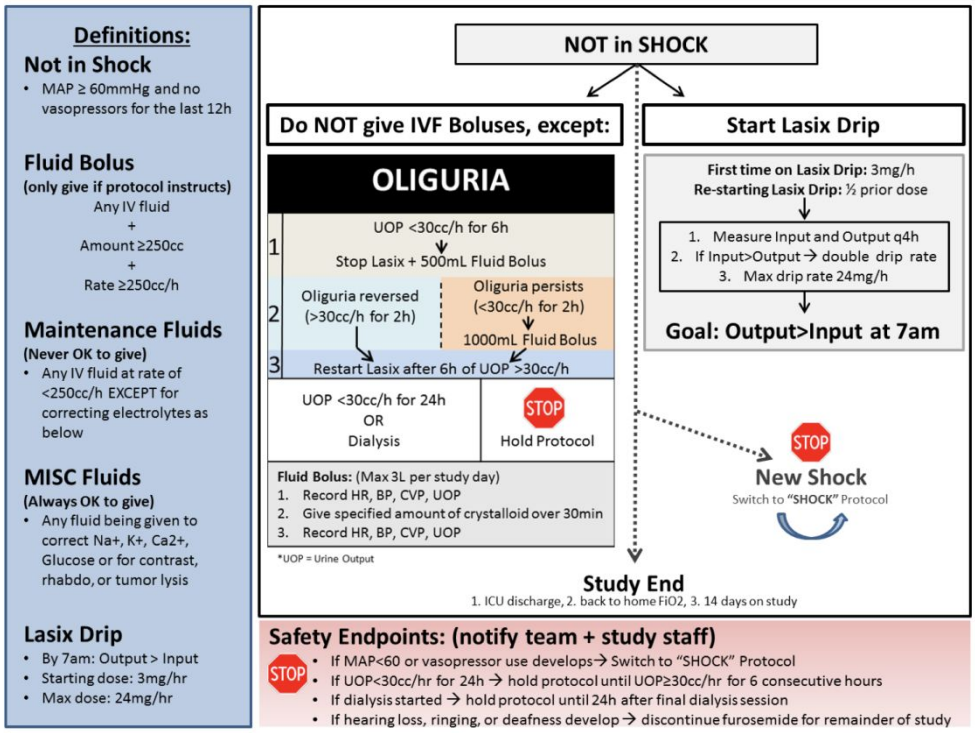
Fluid Bolus Administration: In patients on study not in shock, fluid boluses were only administered as directed by the study protocol for oliguria. If a fluid bolus was directed by the protocol, the specified volume of whichever crystalloid was preferred by the treating clinician was administered. The fluid bolus was administered over 30 minutes and vital signs and urine output were measured and recorded before and after the fluid bolus. The maximum volume of fluid which was given in the form of protocol-directed fluid boluses on a given study day was 3 L. If a fluid bolus was indicated by the study protocol but the treating clinicians felt administering a fluid bolus would be unsafe, the fluid bolus was NOT administered.

New Shock: If mean arterial pressure < 60 mmHg or vasopressor use developed, the nurse notified the clinical team and study staff and the protocol was resumed in "**SHOCK**".

Diuretic Infusion: For patients not in shock, nursing personnel initiated a

continuous intravenous infusion of loop diuretic without a loading dose. If furosemide was clinically available and the patient was not allergic, the diuretic infusion was furosemide beginning at 3 mg/h titrated as needed up to a maximum of 24 mg/h. If the patient was allergic to furosemide OR furosemide was clinically unavailable, the diuretic infusion was bumetanide beginning at 0.1 mg/h titrated as needed to a maximum dose of 0.6 mg/h. For patients previously receiving infusion in whom infusion was held for development of shock or oliguria, it was re-started at half the prior dose. For patients previously receiving infusion in whom it was held for another indication, the infusion was restarted at the prior dose. For the first 4 hours after initiation or re- initiation, total fluid input, total fluid output, and urine output was assessed hourly and if fluid input exceeds output in a given hour the rate of infusion was doubled up to a maximum of 24 mg/h. Subsequently, at least every four hours during the infusion, nursing personnel measured and documented fluid intake, fluid output, and urine output.





8. specific resuscitation therapy of liberal resuscitation strategy or usual care

5)Semler, 2019

For patients assigned to usual care, all aspects of patient care including fluid management were deferred to treating clinicians.

BMJ Open

The effect of restrictive fluid resuscitation on severe acute kidney injury in septic shock: A systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086367.R1
Article Type:	Original research
Date Submitted by the Author:	12-Dec-2024
Complete List of Authors:	Cai, Xin-Er; Southeast University Medical College, Ling, Wan-Ting; Southeast University Medical College Cai, Xiao-Tian; Southeast University Medical College Yan, Ming-Kun; Southeast University Medical College Zhang, Yan-Jie; Southeast University Medical College Xu, Jing-Yuan; Southeast University,
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Medical management
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Acute renal failure < NEPHROLOGY, Mortality

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The effect of restrictive fluid resuscitation on severe acute kidney injury in septic shock: A systematic review and meta-analysis

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Abstract

Objectives: Sepsis associated hypotension or shock is critical stage of sepsis, and a current clinical emergency that has high mortality and multiple complications. A new restrictive fluid resuscitation therapy has been applied, and its influence on patients' renal function remains unclear. The purpose of this study is to evaluate the influence of restrictive fluid resuscitation on incidence of severe acute kidney injury(AKI) in adult patients with sepsis hypotension and shock compared with usual care.

Design: Systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Data sources: Pubmed, Embase, Web of Science and Cochrane Library were searched through 1 November 2024.

Eligibility criteria: We included randomized controlled trials that compared restrictive fluid resuscitation with liberal fluid therapy on patients with sepsis associated hypotension and shock, to find out their effect on the incidence of severe acute kidney injury(AKI). Severe AKI was defined as the acute kidney injury network (AKIN) score 2 to 3 or Kidney Disease Improving Global Outcomes (KDIGO) stage of 2 and 3.

Data extraction and synthesis: Two independent reviewers used standardized methods to search, screen and code included trials. Risk of bias was assessed using the Cochrane Systematic Review Handbook for randomized clinical trials. Meta-analysis was conducted using random effects models. Sensitivity and subgroup analyses, trial sequential analysis (TSA), plus Egger's test and the trim-and-fill

method were performed. Findings were summarized in GRADE evidence profiles and synthesized qualitatively.

Results: 9 trials (3718 participants) were included in this research and the analysis was conducted in random effects model. There was a significant difference in the incidence of severe AKI (RR 0.88, 95%CI 0.79 to 0.97, P=0.01; I^2=0%) and the duration of mechanical ventilation (Mean Difference -41.14, 95%CI -68.80 to -13.48; P=0.004; I^2=74%) between patients receiving restrictive fluid resuscitation and patients receiving liberal fluid resuscitation. TSA showed that the cumulative amount of participants met the required information size (RIS), the positive conclusion had been confirmed. The GRADE assessment results demonstrated moderate confidence on incidence of severe AKI, as well as the results of all second outcomes except the ICU LOS, which received limited confidence. And the result of incidence of worse AKI was rated as of high certainty.

Conclusions: It is conclusive that fluid restriction strategy is superior to usual care when it comes to reducing the incidence of severe acute kidney injury in sepsis associated hypotension and shock. Shorter duration of ventilation is concerned with

fluid restriction as well, but the heterogeneity is substantial. GRADE assessments confirmed moderate and above certainty. Traditional fluid resuscitation therapy has the potential to be further explored for improvements to be more precise and appropriate for a better prognosis.

Trial registration

This study was retrospectively registered at the PROSPERO (International prospective register of systematic reviews) website on 29 July 2023 and the ID was CRD42023449239.

Keywords: Septic shock, Restrictive fluid resuscitation, Acute kidney injury, Mortality

Strengths and limitations of this study

- This systematic review and meta-analysis provided a comprehensive and up-to-date analysis focusing on the kidney function prognosis of patients with septic shock undergoing restrictive fluid resuscitation.
- To evaluate the heterogeneity, we conducted comprehensive subgroup and sensitivity analysis.

- To confirm the reliability of the results, we used various approaches such as TSA, GRADE assessments and the Egger's test.
- Number of included participants was a bit small, but the TSA result confirmed it has reached RIS.
- When extracting the data, we countered some different definitions, but conducted other analysis to reduce the risk of bias.

Introduction

Septic shock is defined as a subset of sepsis in which potential circulatory, cellular, and metabolic damages are serious and profound enough to increase the risk of mortality. [1] It is a common clinical emergency characterized by refractory hypotension, hyperlactatemia and organ dysfunction, which occurs in more than 230,000 US patients each year, leading to over 40000 deaths annually, [2,3] and affecting millions of people around the world each year. [4] AKI is a common complication in critical ill patients with sepsis and/or septic shock. [5,6] When septic shock and AKI are present simultaneously, the mortality rate is up to nearly 50%. [7] And patients with severe AKI have a high risk of stabilizing the situation of chronic

kidney disease (CKD) or progress to complete organ failure and compulsive dialysis requirement. [8,9] This would cause serious health and financial burden on the patients. When it comes to sepsis associated hypotension and septic shock, intravenous fluid resuscitation is a very common therapy in the initial treatment. It aims to increase depleted or functionally reduced intravenous volume that occurs in sepsis owing to a vasodilated vascular network. Initial fluid therapy can augment macrovascular perfusion and microvascular perfusion and counter organ hypo-perfusion. [1,10] And AKI under the circumstance of vascular changes in septic shock is more related to pre-renal factors instead of post-renal or intra-renal, specifically due to micro-vascular abnormalities sand tubular stress. [3] Therefore correction of intravascular hypovolemia is a key component of the prevention and management of AKI in septic shock as well.

But in the case of increased endothelial cell permeability, excessive infusion can exacerbate organ dysfunction. [11] Excessive fluid administration is believed to be associated with development and progression of AKI, so individualized fluid therapy has been taken into consideration, taking into account patients' characteristics, origin

of patients' kidney dysfunction and risks and benefits of fluids. Therefore, this complex situation attached great importance to the choice of fluid resuscitation. A new strategy called restrictive fluid strategy , which is a resuscitating therapy of lower volumes of fluid and earlier initiation of vasopressor agents, are to be taken into consideration. But there is still insufficient evidence to make a recommendation on the use of restrictive or liberal fluid strategies in patients with sepsis associated hypotension and shock who still have sighs of hypo-perfusion and volume depletion after initial resuscitation. [10] A resent pilot multicenter, randomized, controlled trial of critically ill patients with AKI proved that a restrictive fluid management regimen was feasible. [12] Although whether restrictive fluid therapy has a positive impact on septic patients' kidney function is not supported by strong evidence, it is commonly believed that fluid overload has deleterious impact on renal function balance.

The impact restrictive fluid resuscitation therapy has on the incidence of severe AKI may lay out some priority. When combined with severe kidney dysfunction, the mortality and ICU length of stay of patients with higher AKIN score all rise

significantly comparing to patients with lower AKIN score, whether the patients had sepsis or not. [13] It is a much more serious and emergent situation of the kidney function of the patients that needs urgent recognition and treatment.

As intravenous fluid and vasopressor application both have an impact on the patients' organ and tissue perfusion, the renal situation should be taken into consideration. This meta-analysis is conducted in the aim of investigating the effect of the restrictive fluid resuscitation strategy on the occurrence of severe acute kidney injury in adult patients with sepsis associated hypotension and septic shock.

Materials and methods

This study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement methodology [14], a systematic review and meta-analysis of randomized clinical trials. The study was registered at the PROSPERO (International prospective register of systematic reviews) website and the ID was CRD42023449239.

Patient and public involvement

As this is a systematic review and meta-analysis, we completed this research by searching papers through Internet, extracting relevant data from included trials and working on the data statistically. No patients or public involvement were involved in this research directly.

Search strategy and selection of studies

A literature search of PubMed, Web of science, Embase and Cochrane library was undertaken to identify randomized clinical trials. The searches were last updated on 1 November 2024. The search terms used were “acute kidney injury” or “acute kidney failure” or “acute renal failure” or “continuous renal replacement therapy” or “blood purification therapy” or “mortality”, and “restrictive fluid” or “resuscitation”. The search and reviewing of all the articles were conducted by two reviewers (XEC and XTC) independently. When encountered disagreements, a third reviewer (WTL) would provide a suggestion.

Title and abstract screening was conducted for all relevant studies and potentially relevant records were thoroughly read. The inclusion criterions were as follows: 1) the research was limited to randomized clinical trials only, 2) studies conducted on

adult patients(≥18 years) who were diagnosed as septic shock, 3) trials where the intervention assessed was restrictive fluid resuscitation therapy or conservative fluid strategy versus liberal or conventional fluid resuscitation, 4)studies that contained the data of numbers of patients who countered AKI, or the mortality. Trials with the following features were excluded: 1) studies enrolling pregnant patients, 2) studies in which most patients had systematic inflammatory response syndrome secondary to other causes such as burn or pancreatitis without a clear sepsis subgroup, 3) studies that focused on patients undergoing elective surgery, or the therapy was carried out during perioperative period [15,16]. No date, publication status, languages or predefined outcome restriction were applied.

Data extraction and Synthesis

In this meta-analysis, primary outcome was severe AKI which was defined as acute kidney injury network (AKIN) [17] score 2 to 3 or Kidney Disease Improving Global Outcomes (KDIGO) [18] stage of 2 and 3 [19]. Data including primary outcome were extracted by two reviewers (XEC and XTC). If there were disagreements, a discussion was performed with another reviewer (WTL).

Titles and abstract of all reports identified in the literature searches were screened for further review. The data collected form each study included 1) general information (author, year, study design), 2) characteristics of the participants (including gender, age, inclusion and exclusion criteria, initial places where they stayed before admitted into ICU and randomization, and the diagnosis criterions and diagnosing time point of septic shock), 3) outcomes, with primary outcome determined as incidence of severe AKI (with clear clarification of numbers of patients of AKIN score 2 and 3, or KDIGO stage 2 and 3) and secondary outcomes as clinical outcomes including overall mortality (when there was more than one indicator concerning with the mortality of all participants at different times, the mortality of the longest period would be prioritized for inclusion in the meta-analysis), ICU LOS, the incidence of worse AKI (defined as higher stages of KDIGO criterion or higher scores of AKIN), and duration of ventilation.

When countering missing data, the author tent to contact authors of the relevant studies, and searched for other paper of the same trial. The reference lists of included

randomized clinical trials were reviewed for additional trials meeting eligibility criteria.

Dichotomous variables were expressed as counts and proportions. Means and standard deviations (SDs) were used to describe normally distributed continuous variables. Because the ICU length of stay and ventilation time were not normally distributed, all studies involving the data reported the ICU LOS and duration of ventilation by using the median and the first and third quartiles. We estimated the sample mean and standard deviation (SD) value based on the method of mean variance estimation presented by the Hong Kong Baptist University. [20,21,22,23]

Study quality and risk of bias assessment

The risk of bias was assessed for each outcome in all included studies using the Cochrane Systematic Review Handbook for randomized clinical trials. The 9 studies were assessed as being at low, uncertain or high risk of bias for each of 6 domains. The internal validity of the included studies was assessed according to the Cochrane Collaboration methodology (the Cochrane Risk of Bias tool), which consists of 6 domains. [24] The results were output by using the Review Manager((RevMan)

[Computer program]. Version 5.4. The Cochrane Collaboration, 2020.) software, which was applied in the statistical analysis as well. Two reviewers assessed study quality independently (XEC & XTC). If there were disagreements, a discussion was performed with another reviewer (WTL). 6 aspects were performed for assessing the risk of bias, including allocation concealment, random sequence generation, blinding, incomplete outcome data, selective reporting and other bias. Publication bias was evaluated by visual inspection of a funnel plot, and further checked by the Egger linear regression test and a nonparametric trim-and-fill method [25], which was done by the R software (version 4.4.1) formally known as the R Project for Statistical Computing.

Outcome measures

The primary outcome was the incidence of severe AKI of all participants. Key secondary outcomes were all-cause mortality at the latest time of follow-up, ICU LOS, duration of ventilation and the full amount of patients developing worse AKI comparing to the situation of their first admission into the hospital.

Analysis

The meta-analysis was carried out by using a random effects model for outcomes for which two or more randomized studies were available. The results of outcomes were reported in the form of narrative and graphs. We used Risk Ratio(RR) with 95%CI for dichotomous outcomes (incidence of severe AKI, incidence of worse AKI, mortality) and Mean Difference(MD) with 95%CI for continuous outcomes (ICU LOS, duration of ventilation) to estimate the pooled effects. In all analyses, $P<0.05$ was considered significant, and statistically significant.

For key outcomes, we assessed the quality of evidence using the Grades of Recommendation, Assessment, Development and Evaluation(GRADE) approach. [26]

The heterogeneity of these 9 studies was measured by the I^2 which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates that no heterogeneity is observed, 25%, 50%, and 75% represent low, moderate, and high levels of heterogeneity respectively [27].

A sensitivity analysis was performed by removing one study at a time to determine whether a specific trial had a higher contribution to the heterogeneity.

Simultaneously we tested the analysis by including high-quality researches only to see if the results changed utterly [28, 29, 30,31]. Subgroup analysis was carried out to see if the following factors contributed to the result: enrolling patients with an average age ≥70 years or <70 years, places where the patients were admitted from (the emergency department (ED) only, or places including ED, hospital wards, the operation room (OR), and other ICU).

A trial sequential analysis (TSA) was performed to estimate the optimal sample size to reach a plausible conclusion on the research. We used Trial Sequential Analysis (TSA) [Computer program]. Version 0.9.5.10 Beta. The Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital – Rigshospitalet, 2021. Statistical significance was set at a P-value of 0.05.

Results

The search was conducted up to 1 November 2024. And the process of the search of literature is summarized and presented in **Figure 1**. A total of 7249 studies were retrieved from 4 databases and screened title and abstract for potential relevant

researches. 2462 of records were removed for duplication first. 4787 records were identified as ineligible or irrelevant, leaving 90 records for full-text review. 9 studies met criteria for inclusion and were included in the quality assessment. At the end, all 9 randomized clinical trials were included into this meta-analysis covering 3718 participants. Details of the selection process were shown in **Figure 1**.

Description of included randomized trials

Sample sizes ranged from 29 to 1563. Three studies took place in the United State of America(USA), two in Denmark, one in Switzerland, one in Australia and New Zealand, one in the USA and United Kingdom. And one study took place in worldwide. All trials were conducted on adult patients and no pregnant patients were included. All 9 studies evaluated patients with septic shock. Further characteristics of the 9 chosen RCTs were summed up in **Supplement Table 1**. No heterogeneity was observed in these RCTs.

The overall quality of included RCTs was shown in **Figure 2**. The use of random sequence generation and allocation concealment and the risk of reporting bias were

unclear in a number of studies. Confounding by indication and time-dependent exposure might have biased the studies. [29]

Assessment of the risk of bias was summarized in **Figure 2**. Among the 9 RCTs, none of the trials were double blinded. The allocation may be blinded for the statistician. But it was obviously impossible to blind both patients and caregivers in the medical intervention of the trials, we proposed that the outcomes may not be influenced by a lack of blinding. One trial was classified as having an unclear risk of bias in selection reporting.

The incidence of severe AKI

The depiction of AKI differed in 9 RCTs. But they could all come down to the criterion of AKIN score or KDIGO stage. Some defined patients who met the KDIGO stage of 1-3 as AKI [30, 32], or modified the classification into stage 2 or higher, both with higher stages indicating more severe kidney injury [29]. Some chose to reflect the patients' renal situation by the patients' peak AKIN score [33]. Two studies reported numbers of worsening AKI, or new onset of severe AKI, which was defined as worsening of the KDIGO stage (plasma creatinine criteria or use of

renal replacement therapy) [31, 34]. In 2 trials the exact number of patients' of KDIGO stage 2 and 3 was not available neither in the article nor the supplement appendix. [28, 35]. We extracted the numbers of patients receiving continuous renal-replacement therapy (CRRT) treatment according to the information this article provided in their supplement appendix, which met the diagnostic criteria for KDIGO stage 3 or AKIN score 3. In the study conducted by Corl et al. in 2019 [36], serious AKI was narrated as doubling in the triage creatinine within 72 hours, which could be considered as KDIGO stage 2.

A total of 3712 patients were analyzed for renal function. 410 of the 1864 patients analyzed in the restrictive fluid resuscitation group (22.0%)and 477 of the 1849 patients analyzed in the liberal fluid resuscitation group (25.8%)were diagnosed severe AKI or evaluated as KDIGO score of 2 and 3 or reached AKIN score 2 and 3 during the follow-up of the studies (RR 0.88, 95%CI 0.79 to 0.97, P=0.01; I^2=0%). Obviously there was a significant difference in the incidence of acute kidney injury between patients receiving a restrictive or conservative fluid resuscitation strategy

and those who received a liberal fluid resuscitation strategy or usual care therapy. The process was shown in the forest plot in **Figure 3**.

Second outcomes

Mortality

Data on all-cause mortality of the participants were available in all 9 RCTs. A total of 3813 patients were tracked down for their clinical ending at most protracted time point, including 90-day mortality in 7 RCTs, [28,29,30,31,32,33,34], 60-day mortality in one [36], and 30-day mortality in one [35]. We found no significant difference in the mortality between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (RR 0.99,95%CI 0.90 to 1.08; P=0.82; I^2=0%). The result of the I^2 evaluation indicated that there was no heterogeneity observed. Specific data was reported by **Supplement Figure 1** in supplementary appendix.

ICU length of stay

Seven RCTs reported the patients' length of stay in ICU, of which 3 were measured in hours [30,33,36] and 4 were measured in days [29,31,32,35]. All data was extracted in the form of median and IQR and was transformed into value of mean

and SD by the method proposed by the Hong Kong Baptist University. The result was shown in **Supplement Figure 2**, obviously no heterogeneity was detected in the trial neither (Mean Difference -0.33,95%CI -0.79 to 0.13; P=0.16; I^2=0%).

Incidence of worse AKI

Data on the incidence of worse AKI were available in 3 RCTs. We analyzed the full amount of patients developing worse AKI comparing to the situation of their first admission into the hospital. It was narrated as worse situation of AKI in patients who already suffered from AKI, [31,33,34] (according to the KDIGO criteria, higher stage means worse kidney function situation), and for patients without AKI at baseline, development of AKI after randomization was regarded as worsening of AKI. The result was shown in **Supplement Figure 3**. No significant difference was found in the incidence of worse AKI between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (RR 0.76, 95%CI 0.55 to 1.05; P=0.09; I^2=0%). No heterogeneity was detected in the trial.

Duration of ventilation

3 RCTs reported the patients' mechanical ventilation hours [33,35,36]. All data was extracted in the form of median and IQR and was transformed into value of mean and SD by the method proposed by the Hong Kong Baptist University. The result was shown in **Figure 4**. There was a significant statistical difference in the duration of ventilation of patients between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (Mean Difference -41.14, 95%CI -68.80 to -13.48; P=0.004; I^2=74%). High heterogeneity was detected in the trial.

Sensitivity analysis

In the sensitivity analysis, we removed the studies individually to see if any of them had a larger impact on the result. And when trial conducted by Meyhoff et al. [29] was removed, the result reversed and had no statistical meaning. This indicated that this trial took a large position in the analysis. When we included only high-quality researches according to the assessments [28,29,30,31], the result remained statistically meaningful (RR 0.89, 95%CI 0.80 to 0.99; P=0.03; I^2=0%). Through sensitivity analysis of the secondary outcomes, we found that high heterogeneity of the duration of ventilation was mainly related to the Corl et al.'s study [36]. When it

was removed, the heterogeneity could be considered as low (Mean Difference -52.68, 95%CI -73.80 to -31.56; P<0.00001; I^2=9%) comparing to original analysis results. And when other 2 studies were removed individually, the value of I^2 remained above 75%(I^2=76% or 81%).

Subgroup analysis

All 9 RCTs concluded the participants' median age. We calculated the average age and then divided the studies into two divisions according to the criterion(<70 year versus ≥70 years). The role the initial places where the patients were admitted from played was investigated as well. Most patients were extracted from the emergency department (ED) of the hospital. [33,34,35,36] The rest participants were admitted into the ICU from OR, hospital wards or other ICUs, especially in multicenter trials. [28,29,30,31,32] Simultaneously we analyzed whether these factors had an impact on the results of the incidence of severe AKI and the mortality of the patients.

Results showed that there was a significant difference in the incidence of severe AKI between patients receiving restrictive fluid resuscitation in the subgroup analyzing the factor of age above 70 (RR 0.89, 95%CI 0.79 to 0.99; P=0.03; I^2=0%) and the

multiple initial places where the patients were admitted from (RR 0.88, 95%CI 0.80 to 0.98; P=0.02; I^2=0%) (**Supplement Figure 4&5**). This led to the indication that restrictive fluid resuscitation therapy could make an impact on the kidney function of patients over 70 years old. And when patients were admitted from not only the ED, but also the OR, hospital wards and other ICUs, they were more likely to benefit from restrictive fluid resuscitation strategy.

Simultaneously, these two factors above didn't have a connection with the mortality of the patients. No significant difference was found in the subgroup analysis. And no significant heterogeneity was detected. (**Supplement Figure 6&7**)

Trial Sequential Analysis

Trial sequential analysis (TSA) was conducted to calculate the optimal required information size [37,38] (meta-analysis sample size) for our meta-analysis based on a baseline incidence rate of 45% [39,40]in the control group, a relative risk reduction of 10%, 80% of power and a type I error of 5%. TSA showed that the diversity adjusted RIS was 3711 which was less than that in our study (n=3718). Trial sequential adjusted 95% CI of RR was 0.79 to 0.97 in the fixed effects model, and

0.87 to 0.88 in the random effects model. The Begg-Tang random effects model was applied to test the reliability of the result. [41] The results were showed in **Figure 5**. The Z-curve surpassed the conventional boundary and the trial sequential monitoring boundary both for benefit, indicating that the result was reliable and the accuracy was testified. The cumulative amount of participants met the RIS line, this positive conclusion had been confirmed.

Quality of evidence

We assessed the quality of evidence using the GRADE approach (**Supplement Figure 9**). The results demonstrated moderate confidence in the findings on incidence of severe AKI, as well as the results of all second outcomes except the ICU LOS, which received limited confidence. And the result of incidence of worse AKI was rated as of high certainty.

Publication bias

We explored funnel plot, applied Egger linear regression test and the trim-and-fill method for the primary outcome (**Supplement Figure 8**). The result showed a P-value of 0.3929 (P>0.05), meaning that no significant publication bias was detected.

Discussion

This study focused on the influence of the up-to-date restrictive fluid resuscitation therapy on the incidence of severe AKI of patients under such circumstance, which was a topic that little previous studies had ever discussed. And we found that though restricted fluid resuscitation therapy doesn't improve the overall mortality, it did have a strong connection with lower incidence of severe AKI, indicating that it is associated with less degeneration of patients' renal function. Thus, we provided new evidence for the need of more individual and specialized fluid resuscitation therapy for patients with sepsis hypotension and septic shock.

This meta-analysis focused on a neglected topic, included more participants from other countries and centuries, and the specific measures of the intervention were also different. This gave our research unique strengths, such as more comprehensive included studies, different focusing prognosis, certain results and conclusion. Various analysis was conducted to confirm the certainty of the results. The TSA results has confirmed that the result is reliable, and when it comes to decreasing the incidence of severe AKI in

sepsis associated hypotension and shock, restrictive fluid resuscitation is superior to usual care therapy.

Occurrence of AKI remains one of the major causes of mortality in sepsis associated hypotension and septic shock. Kidney injuries may contribute to long-term effects such as secondary episodes of sepsis and multiple organ dysfunction syndrome (MODS). [42] It is of vital significance that we determine the optimal fluid resuscitation strategy and the volume of intravenous fluid for critically ill patients. Previous studies [31,43,44] proposed that it may benefit the patients' renal function, by the strict condition that optimal kinds of fluid and volumes were applied. Our study arrived in the conclusion that lays with this finding. Fluid resuscitation need to be sufficient, but must be in a controlled fashion and be carried out under dynamic assessment monitoring of patients' volume situation [45]. Volumes of intravenous resuscitation fluids directly ameliorate the tissue and organ perfusion, along with vasopressors, the treatment hold a profound meaning for the safety of organs and the resuscitating process. Excessive volume load will lead to increased renal venous pressure, leading to renal interstitial edema, thus decreasing the renal tissue perfusion.

And volume overload will lead to an increase in central venous pressure, which leads to the obstruction of renal venous reflux and decrease of renal perfusion. In addition, severe overload is concerned with an increase in intra-abdominal pressure, which leads to increased renal venous pressure and decreased renal blood flow. This will increase the pressure in the glomerular balloon cavity, leading to worsening AKI [46]. Thus, too rapid and aggressive fluid resuscitation strategy could potentially burden cardiac and renal function, creating an underlying danger to the precarious physical condition of patients with septic shock. The pace of providing intravenous fluids in the beginning time should not be neglected. Simultaneously, we found that restriction on fluid volume is associated with decrease in patients' duration of mechanical ventilation. This indicated benefit of the participants' pulmonary function. Less hours of mechanical ventilation on the patients not only induces less complications like ventilator-associated pneumonia (VAP) [47], but also has economic benefits. High heterogeneity was found between the included 3 trials, which is mainly related to the Corl et al. 's study [36]. It was likely to be concerned with less centers of the study, its more complicated septic shock inclusion criterion compared with the other

2 studies and higher intravenous fluid volume of the restrictive fluid group (**Supplement Table 1**). The general economic assessment was not taken into consideration, which future trials should incorporate.

Subgroup analysis also showed that the influence of restrictive fluid resuscitation strategy was especially obvious on patients with an elderly age of over 70. This may be for the reason that the aged have poor cardiopulmonary function and a narrow volume window. In the presence of septic shock, it is likely that vasoplegia plays an important role in the volume responsiveness assessment. And elder patients' vascular wall elasticity decreases, leading to a decrease in their ability to respond to variety in circulating volume. When patients are admitted from not only the ED, but also other places such as the OR and hospital wards, they generally possess longer hospital stay period and more complicated symptoms. Restriction on their resuscitation fluids may be beneficial for their renal function.

The initial causes of septic shock differed in all participants, and for the sake of patients' safety and to promote the stabilization of patients' vital signs, caregivers all adapted an initial treatment before randomization and admission into the ICU or

emergency department. The treatments aimed to delay the progression of the disease. And all patients included into the RCTs had undergone a similar initial resuscitation treatment. Four trials included in this analysis followed the surviving sepsis campaign bundle which was updated in 2018 [48], and gave their participants an initial fluid volume of 30ml/kg [29,31,35,36]. One trial clear limited the initial infusion of restricted fluid protocol to 1000ml as long as the patients' vital signs had stabled. [28] The other four didn't mention whether the intervention included an initial resuscitation fluid volume [30,32,33,34]. So, the amount of resuscitation fluid can be recognized as sufficient. In all 9 RCTs, 7 of which applied norepinephrine, or to say noradrenaline [28,29,30,31,32,33,35], and two was unclear [34,36]. The timeframe the intervention fluid therapy lasted differed extremely in these trials. Three were within the first 24-h period [28,30,34], two were 72-h [35,36], and the rest were 6-h post randomization [33], 5 days [31] and 14 days [32] individually. The patients received the assigned intervention from the time of randomization until they were discharged from the ICU, for a maximum of 90 days [29]. There was also difference of original countries they took place in, number of patients, difference of

their septic shock inclusion criterion and difference of the details of their intervention. The publication bias of these studies and the lasting period of intervention strategy also had an influence. All these factors may attribute to the heterogeneity measured by the I^2 trial.

Through the study, few evidences were found to definite that the fluid restriction strategy has any influence on the patients' mortality and ICU LOS. This may be because the original infection differed among all the participants, leading to a much-complicated subject to compare the ending of all patients. And ICU LOS is a multifactorial indicator and is very dependent on the patients' condition. Most participants in the studies relied on life-support instruments, exclusively available in the ICU early stages of treatment.

The sensitivity analysis indicated that the trial conducted by Meyhoff et al. [29] took a large position in the analysis. This phenomenon had a lot to do with its number of participants and the long duration of the intervention means. The results of this meta-analysis were confirmed by various analysis, and adding other studies provided more comprehensive insights into this topic.

Results of the GRADE assessments were 1 with high certainty (incidence of worse AKI), 3 with moderate certainty (incidence of severe AKI, mortality, duration of ventilation), and 1 with low certainty (ICU LOS). The uncertainty mainly came from the risk of bias and the imprecision of the included studies. The more studies were involved, the higher risk of bias we saw. The consistency and directness were all ensured in every trial. But when it came to data concerned with time duration or time period, the imprecision was assessed as serious. The heterogeneity and different extraction time nodes of each factor in different trials may also be relevant to the assessments.

Due to lack of data and corresponding issue, some data about severe AKI was represented by numbers of initiation of RRT, which may deviate from the actual results in reality. Unpublished data or data reported in abstract form was not included, which may lead to publication bias. There was little evidence supporting that fluid restriction strategy affects patients' mortality and ICU length of stay. This could be due to differences in the initial causes of infection among all patients, making outcome comparisons complex. The risk of bias of the included trials existed, but the quality of

the results remained reliable, examining by aforementioned analysis. If any relevant required data are available, we will immediately include them in this analysis as supplement. The numbers of included participants may be a bit small, but this meta-analysis strictly included only trials focusing on restrictive fluid resuscitation. And the result of TSA had made sure the sample size reached the RIS. The difference in duration of restrictive fluid resuscitation therapy of these included trials may play an important role in the heterogeneity. Sensitivity analysis showed the result heavily relied on the Meyhoff study. But as narrated before, this analysis had its own irreplaceable strength. And TSA showed promise in the primary outcome.

Conclusion

It is conclusive that fluid restriction strategy is superior to usual care when it comes to reducing the incidence of severe acute kidney injury in sepsis associated hypotension and shock. Shorter duration of ventilation is concerned with fluid restriction as well, but the heterogeneity is substantial. GRADE assessments confirmed moderate and above certainty. Traditional fluid resuscitation therapy has the potential to be further explored for improvements to be more precise and appropriate for a better prognosis.

List of abbreviations

AKI: Acute kidney injury; RCT: randomized controlled trial; ICU: Intensive care unit; TSA: trial sequential analysis; LOS: length of stay; RRT: renal-replacement therapy; RR: relative risk; CI: confidence interval; SD: standard deviation; MD: mean difference; ED: emergency department; OR: operation room; KDIGO: kidney disease improving global outcomes; RIS: required information size; MODS: multiple organ dysfunction syndrome; GRADE: Grades of Recommendation, Assessment, Development and Evaluation

Declarations

Ethics approval and consent to participate

No ethics approval was mandatory for this is a systematic review and meta-analysis, no data was withdrawn directly from patients. We only calculated and synthesized data in published studies.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding statement

This work is partially supported by grants from the National Natural Science Foundations of China (81501705, 82272211), grants from the Scientific Research Foundation of Graduate School of Southeast University (YBPY1604), grants from the Jiangsu Provincial Medical Youth Talent (QNRC2016808), Jiangsu Province's Key Provincial Talents Program (ZDRCA2016082).

Authors' contributions

JYX conceived the study. XEC performed the analysis, synthesis and interpretation of data and wrote the first draft of the manuscript. The search and reviewing of all the articles and the assessment of the studies' quality were conducted by two reviewers (XEC and XTC) independently. When encountered disagreements, a third reviewer (WTL) would provide a suggestion. YJZ and MKY contributed to the progress of the

trial sequential analysis. JYX was responsible for designing and the coordination of the study, and critical revision of the manuscript for important intellectual content. All authors read and approved the final version. JYX is the guarantor.

Acknowledgements

We are sincerely grateful to the investigators and clinical trials group of all the trials included in this study for providing access to their trial data.

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Figures legends

Figure 1. The process of literature search

Figure 2. Risk of bias summary for each included study. Red(-)indicates high risk of bias; yellow(?) indicates unclear risk of bias; green(+) indicates low risk of bias.

Figure 3. Forest plot for primary outcome of the incidence of severe AKI. It illustrates the result of restrictive or conservative fluid resuscitation strategy versus liberal fluid resuscitation or usual care strategy.

Figure 4. Forest plot for second outcome of the duration of ventilation. It shows the result of restrictive fluid resuscitation strategy versus liberal fluid resuscitation strategy on the duration of ventilation of patients with septic shock.

Figure 5. Trial sequential analysis. TSA showed that the diversity-adjusted required information size(RIS) was 3711. The Z-curve surpassed the conventional boundary and the trial sequential monitoring boundary both for benefit, indicating that the result was reliable and the accuracy was testified. The cumulative amount of participants met the RIS line, this positive conclusion had been confirmed.

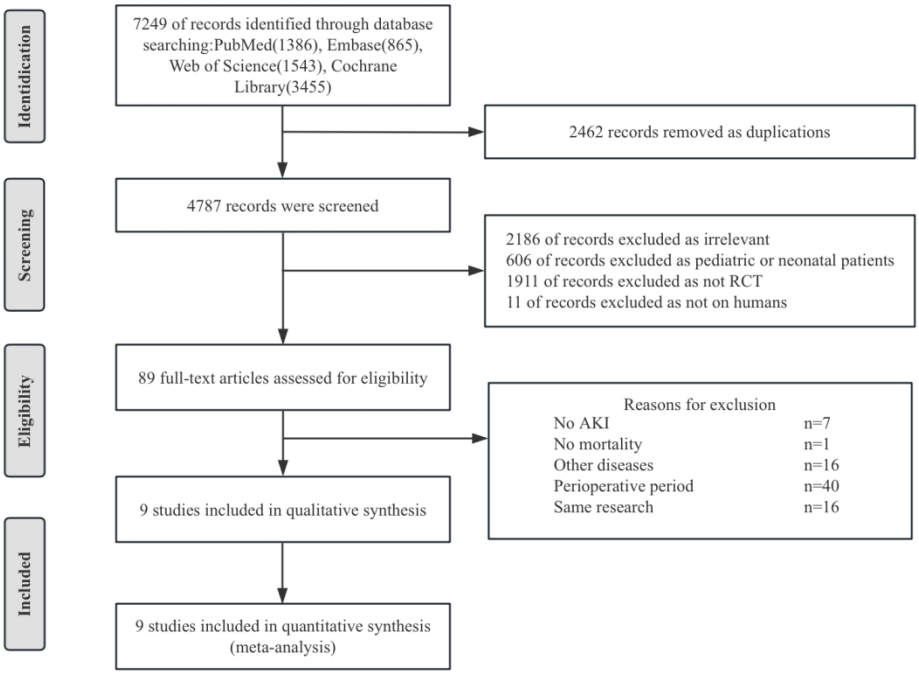

Figure 1. The process of literature search

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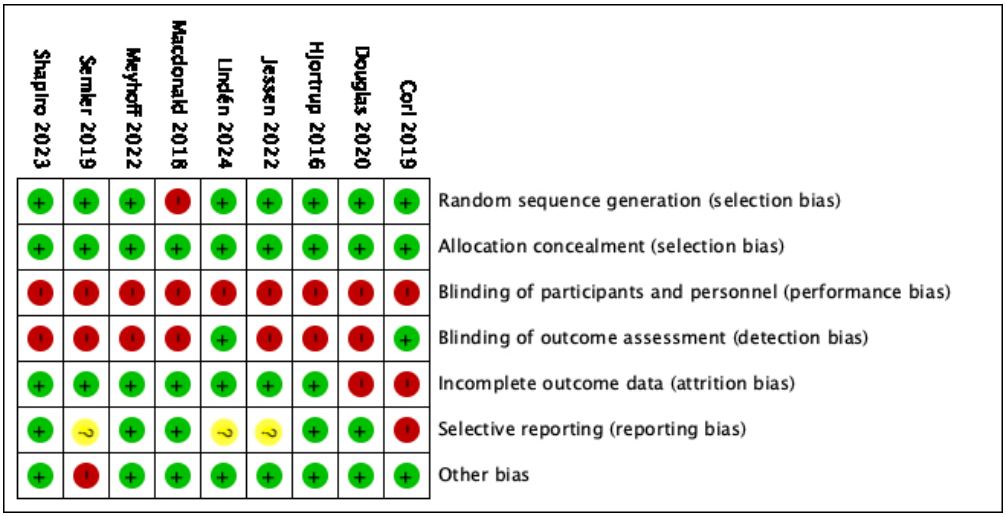

Figure 2. Risk of bias summary for each included study. Red(-)indicates high risk of bias; yellow(?) indicates unclear risk of bias; green(+) indicates low risk of bias.

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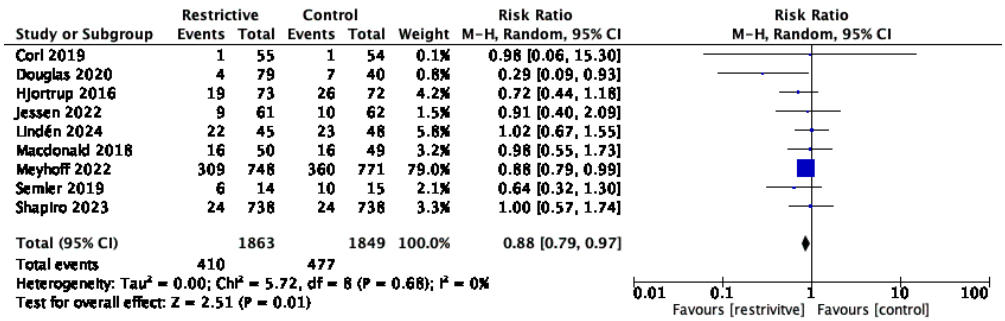

Figure 3. Forest plot for primary outcome of the incidence of severe AKI. It illustrates the result of restrictive or conservative fluid resuscitation strategy versus liberal fluid resuscitation or usual care strategy.

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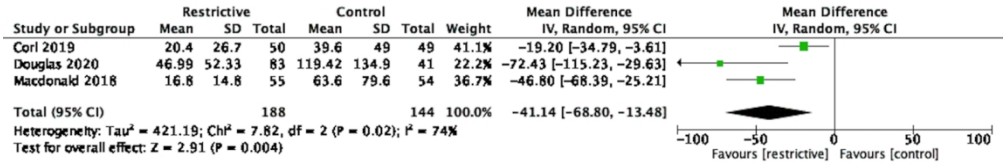

Figure 4. Forest plot for second outcome of the duration of ventilation. It shows the result of restrictive fluid resuscitation strategy versus liberal fluid resuscitation strategy on the duration of ventilation of patients with septic shock.

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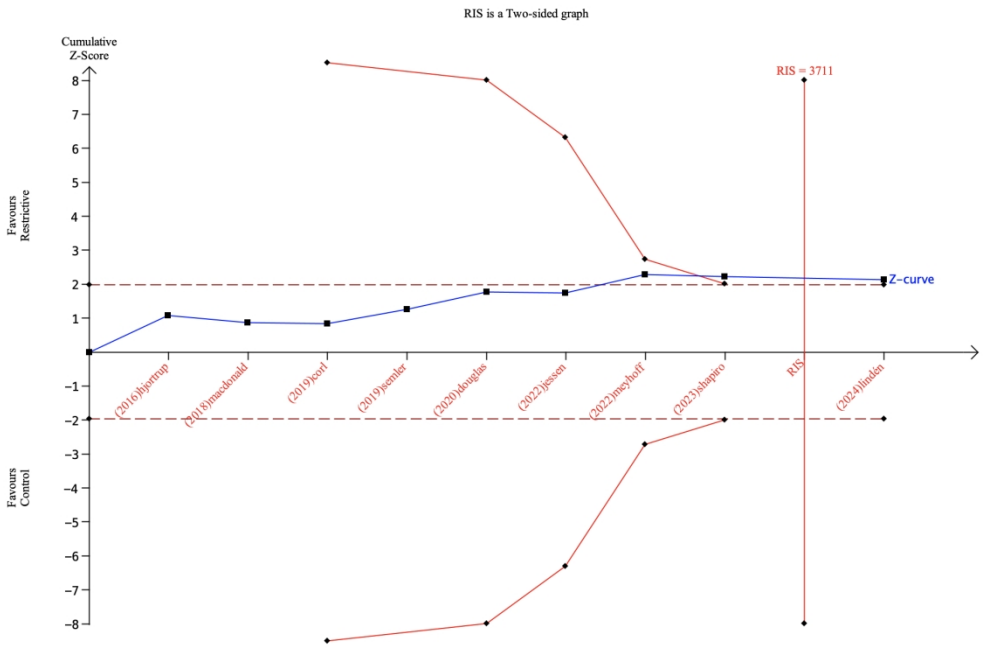

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345x226mm (144 x 144 DPI)

Supplementary appendix

This supplementary appendix provides:

1. Search equation via PubMed, Embase, Web of Science, and Cochrane Library

2. PRISMA checklist

3. Other supplementary Figures

4. Summary of contextual factor data

5. List of citation of excluded potential studies and the reasons to rule out them

6. The GRADE results

7. Table of characteristics of included studies

1. Search equation via PubMed, EMBASE, Medline, and Cochrane Library

Search strategies for the different databases ran on **April 28,2023**

PubMed (1386)

Search: ("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal replacement therapy" OR "blood purification therapy" OR "mortality") AND ("restrictive fluid" OR "resuscitation")

Filters: Randomized Controlled Trial, Humans

Embase (865)

("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal replacement therapy" OR "blood purification therapy" OR "mortality") AND ("restrictive" AND "fluid" AND "resuscitation")

Web of Science (1543)

(TS=("restrictive fluid") OR TS=("resuscitation")) AND TS=(("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal replacement therapy" OR "blood purification therapy" OR "mortality"))

Filters: Clinical Trial +Humans

Cochrane Library (3455)

restrictive fluid OR resuscitation in All Text AND acute kidney injury OR acute kidney failure OR acute renal failure OR continuous renal replacement therapy OR blood purification therapy OR mortality in All Text - in Trials (Word variations have been searched)

The total amount of the studies are 7249 in which the duplication number is 2462, leading 4878 records to be screened.

2. PRISMA checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Yes, as supplementary appendix subheading 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg. 10-11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg.10, supplementary appendix subheading 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary appendix subheading 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg.11, Supplementary appendix subheading 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg.11-12
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 14
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg. 12
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg.13-14
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg.15
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Supplement table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Supplement table 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg.14-16
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg.14-16
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg.15-16
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Supplementary appendix 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg.15
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure1, Pg.16-18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary appendix 5
Study characteristics	17	Cite each included study and present its characteristics.	Supplement table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pg.18 Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pg.18-21, Figure 3-4, Supplement Figure 1-8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg.17
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg.18-21, Figure 3-4, Supplement Figure 1-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg.23-25, Supplement Figure 1-8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg.24-25
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg. 25
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplementary appendix 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg.26-27
	23b	Discuss any limitations of the evidence included in the review.	Pg.30-31
	23c	Discuss any limitations of the review processes used.	Pg.30-31
	23d	Discuss implications of the results for practice, policy, and future research.	Pg.25-26
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg.5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg.5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg.35
Competing interests	26	Declare any competing interests of review authors.	Pg.35
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pg. 35

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71 10.1136/bmj.n71

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PRISMA checklist for abstract

PRISMA 2020 for Abstracts Checklist

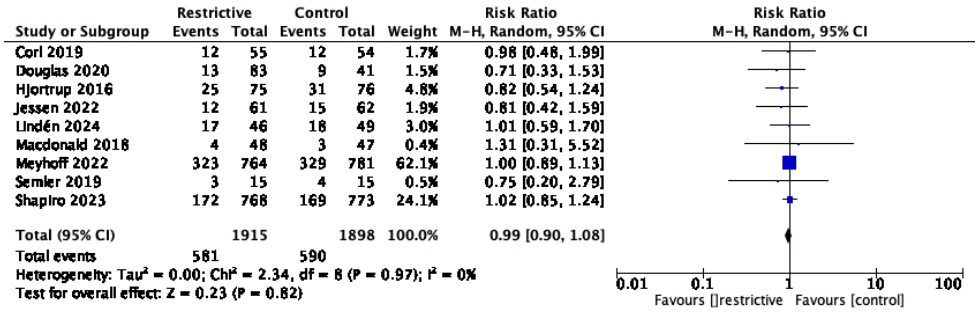
Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

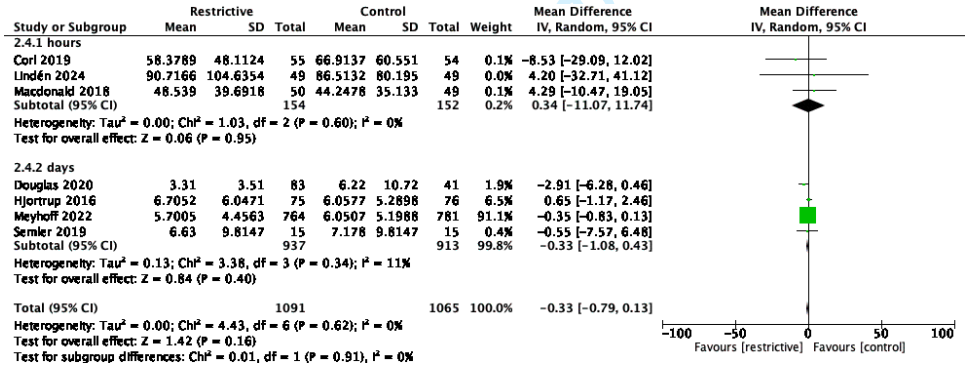
For more information, visit: http://www.prisma-statement.org/

3. Other supplementary Figures

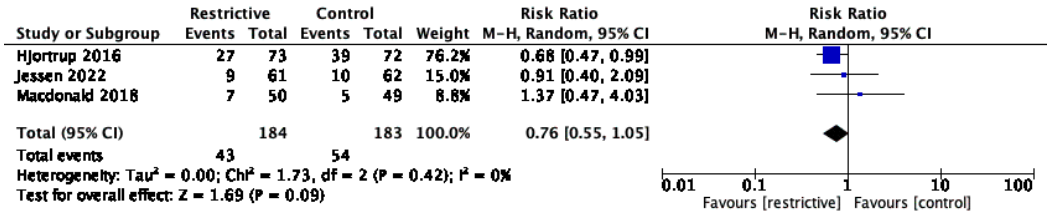
Supplement Figure 1. Forest plot for mortality at most protracted time point available



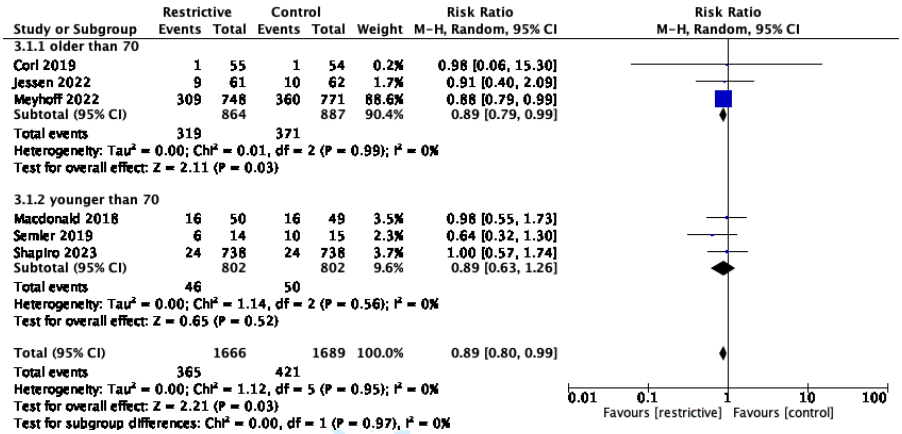
Supplement Figure 2. Forest plot for the ICU length of stay(LOS). The result was compared in two measurements, one in hours and one in days.



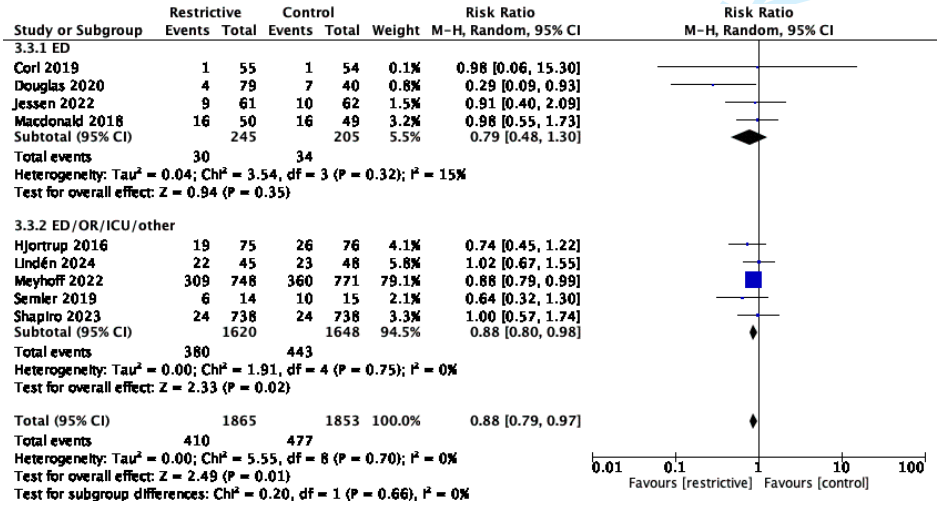
Supplement Figure 3. Forest plot for the incidence of worse AKI.



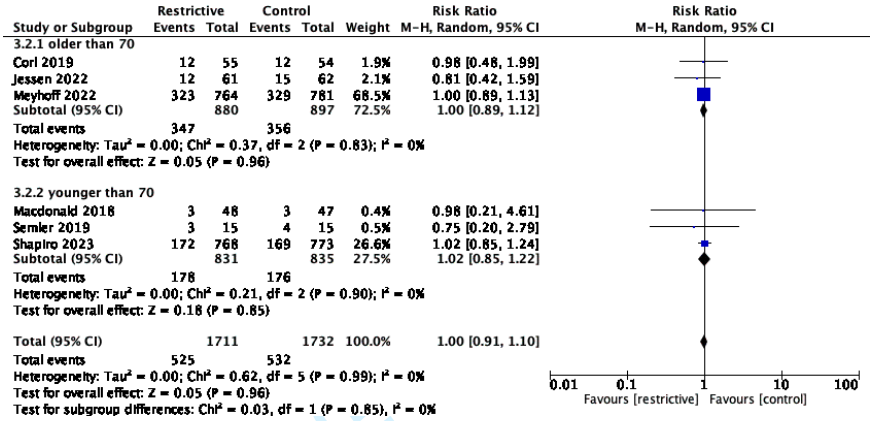
Supplement Figure 4. Forest plot for subgroup analysis on the influence of age on severe AKI. The result was focused on the influence of the factor of age on the incidence of severe AKI in patients in 2 group.



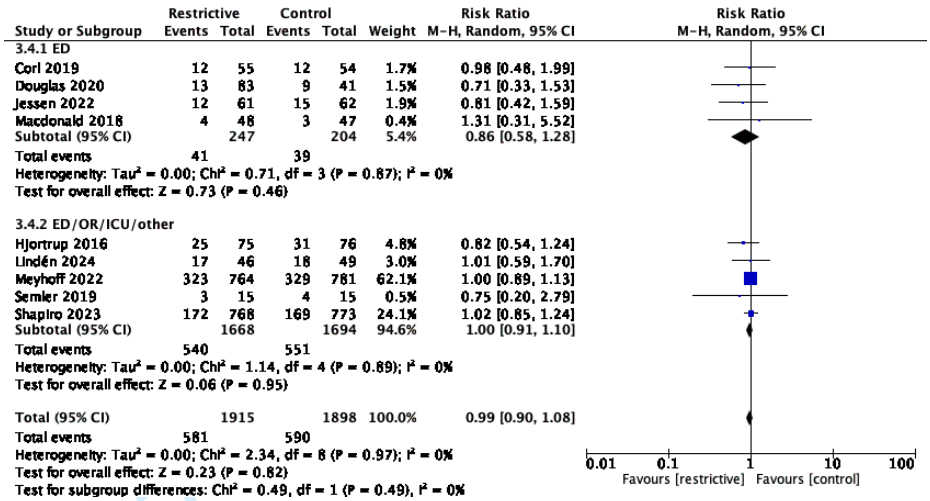
Supplemental Figure 5. Forest plot for the influence of initial places the patients were admitted into on severe AKI. This figure showed the results of the subgroup analysis on the influence of the initial places where the patients stayed before admitted into the ICU before randomization, which was focused on the incidence of severe AKI in patients in 2 group.



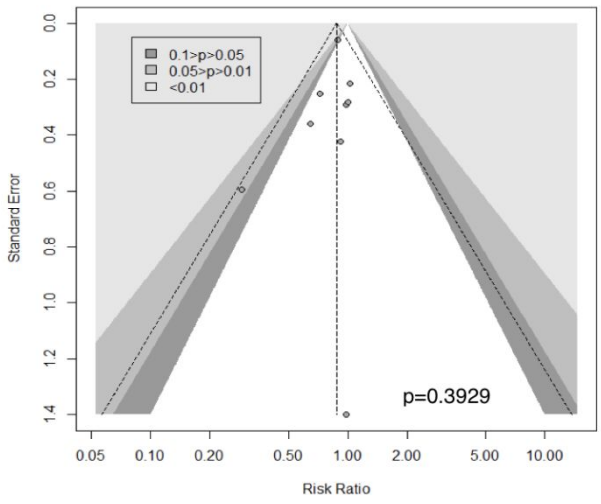
Supplement Figure 6. Forest plot for subgroup analysis on the influence of age on mortality. The result was focused on the influence of the factor of age on mortality of patients.



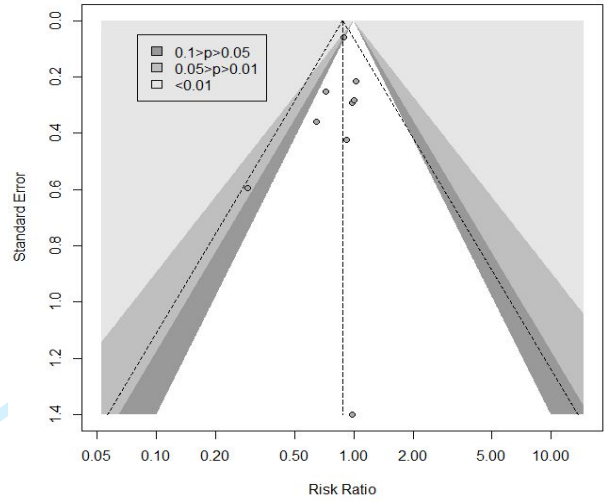
Supplemental Figure 7. Forest plot for the influence of initial places the patients were admitted into on mortality. This figure showed the results of the subgroup analysis on the influence of the initial places where the patients stayed before admitted into the ICU before randomization, which was focused on the mortality in patients in 2 group.



Supplement Figure 8. Funnel plot for the incidence of severe AKI. The result of Egger linear regression test (A1) and trim-and-fill (A2) showed a P-value of 0.3929 (P>0.05), meaning that no significant publication bias was detected.



A1. incidence of severe AKI



A2. incidence of severe AKI(trim-and-fill)

4. Summary of contextual factor data

For analysis of the effects of restrictive fluid resuscitation therapy on patients with septic shock, 9 randomized controlled trials were included into this meta-analysis. The studies contained a total amount of 3718 participants.

Meyhoff et al (2022) enrolled 1554 patients. During the 90-day trial in the ICU, excluding fluids administered with medication and nutrition, the restrictive-fluid group received a median of 1798 ml of intravenous fluid (interquartile range, 500 to 4366); the standard-fluid group received a median of 3811 ml (interquartile range, 1861 to 6762). Severe acute kidney injury was defined as a modified classification of stage 2 or higher according to Kidney Disease: Improving Global Outcomes (KDIGO) on a scale ranging from 1 to 3, with higher stages indicating more severe kidney injury. The incidence of severe AKI was 309 out of 748 (41.3%) in restrictive-fluid group and 360 out of 771 (46.7%).

Macdonald et al (2018) enrolled 99 patients. Median volumes administered from ED arrival to 6 h post randomization were 2387 ml (30 ml/kg) in the restricted volume arm, and 3000 ml (43 ml/kg) in the usual care arm ($p<0.001$). At 24 h respective median cumulative volumes were 3543 ml (40 ml/kg) and 4250 ml (61 ml/ kg), $p=0.005$. The incidence of severe AKI was defined as score 2 or higher according to patients' peak acute kidney injury network (AKIN) score to day 7. The number was 16 out of 50 (32%) in restricted volume group and 16 out of 49 (32.7%) in usual care group.

Hjortrup et al (2016) enrolled 151 patients. During ICU stay after randomization, excluding fluids administered with medication and nutrition, the fluid restriction group received a median of 500 ml of intravenous fluid (interquartile range, 0 to 3250); the standard-fluid group received a median of 2200 ml (interquartile range, 1000 to 4750), p<0.001. Severe acute kidney injury was defined as a modified classification of stage 2 or higher according to the KDIGO criterion. The number of worsening of AKI in patients was 19 out of 73 (26.0%) in fluid restriction group and 26 out of 72 (36.1%) in standard care group.

Corl et al (2019) enrolled 109 patients. During the first 72 hours of care, the restrictive group received significantly less resuscitative IV fluid than the usual care group (47.1 vs 61.1mL/kg; p = 0.01). Severe acute kidney injury defined as a doubling in the triage creatinine. The number of AKI was 1 out of 55 (1.8%) in restrictive fluid group and 1 out of 54 (1.9%) in standard care group, p>0.99.

Semler et al (2019) enrolled 30 patients. Over the course of the trial, patients in the usual care group received a mean volume of fluid from IV boluses of 733 (1083) compared with 300 (560) in the conservative fluid management group (P=0.30). Severe acute kidney injury defined as was defined as stage 2 and 3 on a modified Kidney Disease: Improving Global Outcomes (KDIGO). The number of severe AKI was 6 out of 14 (42.8%) in conservative group and 10 out of 15 (66.7%) in usual care group.

Douglas et al (2020) enrolled 124 patients. Both arms received a similar volume of

resuscitation fluid prior to enrollment (2.4 ± 0.6 L Intervention arm compared to 2.2 ± 0.7 L Usual Care arm). Positive fluid balance at 72 hours or ICU discharge, was significantly less in the Intervention arm (-1.37L favoring Intervention arm, 0.65 ± 2.85L Median: 0.53L Intervention arm vs. 2.02 ± 3.44L Median: 1.22L Usual Care arm, p=0.02). Severe AKI was defined as initiation of renal replacement therapy. The number was 4 out of 79 (5.1%) in restrictive fluid group and 7 out of 40 (17.5%) in standard care group.

Lindén et al (2024) enrolled 98 patients. Median total volume of fluid in the first three days, was 6008 ml (interquartile range [IQR] 3960–8123) in the restrictive fluid group (n = 44), and 9765 ml (IQR 6804–12,401) in the control group (n = 48); corresponding to a Hodges–Lehmann median difference of 3560 ml [95% confidence interval(CI) 1614–5302]; p < 0.001). Severe acute kidney injury defined as was defined as stage 2 and 3 on a modified Kidney Disease: Improving Global Outcomes (KDIGO). The number of severe AKI was 22 out of 45 (48.9%) in restrictive fluid group and 23 out of 48 (47.9%) in usual care group.

Jessen et al (2022) enrolled 123 patients. At 24 h, the mean (±SD) IV crystalloid fluid volumes were 562 (±1076) ml versus 1370 (±1438) ml in the restrictive versus standard care group (mean difference –801 ml, 95% CI −1257 to −345 ml, p = 0.001). Severe AKI was defined as any development or worsening of acute kidney injury, defined as the KDIGO creatinine score > 0 compared to at randomization. The number was 9 out of 61 (14.8%) in restrictive fluid group and 10 out of 62 (16.1%)

in standard care group.

Shapiro et al (2023) enrolled 1563 patients. Resuscitation therapies that were administered during the 24-hour protocol period differed between the two groups; less intravenous fluid was administered in the restrictive fluid group than in the liberal fluid group (difference of medians, −2134 ml; 95% CI −2318 to −1949), whereas the restrictive fluid group had earlier, more prevalent, and longer duration of vasopressor use. Severe AKI was defined as initiation of renal replacement therapy. The number was 24 out of 738 (3.3%) in restrictive fluid group and 24 out of 738 (3.3%) in standard care group.

5. List of citation of excluded potential studies and the reasons to rule out them

5.1No AKI

1)No data on the numbers of AKI patients was found in the following article. Communication with the corresponding author didn't provide enough information in time.

[1] B. M. E. Noureldin, M. Mohamed, N. El shafei, F. A. A. Markos and R. M. S. Ahmed. Comparative Study between Restrictive versus Liberal Intravenous Fluid Administration in Severe Sepsis and Septic Shock; A Randomized Clinical Trial. QJM: an international journal of medicine 2023 Vol. 116 Pages i40-i41. DOI: 10.1093/qjmed/hcad069.093

2) The following were titles and accession numbers of the trial protocol we found in the literature search. The titles and abstracts convinced us the trials were focused on the topic concerning our study, but neither full-text nor information about AKI could be retrieved. The protocol containing their outcomes didn't included indicators about AKI neither.

[2] An Open-label Randomized Controlled Study on the Effects of different Net Ultrafiltration Strategy on Fluid Balance and Prognosis in Patients with Septic Shock [online]. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR 2400083804.

[3] Controlled Fluid Resuscitation Strategy in Sepsis Patient [online]. 2017. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-INR-17011928.

[4] Restrictive Intravenous Fluids Trial in Sepsis [online]. 2017. https://clinicaltrials.gov/show/NCT03137446

3) No data on AKI was found in these articles' full text.

[5] OPTImized Restrictive Strategy Targeting Non-Resuscitative FLUIDs in Septic Shock: pilot Study [online]. https://clinicaltrials.gov/ct2/show/NCT04947904.

[6] Optimized fluid resuscitation strategy for septic shock guided by microcirculation [online]. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2200056310.

[7] W. Zhang. Critical Care Ultrasound Goal-directed Versus Early Goal-directed Therapy in Septic Shock: a Randomized Controlled Study. Intensive care medicine experimental 2021 Vol. 9 Issue SUPPL 1. DOI: 10.1186/s40635-021-00413-8

5.2 No mortality

No data on mortality of patients was mentioned in the following articles, or in the outcomes planned in the trial protocol.

[8] Aung NM, Kaung M, Kyi TT, et al. The Safety of a Conservative Fluid Replacement Strategy in Adults Hospitalised with Malaria. PLoS One. 2015 Nov 18;10(11):e0143062. doi: 10.1371/journal.pone.0143062. PMID: 26581060; PMCID: PMC4651424.

5.3 Perioperative period

The trials were conducted on patients undergoing elective surgery, and the fluid therapy was performed during the perioperative period.

[9] Koers L, van Haperen M, Meijer CGF, et al. Effect of Cognitive Aids on Adherence to Best Practice in the Treatment of Deteriorating Surgical Patients: A Randomized Clinical Trial in a Simulation Setting. JAMA Surg. 2020 Jan 1;155(1):e194704. doi: 10.1001/jamasurg.2019.4704. Epub 2020 Jan 15. PMID: 31774483; PMCID: PMC6902237.

[10] Healy MA, McCahill LE, Chung M, et al. Intraoperative Fluid Resuscitation Strategies in Pancreatectomy: Results from 38 Hospitals in Michigan. Ann Surg Oncol. 2016 Sep;23(9):3047-55. doi: 10.1245/s10434-016-5235-y. Epub 2016 Apr 26. PMID: 27116681.

[11] Alimian M, Mohseni M, Moradi Moghadam O, et al. Effects of Liberal Versus Restrictive Fluid Therapy on Renal Function Indices in Laparoscopic Bariatric Surgery. Anesth Pain Med. 2020 Oct 20;10(5):e95378. doi: 10.5812/aapm.95378. PMID: 34150556; PMCID: PMC8207848.

[12] Behman R, Hanna S, Coburn N, et al. Impact of fluid resuscitation on major adverse events following pancreaticoduodenectomy. Am J Surg. 2015 Nov;210(5):896-903. doi: 10.1016/j.amjsurg.2015.04.020. Epub 2015 Jul 17. PMID: 26255229.

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versus restrictive normovolemic therapy in major open abdominal surgery: A randomized controlled trial. Surgery. 2021 May;169(5):1164-1174. doi: 10.1016/j.surg.2020.09.035. Epub 2020 Nov 2. PMID: 33143931.

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[17] Guan Z, Gao Y, Qiao Q, et al. Effects of intraoperative goal-directed fluid therapy and restrictive fluid therapy combined with enhanced recovery after surgery protocol on complications after thoracoscopic lobectomy in high-risk patients: study protocol for a prospective randomized controlled trial. Trials. 2021 Jan 7;22(1):36. doi: 10.1186/s13063-020-04983-y. PMID: 33413593; PMCID: PMC7792083.

[18] Hendrix RJ, Damle A, Williams C, et al. Restrictive Intraoperative Fluid Therapy is Associated with Decreased Morbidity and Length of Stay Following Hyperthermic Intraperitoneal Chemoperfusion. Ann Surg Oncol. 2019 Feb;26(2):490-496. doi: 10.1245/s10434-018-07092-y. Epub 2018 Dec 4. PMID:

30515670.

[19] Sahmeddini MA, Janatmakan F, Khosravi MB, et al. Restricted Crystalloid Fluid Therapy during Orthotopic Liver Transplant Surgery and its Effect on Respiratory and Renal Insufficiency in the Early Post-operative Period: A Randomized Clinical Trial. Int J Organ Transplant Med. 2014;5(3):113-9. PMID: 25184031; PMCID: PMC4149738.

[20] Fluid restriction following open aortic aneurysm surgery [online]. 2010. https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN52446152

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[27] Effect of Intraoperative Fluid Restriction on Postoperative Outcomes in Video-assisted Thoracic Surgery (VATS) [online]. 2019. https://clinicaltrials.gov/show/NCT00854386.

[28] Intraoperative Fluid Management in Laparoscopic Bariatric Surgery [online]. 2009.https://clinicaltrials.gov/show/NCT00905502.

[29] Restricted Intravenous Fluid Regime Effects on Immunological Indicators of Elderly Patients Operated for Abdominal Cancer [online]. 2011.

https://clinicaltrials.gov/show/NCT01399814.

[30] Impact of Perioperative Intravenous Fluid Utilization on Postoperative Outcomes [online]. 2012. https://clinicaltrials.gov/show/NCT01563991.

[31] Comparison of Stroke Volume Variation-guided Normovolemic and Restrictive Fluid Management During Craniotomy: a Randomized Controlled Trial [online]. 2014. https://clinicaltrials.gov/show/NCT02113358.

[32] Evaluating Fluid Strategies in Thoracic Surgery Patients Utilizing a Goal Directed Approach [online]. 2014. https://clinicaltrials.gov/show/NCT02135146.

[33] Restrictive or Individualized Goal-Directed Fluid Replacement Strategy in Ovarian Cancer Cytoreductive Surgery [online] 2016. https://clinicaltrials.gov/show/NCT03519165.

[34] Brandstrup B, Svendsen PE, Rasmussen M, et al. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? Br J Anaesth. 2012 Aug;109(2):191-9. doi: 10.1093/bja/aes163. Epub 2012 Jun 17. PMID: 22710266.

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hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time: a randomized clinical trial. Anesthesiology. 2014 Feb;120(2):365-77. doi: 10.1097/ALN.0b013e3182a44440. PMID: 23887199.

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5.5 Other disease

The trials or trial protocols were designed to focus on patients with other diseases rather than septic shock., And they didn't include a clear subgroup analysis on septic shock.

[49] Conservative versus liberal fluid therapy in patients with liver disease admitted to the intensive care unit [online]. 2015. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12615000377538.

[50] Conservative use of intravenous fluid in critically ill adults - pilot study [online]. 2016. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12616001670460.

[51] Does conservative fluid therapy compared to usual care change the outcomes in critically ill patients with acute kidney injury [online]. 2022. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12622000030774.

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6. The GRADE results

Supplement Figure 9. The GRADE assessment results. The results demonstrated moderate confidence in the findings on incidence of severe AKI, as well as the results of all second outcomes except the ICU LOS, which received limited confidence. And the result of incidence of worse AKI was rated as of high certainty.

Author(s):
Question: Restrictive fluid resuscitation compared to liberal fluid resuscitation in sepsis associated hypotension and shock
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	restrictive fluid resuscitation	liberal fluid resuscitation	Relative (95% CI)	Absolute (95% CI)		
incidence of severe AKI												
9	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	410/1863 (22.0%)	477/1849 (25.8%)	**RR 0.88** (0.79 to 0.97)	**31 fewer per 1,000** (from 54 fewer to 8 fewer)	⨁⨁⨁◯ Moderate[a,b]	
mortality												
9	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	581/1915 (30.3%)	590/1898 (31.1%)	**RR 0.99** (0.90 to 1.08)	**3 fewer per 1,000** (from 31 fewer to 25 more)	⨁⨁⨁◯ Moderate[a,b]	
ICU LOS												
7	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1091	1065	-	MD **0.33 lower** (0.79 lower to 0.13 higher)	⨁⨁◯◯ Low[a,b]	
incidence of worse AKI												
3	randomised trials	not serious[a]	not serious	not serious	not serious	none	43/184 (23.4%)	54/183 (29.5%)	**RR 0.76** (0.55 to 1.05)	**71 fewer per 1,000** (from 133 fewer to 15 more)	⨁⨁⨁⨁ High[a]	
duration of ventilation												
3	randomised trials	not serious[a]	not serious	not serious	serious[a,b]	none	188	144	-	MD **41.14 lower** (68.8 lower to 13.48 lower)	⨁⨁⨁◯ Moderate[a,b]	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Blinding of participants and personnel(performance bias) and blinding of outcome assessment(detection bias) of all 5 trials were serious.
b. The variation between the numbers of participants in the trials was considerable.

7. Table of characteristics of included studies

Supplement Table 1. Characteristics of included studies

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Meyhoff , 2022	Denmark & Norway & Sweden & Switzerland & Italy & Czech Republic & United Kingdom & Belgium & Finland	31	1554	1798(500 to 4366) after 90 days	3811 (1861 to 6762) after 90 days	death within 90 days after randomization	1.suspected or confirmed infection, a plasma lactate level of 2 mmol per liter (18 mg per deciliter) or higher, receipt of ongoing infusion of a vasopressor or inotropic agent, and receipt of at least 1 liter of intravenous fluids in the 24 hours before screening.13 Patients were included if the onset of shock had been within 12 hours before screening.	A new episode of severe acute kidney injury, as defined by a modified kidney disease: Improving Global Outcomes (KDIGO) stage of 3 on a scale ranging from 1 to 3, with higher stages indicating more severe kidney injury, and the use of a modified classification because urinary output data might not have been available from all patients

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Macdonald,2018	Australia & New Zealand	8	99	2387 (1750 to 2750), 30(32 to 39) ml/kg from presentation to 6h	3000 (2250 to 3900), 43(35 to 50) ml/kg from presentation to 6h	Total fluid administered within 6h post randomization	1.Suspected infection 2. Systolic blood pressure (SBP) <100mmHg*, despite 1000ml intravenous isotonic crystalloid administered over no more than 60 minutes AND 3. Study intervention can be administered within 2 hours of inclusion criteria being met	the Acute Kidney Injury Network (AKIN) criteria based upon creatinine data. Baseline serum creatinine was defined as a stable serum creatinine recorded in the 12 months pre-randomization, or a convalescent creatinine up to 3 months post-randomization. Where no baseline creatinine was available this was estimated using the MDRD formula assuming GFR 75ml/min/1.73m^2

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Hjortrup,2016	Denmark	9	151	500(0 to 2500) for the first 5 days, 500(0 to 3250) during ICU stay after randomization	2000(1000 to 4100) for the first 5 days, 2200(1000 to 4750) during ICU after randomization	the amount of resuscitation fluid in the first 5 days after randomization and during the entire ICU stay	1. adult ICU(≥18yrs) 2.Sepsis defined as at least 2 of 4 SIRS criteria fulfilled within 24 hours according to the College of Critical Care Medicine/American College of Chest Physicians (SCCM/ACCP) 2.Suspected or confirmed site of infection OR positive blood culture 3.Suspected or confirmed circulatory impairment (hypotension/hypoperfusion/hypovolemia) for no more than 12 hours including the hours preceding ICU admission. Circulatory impairment defined as at least one of the following: Systolic blood pressure < 90 mmHg, heart rate > 140 beats/min, lactate ≥ 4 mmol/l, OR use of vasopressors. 4.At least 30 ml/kg ideal bodyweight fluid (colloids, crystalloids or blood products) given in the last 6 hours 5. Shock defined as ongoing infusion of noradrenaline (any dose) to maintain blood pressure	The KDIGO criteria (values of plasma creatinine were assessed in ICU and the use of renal replacement therapy in the 90 days after randomization; the urinary output criteria were not assessed). For patients without AKI at baseline, development of AKI after randomization was regarded as worsening of AKI.

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Corl,2019	America	2	109	(mean ± sd) 47.1±22.3ml/kg of total resuscitation IV fluid	(mean ± sd) 61.1±32.0ml/kg of total resuscitation IV fluid	30-day all-cause mortality	1. Patients with severe sepsis or septic shock, as defined by the 2012 2 International Consensus definitions: temperature > 38°C or < 36°C, heart rate of >90/min, respiratory rate of >20/min or PaCO2 <32 mmHg, white blood cell count >12000/mm3 or < 4000/mm3 or >10% immature bands, with known or suspected infection at the time of enrollment. The worst value for each variable is used obtained between triage time zero and enrollment. Since over 12% of patients ultimately diagnosed with sepsis do not meet SIRS criteria, SIRS negative patients may be enrolled if the treating attending physician clinically diagnoses severe sepsis or septic shock. 3. Severe sepsis or septic shock is defined as refractory hypotension or a lactic acid>4 mmol/L. Refractory hypotension is a systolic blood pressure (SBP)<90 mmHg or a mean arterial pressure (MAP)<65 mmHg for 15 minutes, following 1000 mL of IV fluid, or any blood pressure maintained by vasopressor administration.	Doubling in the triage creatinine from the first recorded value during the study period
Semler,2019	America	1	30	mean of fluid from IV boluses of 300 (560) in the 3 days after enrollment	mean of fluid from IV boluses of 733(1083) in the 3 days after enrollment	mean daily fluid balance (phase II) and ICU-free days (phase III)	Adults (age ≥18 years) admitted to the medical ICU at Vanderbilt University Medical Center who met 2 or more criteria for systemic inflammatory response syndrome, were receiving antimicrobial therapy, and met criteria either for shock (defined as a mean arterial pressure <60 mm Hg or vasopressor receipt) or respiratory insufficiency (defined as receipt of invasive or noninvasive mechanical ventilation or an arterial oxygen saturation <97% while receiving a fraction of inspired oxygen [FiO2] ≥0.3	The KDIGO criteria

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Douglas,2020	America & United Kingdom	13	124	Positive fluid balance at 72 hours or ICU discharge: -1.37L favoring Intervention arm, 0.65 ± 2.85L Median: 0.53L Intervention arm	Positive fluid balance at 72 hours or ICU discharge: 2.02 ± 3.44L Median: 1.22L Usual Care arm	positive fluid balance at 72 hours or ICU discharge, whichever occurred first.	Patients presenting to the Emergency Department with sepsis or septic shock (defined as 2 or more systemic inflammatory response syndrome (SIRS) criteria and a suspected or documented infection) and anticipated ICU admission. Other inclusion criteria included refractory hypotension, (mean arterial pressure < 65mmHg after receiving ≥ 1L and ≥ 2L of fluid) and enrollment within 24 hours of hospital arrival	Initiation of renal replacement therapy which could be count as KDIGO stage 3
Lindén,2024	Switzerland	6	98	6008 ml (interquartile range [IQR] 3960–8123)	9765 ml (IQR 6804–12,401)	the total volume of fluid administered within three days of inclusion	Adult patients (≥18 years of age) with septic shock (suspected/confirmed infection, plasma lactate>2 mmol/l and infusion of vasopressor to maintain MAP > 65 mmHg after adequate fluid resuscitation) within 12-h of admission to the ICU and ongoing vasopressor therapy at the time of inclusion were eligible for inclusion	The KDIGO criteria
Jessen,2022	Denmark	3	123	mean (±SD) IV crystalloid fluid volumes of 562 (±1076) ml at 24-h after randomization	mean (±SD) IV crystalloid fluid volumes of 1370 (±1438) ml at 24-h after randomization	total IV crystalloid fluid volumes at 24 h after randomization	1. unplanned ED admission; 2. age ≥ 18 years; 3. sepsis defined as (1) infection suspected by the treating clinician, (2) blood cultures drawn, (3) IV antibiotics administered or planned, and (4) an infection- related increase in the SOFA score ≥ 2; and 4. expected hospital stay > 24-h as deemed by the treating clinician	Any development or worsening of acute kidney injury, defined as the KDIGO creatinine score > 0 compared to at randomization

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Shapiro,2023	America	60	1563	IQR 500ml (130 to 1097) of IV fluid administration after 6-h after randomization, 1267ml (555 to 2279) after 24-h	IQR 2300ml (2000 to 3000) of IV fluid administration after 6-h after randomization, 3400ml (2500 to 4495) after 24-h	all-cause mortality before discharge home by day 90	Adult patients (≥18 years of age) with a suspected or confirmed infection (broadly defined as the administration or planned administration of antibiotic agents) and sepsis-induced hypotension (systolic blood pressure, <100 mm Hg after the administration of ≥1000 ml of intravenous fluid)	The KDIGO criteria

BMJ Open

The effect of restrictive fluid resuscitation on severe acute kidney injury in septic shock: A systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086367.R2
Article Type:	Original research
Date Submitted by the Author:	22-Jan-2025
Complete List of Authors:	Cai, Xin-Er; Southeast University Medical College, Ling, Wan-Ting; Southeast University Medical College Cai, Xiao-Tian; Southeast University Medical College Yan, Ming-Kun; Southeast University Medical College Zhang, Yan-Jie; Southeast University Medical College Xu, Jing-Yuan; Southeast University,
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Medical management
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Acute renal failure < NEPHROLOGY, Mortality

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The effect of restrictive fluid resuscitation on severe acute kidney injury in septic shock: A systematic review and meta-analysis

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Abstract

Objectives: Sepsis associated hypotension or shock is critical stage of sepsis, and a current clinical emergency that has high mortality and multiple complications. A new restrictive fluid resuscitation therapy has been applied, and its influence on patients' renal function remains unclear. The purpose of this study is to evaluate the influence of restrictive fluid resuscitation on incidence of severe acute kidney injury(AKI) in adult patients with sepsis hypotension and shock compared with usual care.

Design: Systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Data sources: Pubmed, Embase, Web of Science and Cochrane Library were searched through 1 November 2024.

Eligibility criteria: We included randomized controlled trials that compared restrictive fluid resuscitation with liberal fluid therapy on patients with sepsis associated hypotension and shock, to find out their effect on the incidence of severe acute kidney injury(AKI). Severe AKI was defined as the acute kidney injury network (AKIN) score 2 to 3 or Kidney Disease Improving Global Outcomes (KDIGO) stage of 2 and 3.

Data extraction and synthesis: Two independent reviewers used standardized methods to search, screen and code included trials. Risk of bias was assessed using the Cochrane Systematic Review Handbook for randomized clinical trials. Meta-analysis was conducted using random effects models. Sensitivity and subgroup analyses, trial sequential analysis (TSA), plus Egger's test and the trim-and-fill

method were performed. Findings were summarized in GRADE evidence profiles and synthesized qualitatively.

Results: 9 trials (3718 participants) were included in this research and the analysis was conducted in random effects model. There was a significant difference in the incidence of severe AKI (RR 0.88, 95%CI 0.79 to 0.97, P=0.01; I^2=0%) and the duration of mechanical ventilation (Mean Difference -41.14, 95%CI -68.80 to -13.48; P=0.004; I^2=74%) between patients receiving restrictive fluid resuscitation and patients receiving liberal fluid resuscitation. TSA showed that the cumulative amount of participants met the required information size (RIS), the positive conclusion had been confirmed. The GRADE assessment results demonstrated moderate confidence on incidence of severe AKI, as well as the results of all second outcomes except the ICU LOS, which received limited confidence. And the result of incidence of worse AKI was rated as of high certainty.

Conclusions: It is conclusive that fluid restriction strategy is superior to usual care when it comes to reducing the incidence of severe acute kidney injury in sepsis associated hypotension and shock. Shorter duration of ventilation is concerned with

fluid restriction as well, but the heterogeneity is substantial. GRADE assessments confirmed moderate and above certainty. Traditional fluid resuscitation therapy has the potential to be further explored for improvements to be more precise and appropriate for a better prognosis.

Trial registration

This study was retrospectively registered at the PROSPERO (International prospective register of systematic reviews) website on 29 July 2023 and the ID was CRD42023449239.

Keywords: Septic shock, Restrictive fluid resuscitation, Acute kidney injury, Mortality

Strengths and limitations of this study

- The search strategy ensured that the vast majority of relevant studies in the focused area were thoroughly reviewed.
- To evaluate the heterogeneity, we conducted comprehensive subgroup and sensitivity analysis.

- To confirm the reliability of the results, we used various approaches such as TSA, GRADE assessments and the Egger's test.
- Number of included participants was a bit small, but the TSA result confirmed it has reached RIS.
- When extracting the data, we countered some different definitions, but conducted other analysis to reduce the risk of bias.

Introduction

Septic shock is defined as a subset of sepsis in which potential circulatory, cellular, and metabolic damages are serious and profound enough to increase the risk of mortality[1]. It is a common clinical emergency characterized by refractory hypotension, hyperlactatemia and organ dysfunction, which occurs in more than 230,000 US patients each year, leading to over 40000 deaths annually[2][3], and affecting millions of people around the world each year[4]. AKI is a common complication in critical ill patients with sepsis and/or septic shock[5][6]. When septic shock and AKI are present simultaneously, the mortality rate is up to nearly 50%[7]. And patients with severe AKI have a high risk of stabilizing the situation of chronic

kidney disease (CKD) or progress to complete organ failure and compulsive dialysis requirement[8][8]. This would cause serious health and financial burden on the patients. When it comes to sepsis associated hypotension and septic shock, intravenous fluid resuscitation is a very common therapy in the initial treatment. It aims to increase depleted or functionally reduced intravenous volume that occurs in sepsis owing to a vasodilated vascular network. Initial fluid therapy can augment macrovascular perfusion and microvascular perfusion and counter organ hypo-perfusion[1][9]. And AKI under the circumstance of vascular changes in septic shock is more related to pre-renal factors instead of post-renal or intra-renal, specifically due to micro-vascular abnormalities sand tubular stress[3]. Therefore correction of intravascular hypovolemia is a key component of the prevention and management of AKI in septic shock as well.

But in the case of increased endothelial cell permeability, excessive infusion can exacerbate organ dysfunction[10]. Excessive fluid administration is believed to be associated with development and progression of AKI, so individualized fluid therapy has been taken into consideration, taking into account patients' characteristics, origin

of patients' kidney dysfunction and risks and benefits of fluids. Therefore, this complex situation attached great importance to the choice of fluid resuscitation. A new strategy called restrictive fluid strategy, which is a resuscitating therapy of lower volumes of fluid and earlier initiation of vasopressor agents, are to be taken into consideration. But there is still insufficient evidence to make a recommendation on the use of restrictive or liberal fluid strategies in patients with sepsis associated hypotension and shock who still have sighs of hypo-perfusion and volume depletion after initial resuscitation[9]. A resent pilot multicenter, randomized, controlled trial of critically ill patients with AKI proved that a restrictive fluid management regimen was feasible[12]. Although whether restrictive fluid therapy has a positive impact on septic patients' kidney function is not supported by strong evidence, it is commonly believed that fluid overload has deleterious impact on renal function balance.

The impact restrictive fluid resuscitation therapy has on the incidence of severe AKI may lay out some priority. When combined with severe kidney dysfunction, the mortality and ICU length of stay of patients with higher AKIN score all rise significantly comparing to patients with lower AKIN score, whether the patients had

sepsis or not[13]. It is a much more serious and emergent situation of the kidney function of the patients that needs urgent recognition and treatment. As intravenous fluid and vasopressor application both have an impact on the patients' organ and tissue perfusion, the renal situation should be taken into consideration.

A large-scale randomized controlled trial (RCT) conducted by Meyhoff et al.[14] has shown that little statistical difference was found in the incidence of AKI in sepsis patients undergoing restrictive fluid resuscitation therapy. This study, with its robust design and large sample size, has provided valuable insights into the safety of restrictive fluid management. However, it is only one study within a broader and more complex clinical context. There is a critical need to synthesize evidence from other relevant studies to determine whether the findings are consistent across different populations, settings, and methodologies. A comprehensive meta-analysis can provide a more definitive understanding of the impact of this fluid strategy.

This meta-analysis is conducted in the aim of resolving the existing uncertainties and investigating the effect of the restrictive fluid resuscitation strategy on the occurrence

of severe acute kidney injury in adult patients with sepsis associated hypotension and septic shock.

Materials and methods

This study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement methodology[15], a systematic review and meta-analysis of randomized clinical trials. The study was registered at the PROSPERO (International prospective register of systematic reviews) website and the ID was CRD42023449239.

Patient and public involvement

As this is a systematic review and meta-analysis, we completed this research by searching papers through Internet, extracting relevant data from included trials and working on the data statistically. No patients or public involvement were involved in this research directly.

Search strategy and selection of studies

A literature search of PubMed, Web of science, Embase and Cochrane library was undertaken to identify randomized clinical trials. The searches were last updated on

1 November 2024. The search terms used were “acute kidney injury” or “acute kidney failure” or “acute renal failure” or “continuous renal replacement therapy” or “blood purification therapy” or “mortality”, and “restrictive fluid” or “resuscitation”. The search and reviewing of all the articles were conducted by two reviewers (XEC and XTC) independently. When encountered disagreements, a third reviewer (WTL) would provide a suggestion.

Title and abstract screening was conducted for all relevant studies and potentially relevant records were thoroughly read. The inclusion criterions were as follows: 1) the research was limited to randomized clinical trials only, 2) studies conducted on adult patients (≥18 years) who were diagnosed as septic shock, 3) trials where the intervention assessed was restrictive fluid resuscitation therapy or conservative fluid strategy versus liberal or conventional fluid resuscitation, 4) studies that contained the data of numbers of patients who countered AKI, or the mortality. Trials with the following features were excluded: 1) studies enrolling pregnant patients, 2) studies in which most patients had systematic inflammatory response syndrome secondary to other causes such as burn or pancreatitis without a clear sepsis subgroup, 3) studies

that focused on patients undergoing elective surgery, or the therapy was carried out during perioperative period[16][17]. No date, publication status, languages or predefined outcome restriction were applied.

Data extraction and Synthesis

In this meta-analysis, primary outcome was severe AKI which was defined as acute kidney injury network (AKIN)[18] score 2 to 3 or Kidney Disease Improving Global Outcomes (KDIGO)[19] stage of 2 and 3[20]. Data including primary outcome were extracted by two reviewers (XEC and XTC). If there were disagreements, a discussion was performed with another reviewer (WTL).

Titles and abstract of all reports identified in the literature searches were screened for further review. The data collected form each study included 1) general information (author, year, study design), 2) characteristics of the participants (including gender, age, inclusion and exclusion criteria, initial places where they stayed before admitted into ICU and randomization, and the diagnosis criterions and diagnosing time point of septic shock), 3) outcomes, with primary outcome determined as incidence of severe AKI (with clear clarification of numbers of

patients of AKIN score 2 and 3, or KDIGO stage 2 and 3) and secondary outcomes as clinical outcomes including overall mortality (when there was more than one indicator concerning with the mortality of all participants at different times, the mortality of the longest period would be prioritized for inclusion in the meta-analysis), ICU LOS, the incidence of worse AKI (defined as higher stages of KDIGO criterion or higher scores of AKIN), and duration of ventilation.

When countering missing data, the author tent to contact authors of the relevant studies, and searched for other paper of the same trial. The reference lists of included randomized clinical trials were reviewed for additional trials meeting eligibility criteria.

Dichotomous variables were expressed as counts and proportions. Means and standard deviations (SDs) were used to describe normally distributed continuous variables. Because the ICU length of stay and ventilation time were not normally distributed, all studies involving the data reported the ICU LOS and duration of ventilation by using the median and the first and third quartiles. We estimated the

sample mean and standard deviation (SD) value based on the method of mean variance estimation presented by the Hong Kong Baptist University[21][22][23][24].

Study quality and risk of bias assessment

The risk of bias was assessed for each outcome in all included studies using the Cochrane Systematic Review Handbook for randomized clinical trials. The 9 studies were assessed as being at low, uncertain or high risk of bias for each of 6 domains. The internal validity of the included studies was assessed according to the Cochrane Collaboration methodology (the Cochrane Risk of Bias tool), which consists of 6 domains[25]. The results were output by using the Review Manager((RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.) software, which was applied in the statistical analysis as well. Two reviewers assessed study quality independently (XEC & XTC). If there were disagreements, a discussion was performed with another reviewer (WTL). 6 aspects were performed for assessing the risk of bias, including allocation concealment, random sequence generation, blinding, incomplete outcome data, selective reporting and other bias. Publication bias was evaluated by visual inspection of a funnel plot, and further checked by the Egger

linear regression test and a nonparametric trim-and-fill method[26], which was done by the R software (version 4.4.1) formally known as the R Project for Statistical Computing.

Outcome measures

The primary outcome was the incidence of severe AKI of all participants. Key secondary outcomes were all-cause mortality at the latest time of follow-up, ICU LOS, duration of ventilation and the full amount of patients developing worse AKI comparing to the situation of their first admission into the hospital.

Analysis

The meta-analysis was carried out by using a random effects model for outcomes for which two or more randomized studies were available. The results of outcomes were reported in the form of narrative and graphs. We used Risk Ratio(RR) with 95%CI for dichotomous outcomes (incidence of severe AKI, incidence of worse AKI, mortality) and Mean Difference(MD) with 95%CI for continuous outcomes (ICU LOS, duration of ventilation) to estimate the pooled effects. In all analyses, $P<0.05$ was considered significant, and statistically significant.

For key outcomes, we assessed the quality of evidence using the Grades of Recommendation, Assessment, Development and Evaluation(GRADE) approach[27].

The heterogeneity of these 9 studies was measured by the I^2 which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates that no heterogeneity is observed, 25%, 50%, and 75% represent low, moderate, and high levels of heterogeneity respectively[28].

A sensitivity analysis was performed by removing one study at a time to determine whether a specific trial had a higher contribution to the heterogeneity. Simultaneously we tested the analysis by including high-quality researches only to see if the results changed utterly[14][29][30][31]. Subgroup analysis was carried out to see if the following factors contributed to the result: enrolling patients with an average age ≥70 years or <70 years, places where the patients were admitted from (the emergency department (ED) only, or places including ED, hospital wards, the operation room (OR), and other ICU).

A trial sequential analysis (TSA) was performed to estimate the optimal sample size to reach a plausible conclusion on the research. We used Trial Sequential Analysis (TSA) [Computer program]. Version 0.9.5.10 Beta. The Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital – Rigshospitalet, 2021. Statistical significance was set at a P-value of 0.05.

Results

The search was conducted up to 1 November 2024. And the process of the search of literature is summarized and presented in **Figure 1**. A total of 7249 studies were retrieved from 4 databases and screened title and abstract for potential relevant researches. 2462 of records were removed for duplication first. 4787 records were identified as ineligible or irrelevant, leaving 90 records for full-text review. 9 studies met criteria for inclusion and were included in the quality assessment. At the end, all 9 randomized clinical trials were included into this meta-analysis covering 3718 participants. Details of the selection process were shown in **Figure 1**.

Description of included randomized trials

Sample sizes ranged from 29 to 1563. Three studies took place in the United State of America(USA), two in Denmark, one in Switzerland, one in Australia and New Zealand, one in the USA and United Kingdom. And one study took place in worldwide. All trials were conducted on adult patients and no pregnant patients were included. All 9 studies evaluated patients with septic shock. Further characteristics of the 9 chosen RCTs were summed up in **Supplement Table 1**. No heterogeneity was observed in these RCTs.

The overall quality of included RCTs was shown in **Figure 2**. The use of random sequence generation and allocation concealment and the risk of reporting bias were unclear in a number of studies. Confounding by indication and time-dependent exposure might have biased the studies[14].

Assessment of the risk of bias was summarized in **Figure 2**. Among the 9 RCTs, none of the trials were double blinded. The allocation may be blinded for the statistician. But it was obviously impossible to blind both patients and caregivers in the medical intervention of the trials, we proposed that the outcomes may not be

influenced by a lack of blinding. One trial was classified as having an unclear risk of bias in selection reporting.

The incidence of severe AKI

The depiction of AKI differed in 9 RCTs. But they could all come down to the criterion of AKIN score or KDIGO stage. Some defined patients who met the KDIGO stage of 1-3 as AKI[30][32], or modified the classification into stage 2 or higher, both with higher stages indicating more severe kidney injury[14]. Some chose to reflect the patients' renal situation by the patients' peak AKIN score[33]. Two studies reported numbers of worsening AKI, or new onset of severe AKI, which was defined as worsening of the KDIGO stage (plasma creatinine criteria or use of renal replacement therapy)[31][34]. In 2 trials the exact number of patients' of KDIGO stage 2 and 3 was not available neither in the article nor the supplement appendix[29][35]. We extracted the numbers of patients receiving continuous renal-replacement therapy (CRRT) treatment according to the information this article provided in their supplement appendix, which met the diagnostic criteria for KDIGO stage 3 or AKIN score 3. In the study conducted by Corl et al. in 2019 [36], serious

AKI was narrated as doubling in the triage creatinine within 72 hours, which could be considered as KDIGO stage 2.

A total of 3712 patients were analyzed for renal function. 410 of the 1864 patients analyzed in the restrictive fluid resuscitation group (22.0%)and 477 of the 1849 patients analyzed in the liberal fluid resuscitation group (25.8%)were diagnosed severe AKI or evaluated as KDIGO score of 2 and 3 or reached AKIN score 2 and 3 during the follow-up of the studies (RR 0.88, 95%CI 0.79 to 0.97, P=0.01; I^2=0%). Obviously there was a significant difference in the incidence of acute kidney injury between patients receiving a restrictive or conservative fluid resuscitation strategy and those who received a liberal fluid resuscitation strategy or usual care therapy. The process was shown in the forest plot in **Figure 3**.

Second outcomes

Mortality

Data on all-cause mortality of the participants were available in all 9 RCTs. A total of 3813 patients were tracked down for their clinical ending at most protracted time point, including 90-day mortality in 7 RCTs[14][29][30][31][32][33][34], 60-day

mortality in one[36], and 30-day mortality in one[35]. We found no significant difference in the mortality between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (RR 0.99,95%CI 0.90 to 1.08; P=0.82; I^2=0%). The result of the I^2 evaluation indicated that there was no heterogeneity observed. Specific data was reported by **Supplement Figure 1** in supplementary appendix.

ICU length of stay

Seven RCTs reported the patients' length of stay in ICU, of which 3 were measured in hours[30][33][36] and 4 were measured in days[14][31][32][35]. All data was extracted in the form of median and IQR and was transformed into value of mean and SD by the method proposed by the Hong Kong Baptist University. The result was shown in **Supplement Figure 2**, obviously no heterogeneity was detected in the trial neither (Mean Difference -0.33,95%CI -0.79 to 0.13; P=0.16; I^2=0%).

Incidence of worse AKI

Data on the incidence of worse AKI were available in 3 RCTs. We analyzed the full amount of patients developing worse AKI comparing to the situation of their first admission into the hospital. It was narrated as worse situation of AKI in patients who

already suffered from AKI[31][33][34], (according to the KDIGO criteria, higher stage means worse kidney function situation), and for patients without AKI at baseline, development of AKI after randomization was regarded as worsening of AKI. The result was shown in **Supplement Figure 3**. No significant difference was found in the incidence of worse AKI between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (RR 0.76, 95%CI 0.55 to 1.05; P=0.09; I^2=0%). No-heterogeneity was detected in the trial.

Duration of ventilation

3 RCTs reported the patients' mechanical ventilation hours[33][35][36]. All data was extracted in the form of median and IQR and was transformed into value of mean and SD by the method proposed by the Hong Kong Baptist University. The result was shown in **Figure 4**. There was a significant statistical difference in the duration of ventilation of patients between the restrictive fluid resuscitation group and the liberal fluid resuscitation group (Mean Difference -41.14, 95%CI -68.80 to -13.48; P=0.004; I^2=74%). High heterogeneity was detected in the trial.

Sensitivity analysis

In the sensitivity analysis, we removed the studies individually to see if any of them had a larger impact on the result. And when trial conducted by Meyhoff et al.[14] was removed, the result reversed and had no statistical meaning. This indicated that this trial took a large position in the analysis. When we included only high-quality researches according to the assessments[14][29][30][31], the result remained statistically meaningful (RR 0.89, 95%CI 0.80 to 0.99; P=0.03; I^2=0%). Through sensitivity analysis of the secondary outcomes, we found that high heterogeneity of the duration of ventilation was mainly related to the Corl et al.'s study[36]. When it was removed, the heterogeneity could be considered as low (Mean Difference -52.68, 95%CI -73.80 to -31.56; P<0.00001; I^2=9%) comparing to original analysis results. And when other 2 studies were removed individually, the value of I^2 remained above 75%(I^2=76% or 81%).

Subgroup analysis

All 9 RCTs concluded the participants' median age. We calculated the average age and then divided the studies into two divisions according to the criterion (<70 year versus ≥70 years). The role the initial places where the patients were admitted from

played was investigated as well. Most patients were extracted from the emergency department (ED) of the hospital[33][34][35][36]. The rest participants were admitted into the ICU from OR, hospital wards or other ICUs, especially in multicenter trials[14][29][13][30][31][32]. Simultaneously we analyzed whether these factors had an impact on the results of the incidence of severe AKI and the mortality of the patients.

Results showed that there was a significant difference in the incidence of severe AKI between patients receiving restrictive fluid resuscitation in the subgroup analyzing the factor of age above 70 (RR 0.89, 95%CI 0.79 to 0.99; P=0.03; I^2=0%) and the multiple initial places where the patients were admitted from (RR 0.88, 95%CI 0.80 to 0.98; P=0.02; I^2=0%) (**Supplement Figure 4&5**). This led to the indication that restrictive fluid resuscitation therapy could make an impact on the kidney function of patients over 70 years old. And when patients were admitted from not only the ED, but also the OR, hospital wards and other ICUs, they were more likely to benefit from restrictive fluid resuscitation strategy.

Simultaneously, these two factors above didn't have a connection with the mortality of the patients. No significant difference was found in the subgroup analysis. And no significant heterogeneity was detected. (**Supplement Figure 6&7**)

Trial Sequential Analysis

Trial sequential analysis (TSA) was conducted to calculate the optimal required information size[37][38] (meta-analysis sample size) for our meta-analysis based on a baseline incidence rate of 45% [39][40] in the control group, a relative risk reduction of 10%, 80% of power and a type I error of 5%. TSA showed that the diversity adjusted RIS was 3711 which was less than that in our study (n=3718). Trial sequential adjusted 95% CI of RR was 0.79 to 0.97 in the fixed effects model, and 0.87 to 0.88 in the random effects model. The Begg-Tang random effects model was applied to test the reliability of the result[41]. The results were showed in **Figure 5**. The Z-curve surpassed the conventional boundary and the trial sequential monitoring boundary both for benefit, indicating that the result was reliable and the accuracy was testified. The cumulative amount of participants met the RIS line, this positive conclusion had been confirmed.

Quality of evidence

We assessed the quality of evidence using the GRADE approach (**Supplement Figure 9**). The results demonstrated moderate confidence in the findings on incidence of severe AKI, as well as the results of all second outcomes except the ICU LOS, which received limited confidence. And the result of incidence of worse AKI was rated as of high certainty.

Publication bias

We explored funnel plot, applied Egger linear regression test and the trim-and-fill method for the primary outcome (**Supplement Figure 8**). The result showed a P-value of 0.3929 (P>0.05), meaning that no significant publication bias was detected.

Discussion

This study focused on the influence of the up-to-date restrictive fluid resuscitation therapy on the incidence of severe AKI of patients under such circumstance, which was a topic that little previous studies had ever discussed. And we found that though restricted fluid resuscitation therapy doesn't improve the overall mortality, it did have a strong connection with lower incidence of severe AKI, indicating that it is

associated with less degeneration of patients' renal function. Thus, we provided new evidence for the need of more individual and specialized fluid resuscitation therapy for patients with sepsis hypotension and septic shock.

This meta-analysis focused on a neglected topic, included more participants from other countries and centuries, and the specific measures of the intervention were also different. This gave our research unique strengths, such as more comprehensive included studies, different focusing prognosis, certain results and conclusion. Various analysis was conducted to confirm the certainty of the results. The TSA results has confirmed that the result is reliable, and when it comes to decreasing the incidence of severe AKI in sepsis associated hypotension and shock, restrictive fluid resuscitation is superior to usual care therapy.

Occurrence of AKI remains one of the major causes of mortality in sepsis associated hypotension and septic shock. Kidney injuries may contribute to long-term effects such as secondary episodes of sepsis and multiple organ dysfunction syndrome (MODS)[42]. It is of vital significance that we determine the optimal fluid resuscitation strategy and the volume of intravenous fluid for critically ill patients.

Previous studies[31][43][44] proposed that it may benefit the patients' renal function, by the strict condition that optimal kinds of fluid and volumes were applied. Our study arrived in the conclusion that lays with this finding. Fluid resuscitation need to be sufficient, but must be in a controlled fashion and be carried out under dynamic assessment monitoring of patients' volume situation[45]. Volumes of intravenous resuscitation fluids directly ameliorate the tissue and organ perfusion, along with vasopressors, the treatment hold a profound meaning for the safety of organs and the resuscitating process. Excessive volume load will lead to increased renal venous pressure, leading to renal interstitial edema, thus decreasing the renal tissue perfusion. And volume overload will lead to an increase in central venous pressure, which leads to the obstruction of renal venous reflux and decrease of renal perfusion. In addition, severe overload is concerned with an increase in intra-abdominal pressure, which leads to increased renal venous pressure and decreased renal blood flow. This will increase the pressure in the glomerular balloon cavity, leading to worsening AKI[46]. Thus, too rapid and aggressive fluid resuscitation strategy could potentially burden cardiac and renal function, creating an underlying danger to the precarious physical

condition of patients with septic shock. The pace of providing intravenous fluids in the beginning time should not be neglected. Simultaneously, we found that restriction on fluid volume is associated with decrease in patients' duration of mechanical ventilation. This indicated benefit of the participants' pulmonary function. Less hours of mechanical ventilation on the patients not only induces less complications like ventilator-associated pneumonia (VAP)[47], but also has economic benefits. High heterogeneity was found between the included 3 trials, which is mainly related to the Corl et al. 's study[36]. It was likely to be concerned with less centers of the study, its more complicated septic shock inclusion criterion compared with the other 2 studies and higher intravenous fluid volume of the restrictive fluid group (**Supplement Table 1**). The general economic assessment was not taken into consideration, which future trials should incorporate.

Subgroup analysis also showed that the influence of restrictive fluid resuscitation strategy was especially obvious on patients with an elderly age of over 70. This may be for the reason that the aged have poor cardiopulmonary function and a narrow volume window. In the presence of septic shock, it is likely that vasoplegia plays an

important role in the volume responsiveness assessment. And elder patients' vascular wall elasticity decreases, leading to a decrease in their ability to respond to variety in circulating volume. When patients are admitted from not only the ED, but also other places such as the OR and hospital wards, they generally possess longer hospital stay period and more complicated symptoms. Restriction on their resuscitation fluids may be beneficial for their renal function.

The initial causes of septic shock differed in all participants, and for the sake of patients' safety and to promote the stabilization of patients' vital signs, caregivers all adapted an initial treatment before randomization and admission into the ICU or emergency department. The treatments aimed to delay the progression of the disease. And all patients included into the RCTs had undergone a similar initial resuscitation treatment. Four trials included in this analysis followed the surviving sepsis campaign bundle which was updated in 2018[48], and gave their participants an initial fluid volume of 30ml/kg[14][31][35][36]. One trial clear limited the initial infusion of restricted fluid protocol to 1000ml as long as the patients' vital signs had stabled[29]. The other four didn't mention whether the intervention included an

initial resuscitation fluid volume[30][32][33][34]. So, the amount of resuscitation fluid can be recognized as sufficient. In all 9 RCTs, 7 of which applied norepinephrine, or to say noradrenaline[14][29][30][31][32][33][35], and two was unclear[34][36]. The timeframe the intervention fluid therapy lasted differed extremely in these trials. Three were within the first 24-h period[29][30][34], two were 72-h[35][36], and the rest were 6-h post randomization[33], 5 days[31] and 14 days[32] individually. The patients received the assigned intervention from the time of randomization until they were discharged from the ICU, for a maximum of 90 days[14]. There was also difference of original countries they took place in, number of patients, difference of their septic shock inclusion criterion and difference of the details of their intervention. The publication bias of these studies and the lasting period of intervention strategy also had an influence. All these factors may attribute to the heterogeneity measured by the I^2 trial.

Through the study, few evidences were found to definite that the fluid restriction strategy has any influence on the patients' mortality and ICU LOS. This may be because the original infection differed among all the participants, leading to a much-

complicated subject to compare the ending of all patients. And ICU LOS is a multifactorial indicator and is very dependent on the patients' condition. Most participants in the studies relied on life-support instruments, exclusively available in the ICU early stages of treatment.

The sensitivity analysis indicated that the trial conducted by Meyhoff et al.[14] took a large position in the analysis. This phenomenon had a lot to do with its number of participants and the long duration of the intervention means. The results of this meta-analysis were confirmed by various analysis, and adding other studies provided more comprehensive insights into this topic.

Results of the GRADE assessments were 1 with high certainty (incidence of worse AKI), 3 with moderate certainty (incidence of severe AKI, mortality, duration of ventilation), and 1 with low certainty (ICU LOS). The uncertainty mainly came from the risk of bias and the imprecision of the included studies. The more studies were involved, the higher risk of bias we saw. The consistency and directness were all ensured in every trial. But when it came to data concerned with time duration or time period, the imprecision was assessed as serious. The heterogeneity and different

extraction time nodes of each factor in different trials may also be relevant to the assessments.

Due to lack of data and corresponding issue, some data about severe AKI was represented by numbers of initiation of RRT, which may deviate from the actual results in reality. Unpublished data or data reported in abstract form was not included, which may lead to publication bias. There was little evidence supporting that fluid restriction strategy affects patients' mortality and ICU length of stay. This could be due to differences in the initial causes of infection among all patients, making outcome comparisons complex. The risk of bias of the included trials existed, but the quality of the results remained reliable, examining by aforementioned analysis. If any relevant required data are available, we will immediately include them in this analysis as supplement. The numbers of included participants may be a bit small, but this meta-analysis strictly included only trials focusing on restrictive fluid resuscitation. And the result of TSA had made sure the sample size reached the RIS. The difference in duration of restrictive fluid resuscitation therapy of these included trials may play an important role in the heterogeneity. Sensitivity analysis showed the result heavily relied on the

Meyhoff study. But as narrated before, this analysis had its own irreplaceable strength. And TSA showed promise in the primary outcome.

Conclusion

It is conclusive that fluid restriction strategy is superior to usual care when it comes to reducing the incidence of severe acute kidney injury in sepsis associated hypotension and shock. Shorter duration of ventilation is concerned with fluid restriction as well, but the heterogeneity is substantial. GRADE assessments confirmed moderate and above certainty. Traditional fluid resuscitation therapy has the potential to be further explored for improvements to be more precise and appropriate for a better prognosis.

List of abbreviations

AKI: Acute kidney injury; RCT: randomized controlled trial; ICU: Intensive care unit; TSA: trial sequential analysis; LOS: length of stay; RRT: renal-replacement therapy; RR: relative risk; CI: confidence interval; SD: standard deviation; MD: mean difference; ED: emergency department; OR: operation room; KDIGO: kidney disease improving global outcomes; RIS: required information size; MODS: multiple organ dysfunction

syndrome; GRADE: Grades of Recommendation, Assessment, Development and Evaluation

Declarations

Ethics approval and consent to participate

No ethics approval was mandatory for this is a systematic review and meta-analysis, no data was withdrawn directly from patients. We only calculated and synthesized data in published studies.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding statement

This work is partially supported by grants from the National Natural Science Foundations of China (81501705, 82272211), grants from the Scientific Research Foundation of Graduate School of Southeast University (YBPY1604), grants from the Jiangsu Provincial Medical Youth Talent (QNRC2016808), Jiangsu Province's Key Provincial Talents Program (ZDRCA2016082).

Authors' contributions

JYX conceived the study. XEC performed the analysis, synthesis and interpretation of data and wrote the first draft of the manuscript. The search and reviewing of all the articles and the assessment of the studies' quality were conducted by two reviewers (XEC and XTC) independently. When encountered disagreements, a third reviewer (WTL) would provide a suggestion. YJZ and MKY contributed to the progress of the trial sequential analysis. JYX was responsible for designing and the coordination of the study, and critical revision of the manuscript for important intellectual content. All authors read and approved the final version. JYX is the guarantor.

Acknowledgements

We are sincerely grateful to the investigators and clinical trials group of all the trials included in this study for providing access to their trial data.

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750 **Figures legends**

751 **Figure 1. The process of literature search**

752 **Figure 2. Risk of bias summary for each included study.** Red(-)indicates high risk
753 of bias; yellow(?) indicates unclear risk of bias; green(+) indicates low risk of bias.

Figure 3. Forest plot for primary outcome of the incidence of severe AKI. It illustrates the result of restrictive or conservative fluid resuscitation strategy versus liberal fluid resuscitation or usual care strategy.

Figure 4. Forest plot for second outcome of the duration of ventilation. It shows the result of restrictive fluid resuscitation strategy versus liberal fluid resuscitation strategy on the duration of ventilation of patients with septic shock.

Figure 5. Trial sequential analysis. TSA showed that the diversity-adjusted required information size(RIS) was 3711. The Z-curve surpassed the conventional boundary and the trial sequential monitoring boundary both for benefit, indicating that the result was reliable and the accuracy was testified. The cumulative amount of participants met the RIS line, this positive conclusion had been confirmed.

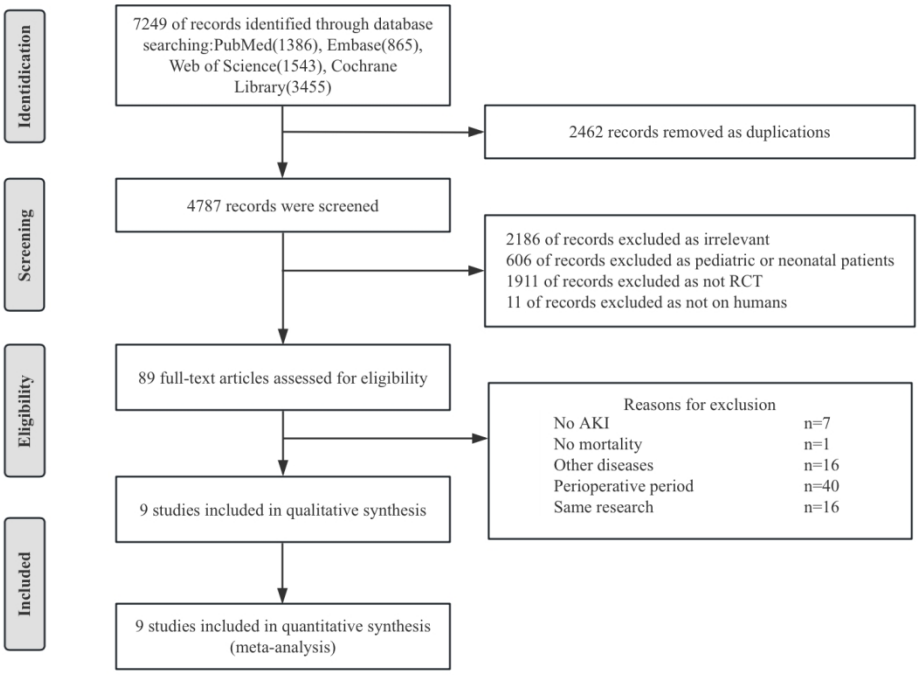

Figure 1. The process of literature search

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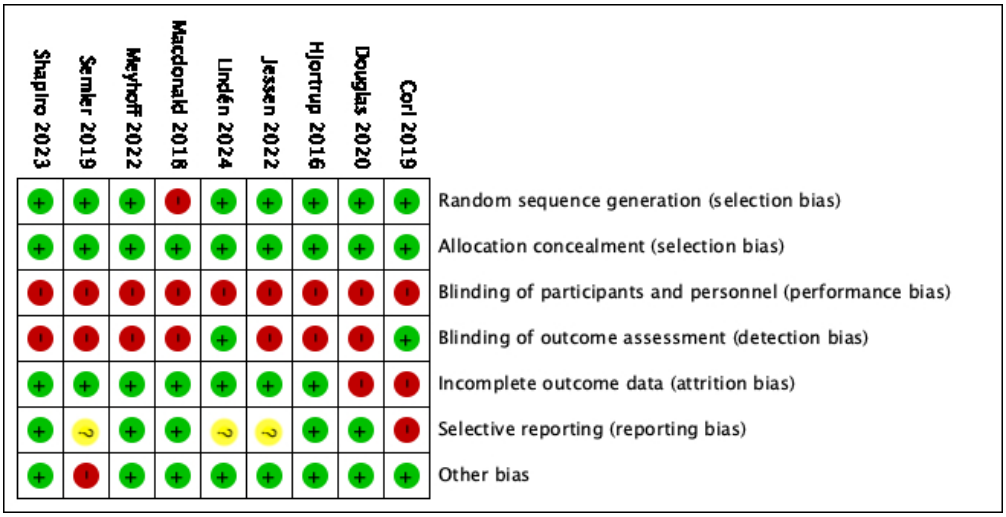

Figure 2. Risk of bias summary for each included study. Red(-)indicates high risk of bias; yellow(?) indicates unclear risk of bias; green(+) indicates low risk of bias.

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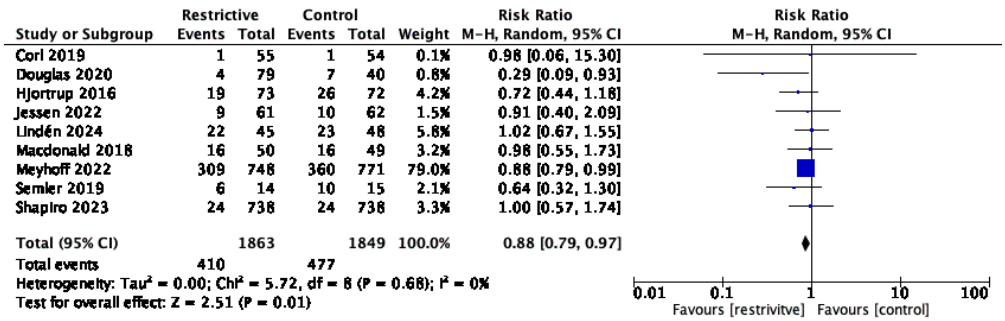

Figure 3. Forest plot for primary outcome of the incidence of severe AKI. It illustrates the result of restrictive or conservative fluid resuscitation strategy versus liberal fluid resuscitation or usual care strategy.

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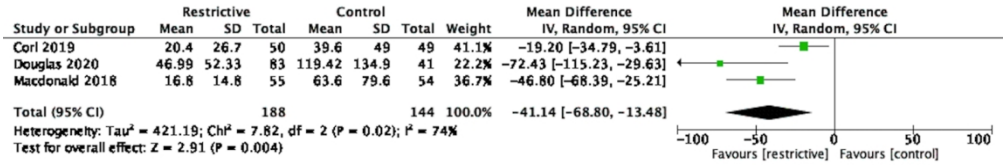


Figure 4. Forest plot for second outcome of the duration of ventilation. It shows the result of restrictive fluid resuscitation strategy versus liberal fluid resuscitation strategy on the duration of ventilation of patients with septic shock.

566x94mm (72 x 72 DPI)

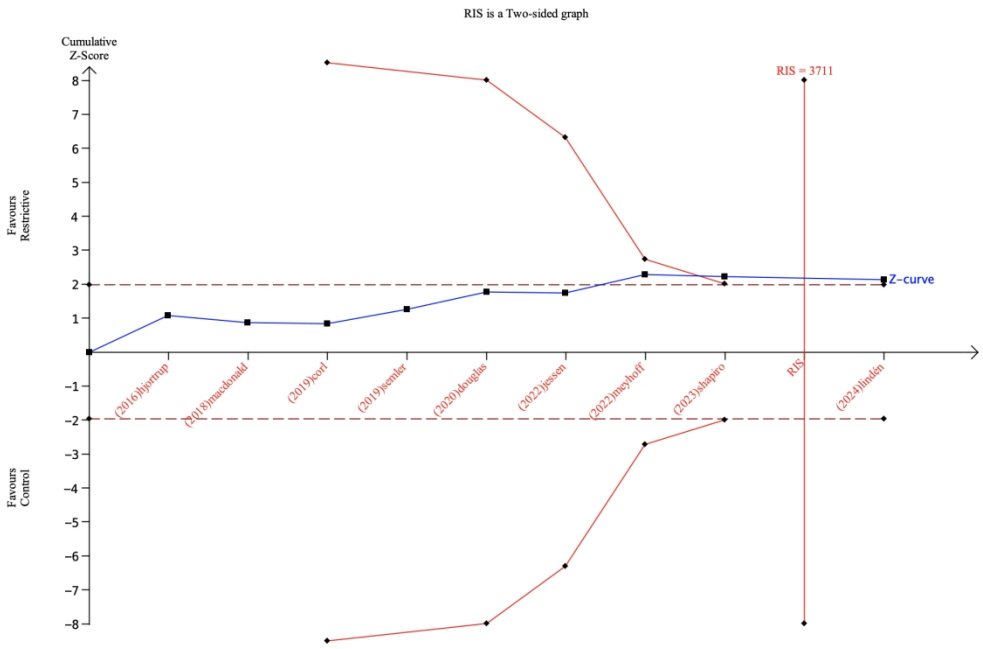


Figure 5. Trial sequential analysis. TSA showed that the diversity-adjusted required information size(RIS) was 3711. The Z-curve surpassed the conventional boundary and the trial sequential monitoring boundary both for benefit, indicating that the result was reliable and the accuracy was testified. The cumulative amount of participants met the RIS line, this positive conclusion had been confirmed.

345x226mm (144 x 144 DPI)

Supplementary appendix

This supplementary appendix provides:

1. Search equation via PubMed, Embase, Web of Science, and Cochrane Library

2. PRISMA checklist

3. Other supplementary Figures

4. Summary of contextual factor data

5. List of citation of excluded potential studies and the reasons to rule out them

6. The GRADE results

7. Table of characteristics of included studies

1. Search equation via PubMed, EMBASE, Medline, and Cochrane Library

Search strategies for the different databases ran on **April 28,2023**

PubMed (1386)

Search: ("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal replacement therapy" OR "blood purification therapy" OR "mortality") AND ("restrictive fluid" OR "resuscitation")

Filters: Randomized Controlled Trial, Humans

Embase (865)

("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal replacement therapy" OR "blood purification therapy" OR "mortality") AND ("restrictive" AND "fluid" AND "resuscitation")

Web of Science (1543)

(TS=("restrictive fluid") OR TS=("resuscitation")) AND TS=(("acute kidney injury" OR "acute kidney failure" OR "acute renal failure" OR "continuous renal replacement therapy" OR "blood purification therapy" OR "mortality"))

Filters: Clinical Trial +Humans

Cochrane Library (3455)

restrictive fluid OR resuscitation in All Text AND acute kidney injury OR acute kidney failure OR acute renal failure OR continuous renal replacement therapy OR blood purification therapy OR mortality in All Text - in Trials (Word variations have been searched)

The total amount of the studies are 7249 in which the duplication number is 2462, leading 4878 records to be screened.

2. PRISMA checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Yes, as supplementary appendix subheading 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg. 10-11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg.10, supplementary appendix subheading 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary appendix subheading 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg.11, Supplementary appendix subheading 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg.11-12
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 14
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg. 12
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg.13-14
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg.15
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Supplement table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Supplement table 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg.14-16
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg.14-16
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg.15-16
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Supplementary appendix 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg.15
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure1, Pg.16-18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary appendix 5
Study characteristics	17	Cite each included study and present its characteristics.	Supplement table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pg.18 Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pg.18-21, Figure 3-4, Supplement Figure 1-8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg.17
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg.18-21, Figure 3-4, Supplement Figure 1-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg.23-25, Supplement Figure 1-8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg.24-25
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg. 25
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplementary appendix 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg.26-27
	23b	Discuss any limitations of the evidence included in the review.	Pg.30-31
	23c	Discuss any limitations of the review processes used.	Pg.30-31
	23d	Discuss implications of the results for practice, policy, and future research.	Pg.25-26
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg.5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg.5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg.35
Competing interests	26	Declare any competing interests of review authors.	Pg.35
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pg. 35

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA checklist for abstract

PRISMA 2020 for Abstracts Checklist

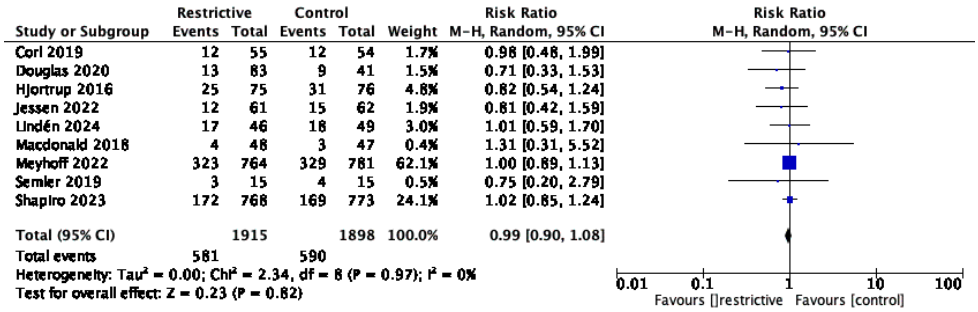
Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

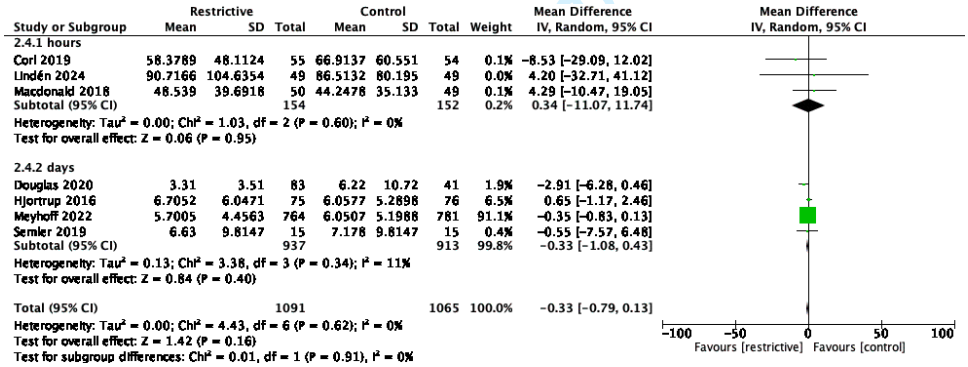
For more information, visit: http://www.prisma-statement.org/

3. Other supplementary Figures

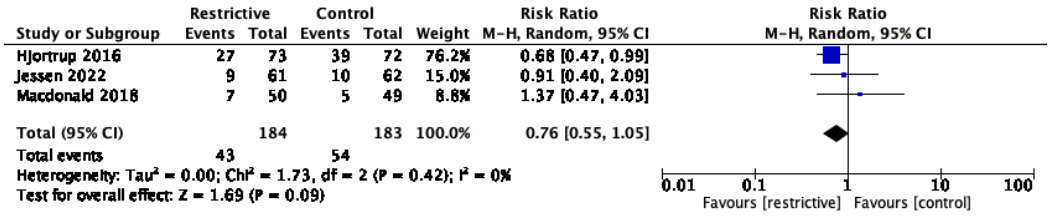
Supplement Figure 1. Forest plot for mortality at most protracted time point available



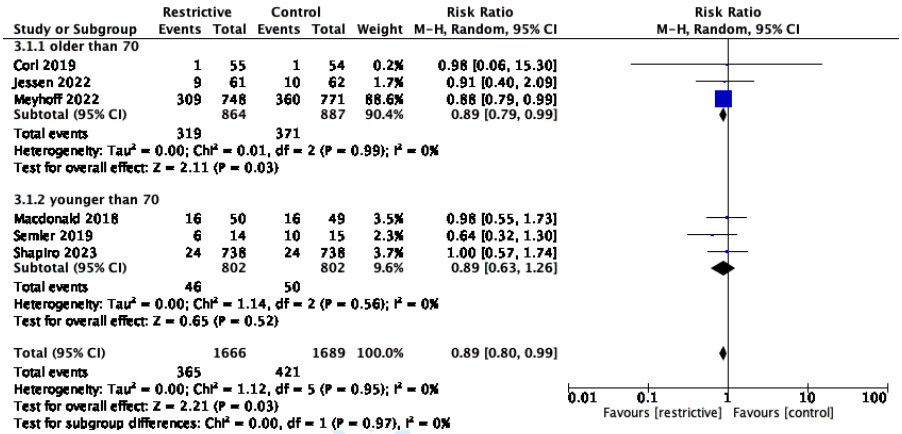
Supplement Figure 2. Forest plot for the ICU length of stay(LOS). The result was compared in two measurements, one in hours and one in days.



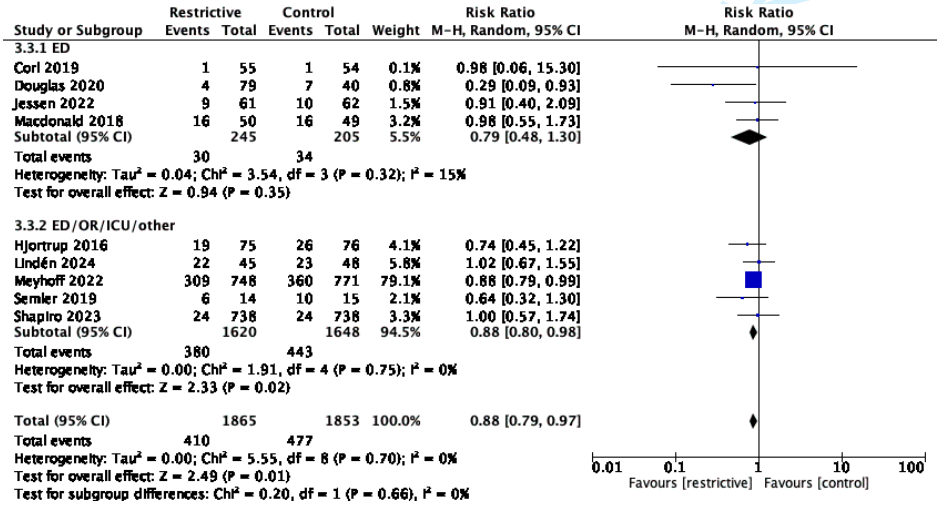
Supplement Figure 3. Forest plot for the incidence of worse AKI.



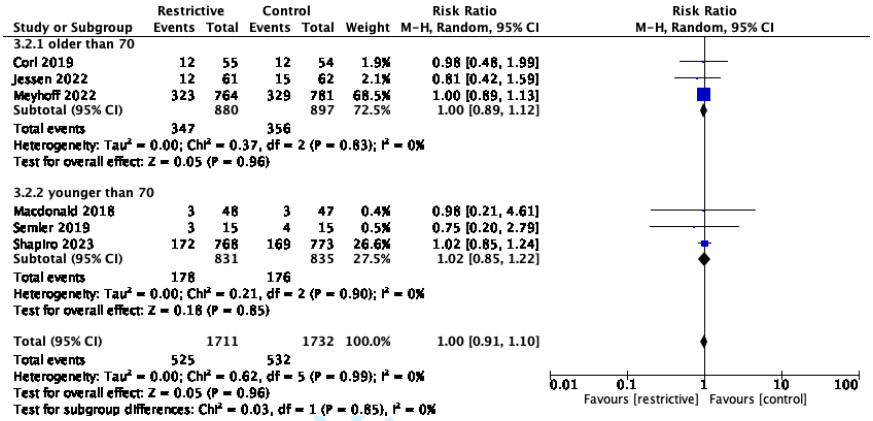
Supplement Figure 4. Forest plot for subgroup analysis on the influence of age on severe AKI. The result was focused on the influence of the factor of age on the incidence of severe AKI in patients in 2 group.



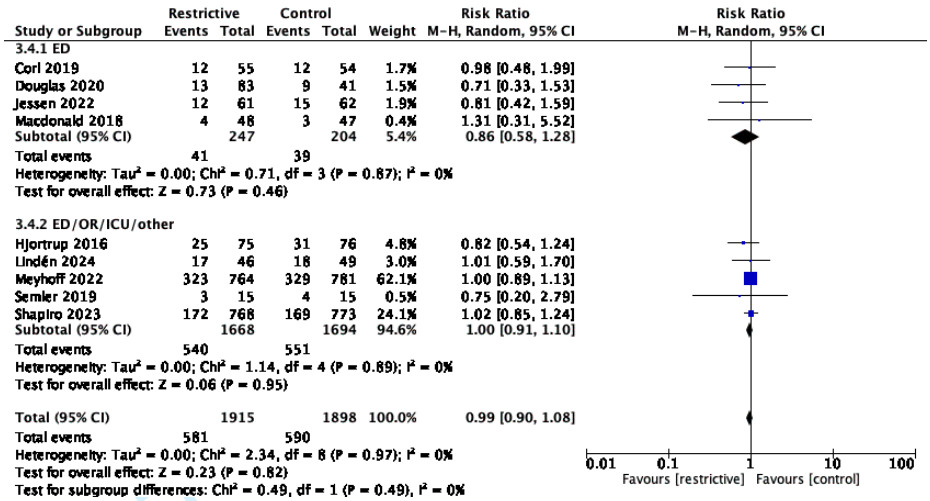
Supplemental Figure 5. Forest plot for the influence of initial places the patients were admitted into on severe AKI. This figure showed the results of the subgroup analysis on the influence of the initial places where the patients stayed before admitted into the ICU before randomization, which was focused on the incidence of severe AKI in patients in 2 group.



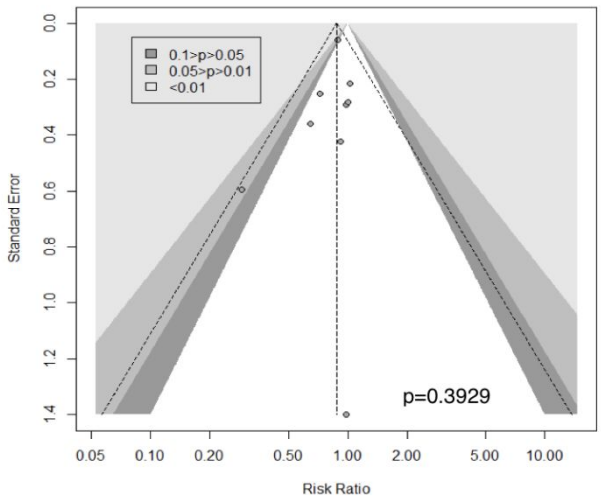
Supplement Figure 6. Forest plot for subgroup analysis on the influence of age on mortality. The result was focused on the influence of the factor of age on mortality of patients.



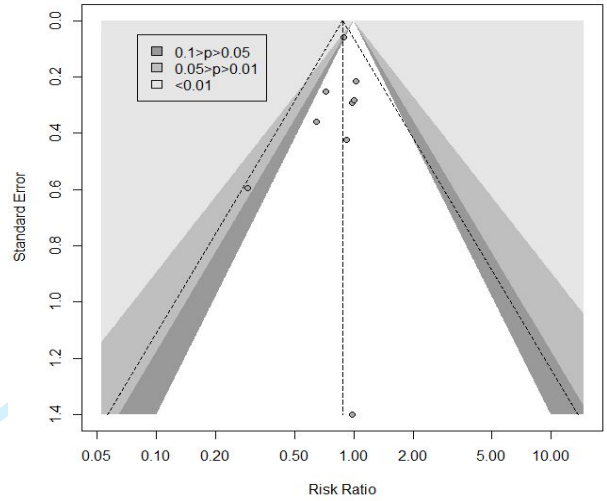
Supplemental Figure 7. Forest plot for the influence of initial places the patients were admitted into on mortality. This figure showed the results of the subgroup analysis on the influence of the initial places where the patients stayed before admitted into the ICU before randomization, which was focused on the mortality in patients in 2 group.



Supplement Figure 8. Funnel plot for the incidence of severe AKI. The result of Egger linear regression test (A1) and trim-and-fill (A2) showed a P-value of 0.3929 (P>0.05), meaning that no significant publication bias was detected.



A1. incidence of severe AKI



A2. incidence of severe AKI(trim-and-fill)

4. Summary of contextual factor data

For analysis of the effects of restrictive fluid resuscitation therapy on patients with septic shock, 9 randomized controlled trials were included into this meta-analysis. The studies contained a total amount of 3718 participants.

Meyhoff et al (2022) enrolled 1554 patients. During the 90-day trial in the ICU, excluding fluids administered with medication and nutrition, the restrictive-fluid group received a median of 1798 ml of intravenous fluid (interquartile range, 500 to 4366); the standard-fluid group received a median of 3811 ml (interquartile range, 1861 to 6762). Severe acute kidney injury was defined as a modified classification of stage 2 or higher according to Kidney Disease: Improving Global Outcomes (KDIGO) on a scale ranging from 1 to 3, with higher stages indicating more severe kidney injury. The incidence of severe AKI was 309 out of 748 (41.3%) in restrictive-fluid group and 360 out of 771 (46.7%).

Macdonald et al (2018) enrolled 99 patients. Median volumes administered from ED arrival to 6 h post randomization were 2387 ml (30 ml/kg) in the restricted volume arm, and 3000 ml (43 ml/kg) in the usual care arm ($p<0.001$). At 24 h respective median cumulative volumes were 3543 ml (40 ml/kg) and 4250 ml (61 ml/ kg), $p=0.005$. The incidence of severe AKI was defined as score 2 or higher according to patients' peak acute kidney injury network (AKIN) score to day 7. The number was 16 out of 50 (32%) in restricted volume group and 16 out of 49 (32.7%) in usual care group.

Hjortrup et al (2016) enrolled 151 patients. During ICU stay after randomization, excluding fluids administered with medication and nutrition, the fluid restriction group received a median of 500 ml of intravenous fluid (interquartile range, 0 to 3250); the standard-fluid group received a median of 2200 ml (interquartile range, 1000 to 4750), p<0.001. Severe acute kidney injury was defined as a modified classification of stage 2 or higher according to the KDIGO criterion. The number of worsening of AKI in patients was 19 out of 73 (26.0%) in fluid restriction group and 26 out of 72 (36.1%) in standard care group.

Corl et al (2019) enrolled 109 patients. During the first 72 hours of care, the restrictive group received significantly less resuscitative IV fluid than the usual care group (47.1 vs 61.1mL/kg; p = 0.01). Severe acute kidney injury defined as a doubling in the triage creatinine. The number of AKI was 1 out of 55 (1.8%) in restrictive fluid group and 1 out of 54 (1.9%) in standard care group, p>0.99.

Semler et al (2019) enrolled 30 patients. Over the course of the trial, patients in the usual care group received a mean volume of fluid from IV boluses of 733 (1083) compared with 300 (560) in the conservative fluid management group (P=0.30). Severe acute kidney injury defined as was defined as stage 2 and 3 on a modified Kidney Disease: Improving Global Outcomes (KDIGO). The number of severe AKI was 6 out of 14 (42.8%) in conservative group and 10 out of 15 (66.7%) in usual care group.

Douglas et al (2020) enrolled 124 patients. Both arms received a similar volume of

resuscitation fluid prior to enrollment (2.4 ± 0.6 L Intervention arm compared to 2.2 ± 0.7 L Usual Care arm). Positive fluid balance at 72 hours or ICU discharge, was significantly less in the Intervention arm (-1.37L favoring Intervention arm, 0.65 ± 2.85L Median: 0.53L Intervention arm vs. 2.02 ± 3.44L Median: 1.22L Usual Care arm, p=0.02). Severe AKI was defined as initiation of renal replacement therapy. The number was 4 out of 79 (5.1%) in restrictive fluid group and 7 out of 40 (17.5%) in standard care group.

Lindén et al (2024) enrolled 98 patients. Median total volume of fluid in the first three days, was 6008 ml (interquartile range [IQR] 3960–8123) in the restrictive fluid group (n = 44), and 9765 ml (IQR 6804–12,401) in the control group (n = 48); corresponding to a Hodges–Lehmann median difference of 3560 ml [95% confidence interval(CI) 1614–5302]; p < 0.001). Severe acute kidney injury defined as was defined as stage 2 and 3 on a modified Kidney Disease: Improving Global Outcomes (KDIGO). The number of severe AKI was 22 out of 45 (48.9%) in restrictive fluid group and 23 out of 48 (47.9%) in usual care group.

Jessen et al (2022) enrolled 123 patients. At 24 h, the mean (±SD) IV crystalloid fluid volumes were 562 (±1076) ml versus 1370 (±1438) ml in the restrictive versus standard care group (mean difference –801 ml, 95% CI −1257 to −345 ml, p = 0.001). Severe AKI was defined as any development or worsening of acute kidney injury, defined as the KDIGO creatinine score > 0 compared to at randomization. The number was 9 out of 61 (14.8%) in restrictive fluid group and 10 out of 62 (16.1%)

in standard care group.

Shapiro et al (2023) enrolled 1563 patients. Resuscitation therapies that were administered during the 24-hour protocol period differed between the two groups; less intravenous fluid was administered in the restrictive fluid group than in the liberal fluid group (difference of medians, −2134 ml; 95% CI −2318 to −1949), whereas the restrictive fluid group had earlier, more prevalent, and longer duration of vasopressor use. Severe AKI was defined as initiation of renal replacement therapy. The number was 24 out of 738 (3.3%) in restrictive fluid group and 24 out of 738 (3.3%) in standard care group.

5. List of citation of excluded potential studies and the reasons to rule out them

5.1No AKI

1)No data on the numbers of AKI patients was found in the following article. Communication with the corresponding author didn't provide enough information in time.

[1] B. M. E. Noureldin, M. Mohamed, N. El shafei, F. A. A. Markos and R. M. S. Ahmed. Comparative Study between Restrictive versus Liberal Intravenous Fluid Administration in Severe Sepsis and Septic Shock; A Randomized Clinical Trial. QJM: an international journal of medicine 2023 Vol. 116 Pages i40-i41. DOI: 10.1093/qjmed/hcad069.093

2) The following were titles and accession numbers of the trial protocol we found in the literature search. The titles and abstracts convinced us the trials were focused on the topic concerning our study, but neither full-text nor information about AKI could be retrieved. The protocol containing their outcomes didn't included indicators about AKI neither.

[2] An Open-label Randomized Controlled Study on the Effects of different Net Ultrafiltration Strategy on Fluid Balance and Prognosis in Patients with Septic Shock [online]. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR 2400083804.

[3] Controlled Fluid Resuscitation Strategy in Sepsis Patient [online]. 2017. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-INR-17011928.

[4] Restrictive Intravenous Fluids Trial in Sepsis [online]. 2017. https://clinicaltrials.gov/show/NCT03137446

3) No data on AKI was found in these articles' full text.

[5] OPTImized Restrictive Strategy Targeting Non-Resuscitative FLUIDs in Septic Shock: pilot Study [online]. https://clinicaltrials.gov/ct2/show/NCT04947904.

[6] Optimized fluid resuscitation strategy for septic shock guided by microcirculation [online]. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2200056310.

[7] W. Zhang. Critical Care Ultrasound Goal-directed Versus Early Goal-directed Therapy in Septic Shock: a Randomized Controlled Study. Intensive care medicine experimental 2021 Vol. 9 Issue SUPPL 1. DOI: 10.1186/s40635-021-00413-8

5.2 No mortality

No data on mortality of patients was mentioned in the following articles, or in the outcomes planned in the trial protocol.

[8] Aung NM, Kaung M, Kyi TT, et al. The Safety of a Conservative Fluid Replacement Strategy in Adults Hospitalised with Malaria. PLoS One. 2015 Nov 18;10(11):e0143062. doi: 10.1371/journal.pone.0143062. PMID: 26581060; PMCID: PMC4651424.

5.3 Perioperative period

The trials were conducted on patients undergoing elective surgery, and the fluid therapy was performed during the perioperative period.

[9] Koers L, van Haperen M, Meijer CGF, et al. Effect of Cognitive Aids on Adherence to Best Practice in the Treatment of Deteriorating Surgical Patients: A Randomized Clinical Trial in a Simulation Setting. JAMA Surg. 2020 Jan 1;155(1):e194704. doi: 10.1001/jamasurg.2019.4704. Epub 2020 Jan 15. PMID: 31774483; PMCID: PMC6902237.

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[11] Alimian M, Mohseni M, Moradi Moghadam O, et al. Effects of Liberal Versus Restrictive Fluid Therapy on Renal Function Indices in Laparoscopic Bariatric Surgery. Anesth Pain Med. 2020 Oct 20;10(5):e95378. doi: 10.5812/aapm.95378. PMID: 34150556; PMCID: PMC8207848.

[12] Behman R, Hanna S, Coburn N, et al. Impact of fluid resuscitation on major adverse events following pancreaticoduodenectomy. Am J Surg. 2015 Nov;210(5):896-903. doi: 10.1016/j.amjsurg.2015.04.020. Epub 2015 Jul 17. PMID: 26255229.

[13] Dahal R, Bhandari R.S, Lakhey P.J, Restrictive versus Liberal Fluid Therapy in Patients Undergoing Pancreaticoduodenectomy, HPB, Volume 24, Supplement 1, 2022, Page S260, ISSN 1365-182X, doi:10.1016/j.hpb.2022.05.546.

[14] Diaper J, Schiffer E, Barcelos GK, et al. Goal-directed hemodynamic therapy

versus restrictive normovolemic therapy in major open abdominal surgery: A randomized controlled trial. Surgery. 2021 May;169(5):1164-1174. doi: 10.1016/j.surg.2020.09.035. Epub 2020 Nov 2. PMID: 33143931.

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[17] Guan Z, Gao Y, Qiao Q, et al. Effects of intraoperative goal-directed fluid therapy and restrictive fluid therapy combined with enhanced recovery after surgery protocol on complications after thoracoscopic lobectomy in high-risk patients: study protocol for a prospective randomized controlled trial. Trials. 2021 Jan 7;22(1):36. doi: 10.1186/s13063-020-04983-y. PMID: 33413593; PMCID: PMC7792083.

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30515670.

[19] Sahmeddini MA, Janatmakan F, Khosravi MB, et al. Restricted Crystalloid Fluid Therapy during Orthotopic Liver Transplant Surgery and its Effect on Respiratory and Renal Insufficiency in the Early Post-operative Period: A Randomized Clinical Trial. Int J Organ Transplant Med. 2014;5(3):113-9. PMID: 25184031; PMCID: PMC4149738.

[20] Fluid restriction following open aortic aneurysm surgery [online]. 2010. https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN52446152

[21] Jie HY, Ye JL, Zhou HH, et al. Perioperative restricted fluid therapy preserves immunological function in patients with colorectal cancer. World J Gastroenterol. 2014 Nov 14;20(42):15852-9. doi: 10.3748/wjg.v20.i42.15852. PMID: 25400472; PMCID: PMC4229553.

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[26] Myles PS, Bellomo R, Corcoran T, et al. Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. N Engl J Med. 2018 Jun 14;378(24):2263-2274. doi: 10.1056/NEJMoa1801601. Epub 2018 May 9. PMID: 29742967.

[27] Effect of Intraoperative Fluid Restriction on Postoperative Outcomes in Video-assisted Thoracic Surgery (VATS) [online]. 2019. https://clinicaltrials.gov/show/NCT00854386.

[28] Intraoperative Fluid Management in Laparoscopic Bariatric Surgery [online]. 2009.https://clinicaltrials.gov/show/NCT00905502.

[29] Restricted Intravenous Fluid Regime Effects on Immunological Indicators of Elderly Patients Operated for Abdominal Cancer [online]. 2011.

https://clinicaltrials.gov/show/NCT01399814.

[30] Impact of Perioperative Intravenous Fluid Utilization on Postoperative Outcomes [online]. 2012. https://clinicaltrials.gov/show/NCT01563991.

[31] Comparison of Stroke Volume Variation-guided Normovolemic and Restrictive Fluid Management During Craniotomy: a Randomized Controlled Trial [online]. 2014. https://clinicaltrials.gov/show/NCT02113358.

[32] Evaluating Fluid Strategies in Thoracic Surgery Patients Utilizing a Goal Directed Approach [online]. 2014. https://clinicaltrials.gov/show/NCT02135146.

[33] Restrictive or Individualized Goal-Directed Fluid Replacement Strategy in Ovarian Cancer Cytoreductive Surgery [online] 2016. https://clinicaltrials.gov/show/NCT03519165.

[34] Brandstrup B, Svendsen PE, Rasmussen M, et al. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? Br J Anaesth. 2012 Aug;109(2):191-9. doi: 10.1093/bja/aes163. Epub 2012 Jun 17. PMID: 22710266.

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[36] Comparison of Liberal and Restrictive Fluid Management on the Endothelial Glycocalyx in Radical Cystectomy [online]. 2021. https://clinicaltrials.gov/show/NCT04780490 1.

[37] Piljic D, Petricevic M, Piljic D, et al. Restrictive versus Standard Fluid Regimen in Elective Minilaparotomy Abdominal Aortic Repair-Prospective Randomized Controlled Trial. Thorac Cardiovasc Surg. 2016 Jun;64(4):296-303. doi: 10.1055/s-0035-1548736. Epub 2015 Mar 31. PMID: 25826678.

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[40] Silva WAD, Varela CVA, Pinheiro AM, et al. Restrictive versus Liberal Fluid Therapy for Post-Cesarean Acute Kidney Injury in Severe Preeclampsia: a Pilot Randomized Clinical Trial. Clinics (Sao Paulo). 2020;75:e1797. doi: 10.6061/clinics/2020/e1797. Epub 2020 Jul 22. PMID: 32725073; PMCID: PMC7362722.

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hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time: a randomized clinical trial. Anesthesiology. 2014 Feb;120(2):365-77. doi: 10.1097/ALN.0b013e3182a44440. PMID: 23887199.

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5.5 Other disease

The trials or trial protocols were designed to focus on patients with other diseases rather than septic shock., And they didn't include a clear subgroup analysis on septic shock.

[49] Conservative versus liberal fluid therapy in patients with liver disease admitted to the intensive care unit [online]. 2015. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12615000377538.

[50] Conservative use of intravenous fluid in critically ill adults - pilot study [online]. 2016. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12616001670460.

[51] Does conservative fluid therapy compared to usual care change the outcomes in critically ill patients with acute kidney injury [online]. 2022. https://trialsearch.who.int/Trial2.aspx?TrialID=ACTRN12622000030774.

[52] Restricted fluid resuscitation among pregnant women with hemorrhagic shock: a randomised clinical study [online]. 2011. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-TRC-11001275.

[53] Effect of goal directed fluid resuscitation on severe acute pancreatitis [online]. 2018. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1800020062.

[54] de Lange N, Schol P, Lancé M, et al. Restrictive Versus Massive Fluid Resuscitation Strategy (REFILL study), influence on blood loss and hemostatic parameters in obstetric hemorrhage: study protocol for a randomized controlled trial. Trials. 2018 Mar 6;19(1):166. doi: 10.1186/s13063-018-2512-z. PMID: 29510717; PMCID: PMC5838856.

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[62] Vaara ST, Ostermann M, Selander T, et al. Protocol and statistical analysis plan for the REstricted fluid therapy VERsus Standard trEatment in Acute Kidney Injury-REVERSE-AKI randomized controlled pilot trial. Acta Anaesthesiol Scand. 2020 Jul;64(6):831-838. doi: 10.1111/aas.13557. Epub 2020 Feb 26. PMID: 32022904; PMCID: PMC7384021.

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[64] Zou Q, Li Q, Liu J, et al. Application value of limited fluid resuscitation in early treatment of hemorrhagic shock. Biomed Res 2017;28:7191–4.

5.6 Same research

The studies described in these articles overlapped with previous studies that had been excluded before, or included into the meta-analysis, according to their trial registration numbers.

[65] Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care [online]. 2014. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2014-000902-37-DK.

[66] Restrictive Fluid Administration vs. Standard of Care in Emergency Department Sepsis Patients - a Multicenter, Randomized Clinical Feasibility Trial [online]. 2021.

https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2021-000224-35-DK.

[67]Jessen MK, Andersen LW, Thomsen MH, et al. Restrictive Fluid Administration vs. Standard of Care in Emergency Department Sepsis Patients (REFACED Sepsis)-protocol for a multicenter, randomized, clinical, proof-of-concept trial. Pilot Feasibility Study. 2022 Mar 29;8(1):75. doi: 10.1186/s40814-022-01034-y. PMID: 35351214; PMCID: PMC8962933.

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6. The GRADE results

Supplement Figure 9. The GRADE assessment results. The results demonstrated moderate confidence in the findings on incidence of severe AKI, as well as the results of all second outcomes except the ICU LOS, which received limited confidence. And the result of incidence of worse AKI was rated as of high certainty.

Author(s):
Question: Restrictive fluid resuscitation compared to liberal fluid resuscitation in sepsis associated hypotension and shock
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	restrictive fluid resuscitation	liberal fluid resuscitation	Relative (95% CI)	Absolute (95% CI)		
incidence of severe AKI												
9	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	410/1863 (22.0%)	477/1849 (25.8%)	**RR 0.88** (0.79 to 0.97)	**31 fewer per 1,000** (from 54 fewer to 8 fewer)	⨁⨁⨁◯ Moderate[a,b]	
mortality												
9	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	581/1915 (30.3%)	590/1898 (31.1%)	**RR 0.99** (0.90 to 1.08)	**3 fewer per 1,000** (from 31 fewer to 25 more)	⨁⨁⨁◯ Moderate[a,b]	
ICU LOS												
7	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1091	1065	-	MD **0.33 lower** (0.79 lower to 0.13 higher)	⨁⨁◯◯ Low[a,b]	
incidence of worse AKI												
3	randomised trials	not serious[a]	not serious	not serious	not serious	none	43/184 (23.4%)	54/183 (29.5%)	**RR 0.76** (0.55 to 1.05)	**71 fewer per 1,000** (from 133 fewer to 15 more)	⨁⨁⨁⨁ High[a]	
duration of ventilation												
3	randomised trials	not serious[a]	not serious	not serious	serious[a,b]	none	188	144	-	MD **41.14 lower** (68.8 lower to 13.48 lower)	⨁⨁⨁◯ Moderate[a,b]	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Blinding of participants and personnel(performance bias) and blinding of outcome assessment(detection bias) of all 5 trials were serious.
b. The variation between the numbers of participants in the trials was considerable.

7. Table of characteristics of included studies

Supplement Table 1. Characteristics of included studies

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Meyhoff , 2022	Denmark & Norway & Sweden & Switzerland & Italy & Czech Republic & United Kingdom & Belgium & Finland	31	1554	1798(500 to 4366) after 90 days	3811 (1861 to 6762) after 90 days	death within 90 days after randomization	1.suspected or confirmed infection, a plasma lactate level of 2 mmol per liter (18 mg per deciliter) or higher, receipt of ongoing infusion of a vasopressor or inotropic agent, and receipt of at least 1 liter of intravenous fluids in the 24 hours before screening.13 Patients were included if the onset of shock had been within 12 hours before screening.	A new episode of severe acute kidney injury, as defined by a modified kidney disease: Improving Global Outcomes (KDIGO) stage of 3 on a scale ranging from 1 to 3, with higher stages indicating more severe kidney injury, and the use of a modified classification because urinary output data might not have been available from all patients

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Macdonald,2018	Australia & New Zealand	8	99	2387 (1750 to 2750), 30(32 to 39) ml/kg from presentation to 6h	3000 (2250 to 3900), 43(35 to 50) ml/kg from presentation to 6h	Total fluid administered within 6h post randomization	1.Suspected infection 2. Systolic blood pressure (SBP) <100mmHg*, despite 1000ml intravenous isotonic crystalloid administered over no more than 60 minutes AND 3. Study intervention can be administered within 2 hours of inclusion criteria being met	the Acute Kidney Injury Network (AKIN) criteria based upon creatinine data. Baseline serum creatinine was defined as a stable serum creatinine recorded in the 12 months pre-randomization, or a convalescent creatinine up to 3 months post-randomization. Where no baseline creatinine was available this was estimated using the MDRD formula assuming GFR 75ml/min/1.73m^2

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Hjortrup,2016	Denmark	9	151	500(0 to 2500) for the first 5 days, 500(0 to 3250) during ICU stay after randomization	2000(1000 to 4100) for the first 5 days, 2200(1000 to 4750) during ICU after randomization	the amount of resuscitation fluid in the first 5 days after randomization and during the entire ICU stay	1. adult ICU(≥18yrs) 2.Sepsis defined as at least 2 of 4 SIRS criteria fulfilled within 24 hours according to the College of Critical Care Medicine/American College of Chest Physicians (SCCM/ACCP) 2.Suspected or confirmed site of infection OR positive blood culture 3.Suspected or confirmed circulatory impairment (hypotension/hypoperfusion/hypovolemia) for no more than 12 hours including the hours preceding ICU admission. Circulatory impairment defined as at least one of the following: Systolic blood pressure < 90 mmHg, heart rate > 140 beats/min, lactate ≥ 4 mmol/l, OR use of vasopressors. 4.At least 30 ml/kg ideal bodyweight fluid (colloids, crystalloids or blood products) given in the last 6 hours 5. Shock defined as ongoing infusion of noradrenaline (any dose) to maintain blood pressure	The KDIGO criteria (values of plasma creatinine were assessed in ICU and the use of renal replacement therapy in the 90 days after randomization; the urinary output criteria were not assessed). For patients without AKI at baseline, development of AKI after randomization was regarded as worsening of AKI.

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Corl,2019	America	2	109	(mean ± sd) 47.1±22.3ml/kg of total resuscitation IV fluid	(mean ± sd) 61.1±32.0ml/kg of total resuscitation IV fluid	30-day all-cause mortality	1. Patients with severe sepsis or septic shock, as defined by the 2012 2 International Consensus definitions: temperature > 38°C or < 36°C, heart rate of >90/min, respiratory rate of >20/min or PaCO2 <32 mmHg, white blood cell count >12000/mm3 or < 4000/mm3 or >10% immature bands, with known or suspected infection at the time of enrollment. The worst value for each variable is used obtained between triage time zero and enrollment. Since over 12% of patients ultimately diagnosed with sepsis do not meet SIRS criteria, SIRS negative patients may be enrolled if the treating attending physician clinically diagnoses severe sepsis or septic shock. 3. Severe sepsis or septic shock is defined as refractory hypotension or a lactic acid>4 mmol/L. Refractory hypotension is a systolic blood pressure (SBP)<90 mmHg or a mean arterial pressure (MAP)<65 mmHg for 15 minutes, following 1000 mL of IV fluid, or any blood pressure maintained by vasopressor administration.	Doubling in the triage creatinine from the first recorded value during the study period
Semler,2019	America	1	30	mean of fluid from IV boluses of 300 (560) in the 3 days after enrollment	mean of fluid from IV boluses of 733(1083) in the 3 days after enrollment	mean daily fluid balance (phase II) and ICU-free days (phase III)	Adults (age ≥18 years) admitted to the medical ICU at Vanderbilt University Medical Center who met 2 or more criteria for systemic inflammatory response syndrome, were receiving antimicrobial therapy, and met criteria either for shock (defined as a mean arterial pressure <60 mm Hg or vasopressor receipt) or respiratory insufficiency (defined as receipt of invasive or noninvasive mechanical ventilation or an arterial oxygen saturation <97% while receiving a fraction of inspired oxygen [FiO2] ≥0.3	The KDIGO criteria

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Douglas,2020	America & United Kingdom	13	124	Positive fluid balance at 72 hours or ICU discharge: -1.37L favoring Intervention arm, 0.65 ± 2.85L Median: 0.53L Intervention arm	Positive fluid balance at 72 hours or ICU discharge: 2.02 ± 3.44L Median: 1.22L Usual Care arm	positive fluid balance at 72 hours or ICU discharge, whichever occurred first.	Patients presenting to the Emergency Department with sepsis or septic shock (defined as 2 or more systemic inflammatory response syndrome (SIRS) criteria and a suspected or documented infection) and anticipated ICU admission. Other inclusion criteria included refractory hypotension, (mean arterial pressure < 65mmHg after receiving ≥ 1L and ≥ 2L of fluid) and enrollment within 24 hours of hospital arrival	Initiation of renal replacement therapy which could be count as KDIGO stage 3
Lindén,2024	Switzerland	6	98	6008 ml (interquartile range [IQR] 3960–8123)	9765 ml (IQR 6804–12,401)	the total volume of fluid administered within three days of inclusion	Adult patients (≥18 years of age) with septic shock (suspected/confirmed infection, plasma lactate>2 mmol/l and infusion of vasopressor to maintain MAP > 65 mmHg after adequate fluid resuscitation) within 12-h of admission to the ICU and ongoing vasopressor therapy at the time of inclusion were eligible for inclusion	The KDIGO criteria
Jessen,2022	Denmark	3	123	mean (±SD) IV crystalloid fluid volumes of 562 (±1076) ml at 24-h after randomization	mean (±SD) IV crystalloid fluid volumes of 1370 (±1438) ml at 24-h after randomization	total IV crystalloid fluid volumes at 24 h after randomization	1. unplanned ED admission; 2. age ≥ 18 years; 3. sepsis defined as (1) infection suspected by the treating clinician, (2) blood cultures drawn, (3) IV antibiotics administered or planned, and (4) an infection- related increase in the SOFA score ≥ 2; and 4. expected hospital stay > 24-h as deemed by the treating clinician	Any development or worsening of acute kidney injury, defined as the KDIGO creatinine score > 0 compared to at randomization

Study, Year (Reference)	Country	Centers, n	Participants, n	Fluid volume of restrictive or conservative resuscitation strategy, ml	Fluid volume of liberal resuscitation strategy or usual care, ml	Primary outcome	Septic shock inclusion criterion	AKI diagnosis criterion
Shapiro,2023	America	60	1563	IQR 500ml (130 to 1097) of IV fluid administration after 6-h after randomization, 1267ml (555 to 2279) after 24-h	IQR 2300ml (2000 to 3000) of IV fluid administration after 6-h after randomization, 3400ml (2500 to 4495) after 24-h	all-cause mortality before discharge home by day 90	Adult patients (≥18 years of age) with a suspected or confirmed infection (broadly defined as the administration or planned administration of antibiotic agents) and sepsis-induced hypotension (systolic blood pressure, <100 mm Hg after the administration of ≥1000 ml of intravenous fluid)	The KDIGO criteria