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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 a 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 randomised 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 AKI. Severe AKI was defined as the AKI network score 2–3 or Kidney Disease Improving Global Outcomes stages 2 and 3.

Data extraction and synthesis Two independent reviewers used standardised methods to search, screen and code included trials. Risk of bias was assessed using the Cochrane Systematic Review Handbook for randomised clinical trials. Meta-analysis was conducted using random effects models. Sensitivity and subgroup analyses, trial sequential analysis (TSA), Egger's test and the trim-and-fill method were performed. Findings were summarised in GRADE evidence profiles and synthesised qualitatively.

Results Nine 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 (risk ratio 0.87, 95% CI 0.79 to 0.96, p=0.006; 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, the positive conclusion had been confirmed. The GRADE assessment results demonstrated moderate confidence in the incidence of severe AKI, as well as the results of all second outcomes except the Intensive Care Unit length of stay (ICU LOS), which received limited confidence. 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 AKI 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.

PROSPERO registration number CRD42023449239.

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 trial sequential analysis (TSA), GRADE assessments and the Egger's test.
⇒ The number of included participants was a bit small, but the TSA result confirmed it has reached required information size.
⇒ 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 characterised by refractory hypotension, hyperlactataemia and organ dysfunction, which occurs in more than 230 000 US patients each year, leading to over 40 000 deaths annually[2 3] and affecting millions of people around the world each year.[4] Acute kidney injury (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] Patients with severe AKI have a high risk of stabilising the situation of chronic kidney disease 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 hypoperfusion.[1 10] AKI under the circumstance of vascular changes in septic shock is more related to prerenal factors instead of postrenal or intrarenal, specifically due to microvascular abnormalities sand tubular stress.[3] Therefore, correction of intravascular hypovolaemia 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 individualised 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, is to be taken into consideration. However, 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 hypoperfusion and volume depletion after initial resuscitation.[9] A resent pilot multicentre, randomised, controlled trial of critically ill patients with AKI proved that a restrictive fluid management regimen was feasible.[12] Although 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 Intensive Care Unit length of stay (ICU LOS) of patients with higher AKI network (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 randomised 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 synthesise 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 with the aim of resolving the existing uncertainties and investigating the effect of the restrictive fluid resuscitation strategy on the occurrence of severe AKI in adult patients with sepsis-associated hypotension and septic shock.

MATERIALS AND METHODS

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement methodology,[15] a systematic review and meta-analysis of randomised 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 randomised 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 (X-EC and X-TC) independently. When encountered disagreements, a third reviewer (W-TL) would provide a suggestion.

Title and abstract screening was conducted for all relevant studies and potentially relevant records were thoroughly read. The inclusion criteria were as follows: (1) the research was limited to randomised 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 and (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 AKIN[18] score 2–3 or Kidney Disease Improving Global Outcomes (KDIGO)[19] stages 2 and 3.[20] Data including primary outcome were extracted by two reviewers (X-EC and X-TC). If there were disagreements, a discussion was performed with another reviewer (W-TL).

Titles and abstracts of all reports identified in the literature searches were screened for further review. The data collected from 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 randomisation and the diagnosis criteria 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 prioritised 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 randomised clinical trials were reviewed for additional trials meeting eligibility criteria.

Dichotomous variables were expressed as counts and proportions. Means and SDs were used to describe normally distributed continuous variables. Because the ICU LOS 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 SD value based on the method of mean variance estimation presented by the Hong Kong Baptist University.[21–24]

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 randomised clinical trials. The nine studies were assessed as being at low, uncertain or high risk of bias for each of six 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 six domains.[25] The results were output by using the Review Manager ((RevMan) (Computer program) V.5.4. The Cochrane Collaboration, 2020 software was applied in the statistical analysis as well. Two reviewers assessed study quality independently (X-EC and X-TC). If there were disagreements, a discussion was performed with another reviewer (W-TL). Six 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 (V.4.4.1) formally known as the R Project for Statistical Computing.

Outcome measures

The primary outcome was the incidence of severe AKI in 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 randomised 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, a $p<0.05$ 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 nine 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 research only to see if the results changed utterly.[14 29–31] 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 (the emergency department (ED)

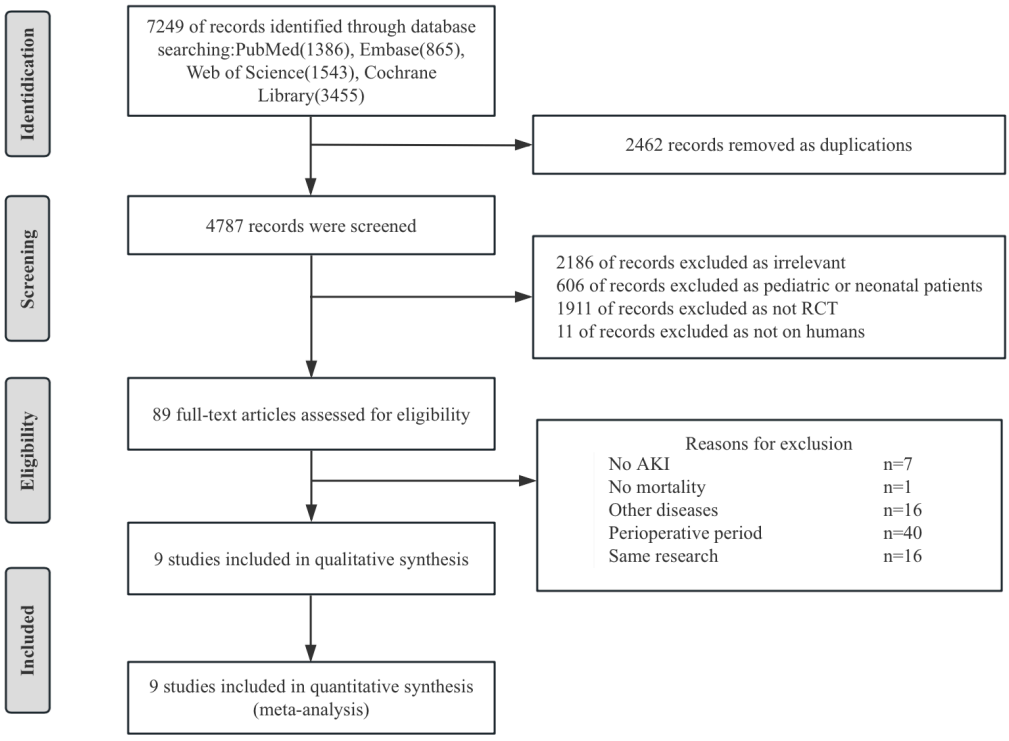

Figure 1 The process of literature search. AKI, acute kidney injury; RCT, randomised controlled trial.

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 TSA (Computer program) V.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. The process of the search of literature is summarised 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 records were removed for duplication first. 4787 records were identified as ineligible or irrelevant, leaving 90 records for full-text review. Nine studies met criteria for inclusion and were included in the quality assessment. In the end, all 9 randomised clinical trials were included in this meta-analysis covering 3718 participants. Details of the selection process are shown in figure 1.

Description of included randomised trials

Sample sizes ranged from 29 to 1563. Three studies took place in the USA, two in Denmark, one in Switzerland, one in Australia and New Zealand, one in the USA and UK. One study took place worldwide. All trials were conducted on adult patients and no pregnant patients were included. All nine studies evaluated patients with septic shock. Further characteristics of the nine chosen RCTs are summed up in online supplemental table 1. No heterogeneity was observed in these RCTs.

The overall quality of included RCTs is 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 is summarised in figure 2. Among the nine RCTs, none of the trials were double-blinded. The allocation may be blinded for the statistician. However, it was obviously impossible to blind both patients and caregivers in the medical intervention of the trials, so 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 nine 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

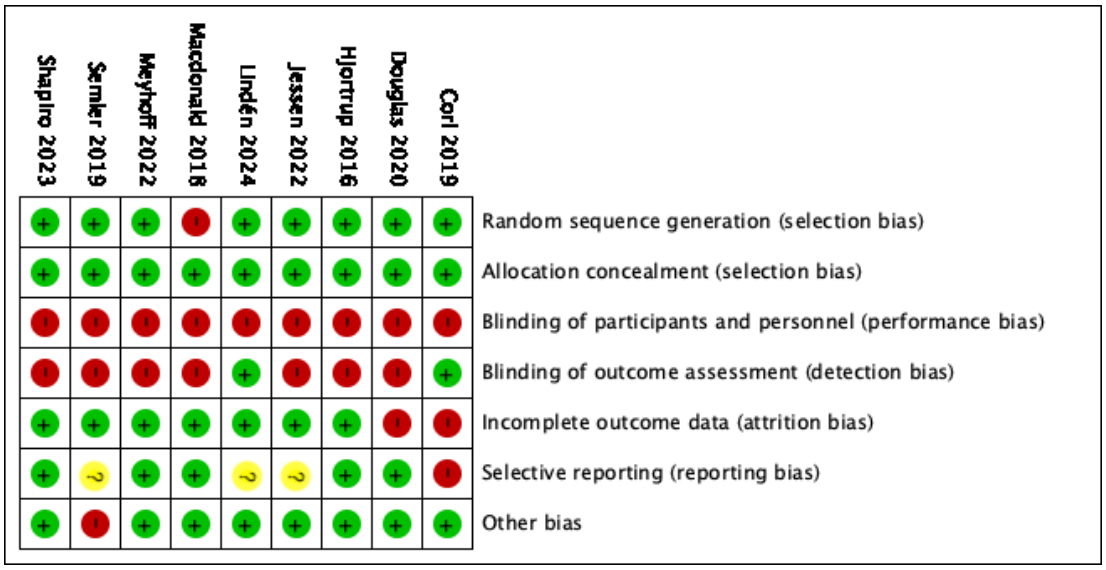

Figure 2 Risk of bias summary for each included study. Red (-) indicates high risk of bias; yellow (?) indicates unclear risk of bias; green (+) indicates low risk of bias.

onset of severe AKI, which was defined as worsening of the KDIGO stage (plasma creatinine criteria or use of renal replacement therapy (RRT)).[31 34] In two trials, the exact number of patients' of KDIGO stages 2 and 3 was not available neither in the article nor the supplement appendix.[29 35] We extracted the numbers of patients receiving continuous RRT 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*,[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 analysed for renal function. 418 of the 1863 patients analysed in the restrictive fluid resuscitation group (22.4%)and 490 of the 1849 patients analysed in the liberal fluid resuscitation group (26.5%) were diagnosed severe AKI or evaluated as KDIGO scores of 2 and 3 or reached AKIN score 2 and 3 during the follow-up of the studies (RR 0.87, 95% CI 0.79 to 0.96, p=0.006; I^2=0%). Obviously, there was a significant difference in the incidence of AKI 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 is shown in the forest plot in figure 3.

Second outcomes

Mortality

Data on all-cause mortality of the participants were available in all nine RCTs. A total of 3813 patients were tracked down for their clinical ending at the most protracted time point, including 90-day mortality in 7 RCTs,[14 29–34] 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 online supplemental figure 1.

ICU length of stay

Seven RCTs reported the patients' length of stay in ICU, of which three were measured in hours[30 33 36] and four were measured in days.[14 31 32 35] All data were extracted in the form of median and IQR and was transformed

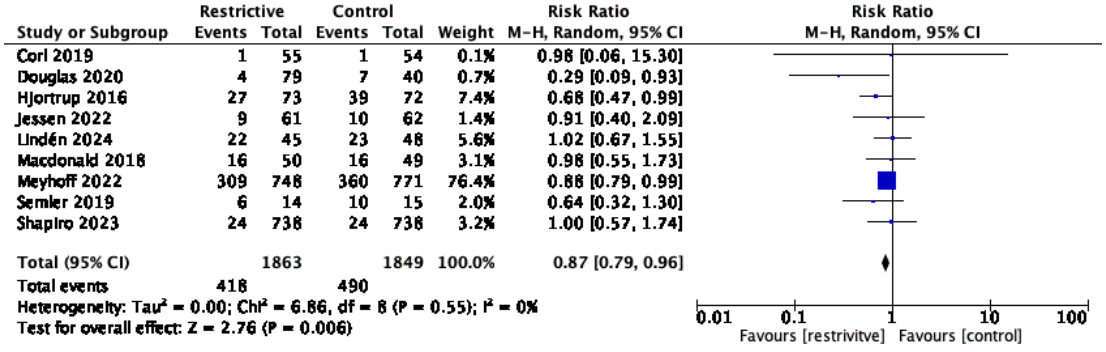

Figure 3 Forest plot for primary outcome of the incidence of severe AKI. It illustrates the result of restrictive or conservative fluid resuscitation strategy versus liberal fluid resuscitation or usual care strategy. AKI, acute kidney injury.

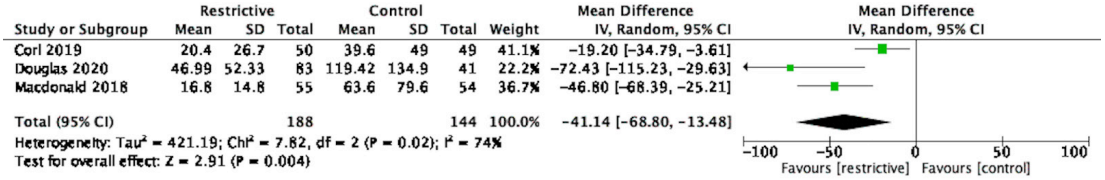

Figure 4 Forest plot for second outcome of the duration of ventilation. It shows the result of restrictive fluid resuscitation strategy versus liberal fluid resuscitation strategy on the duration of ventilation of patients with septic shock.

into value of mean and SD by the method proposed by the Hong Kong Baptist University. The result is shown in online supplemental figure 2, obviously, no heterogeneity was detected in the trial either (MD −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 three RCTs. We analysed 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 randomisation was regarded as worsening of AKI. The result is shown in online supplemental 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

Three RCTs reported the patients' mechanical ventilation hours.[33 35 36] All data were 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 is 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 (MD −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. 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 29–31] the result remained statistically meaningful (RR 0.88, 95% CI 0.79 to 0.97; p=0.01; 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 (MD −52.68, 95% CI −73.80 to −31.56; p<0.00001; I^2=9%) comparing to original analysis results. And when other two studies were removed individually, the value of I^2 remained above 75% (I^2=76% or 81%).

Subgroup analysis

All nine RCTs concluded the participants' median age. We calculated the average age and then divided the studies into two divisions according to the criterion (<70 years vs ≥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.[33–36] The rest participants were admitted into the ICU from OR, hospital wards or other ICUs, especially in multicentre trials.[13 14 29–32] Simultaneously, we analysed 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 analysing 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 0.87, 95% CI 0.79 to 0.97; p=0.009; I^2=0%) (online supplemental figure 4 and 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 did not have a connection with the mortality of the patients. No significant difference was found in the subgroup analysis. And no significant heterogeneity was detected (online supplemental figure 6 and 7).

Trial sequential analysis

TSA was conducted to calculate the optimal required information size (RIS)[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 2975 which was less than that in our study (n=3718). Trial sequential adjusted 95% CI of RR was 0.79 to 0.96 in the fixed effects model, and 0.86 to 0.87 in the random effects model. The Begg-Tang random effects model was applied to test the reliability of the result.[26] The results are shown in figure 5. The Z-curve surpassed the conventional boundary and

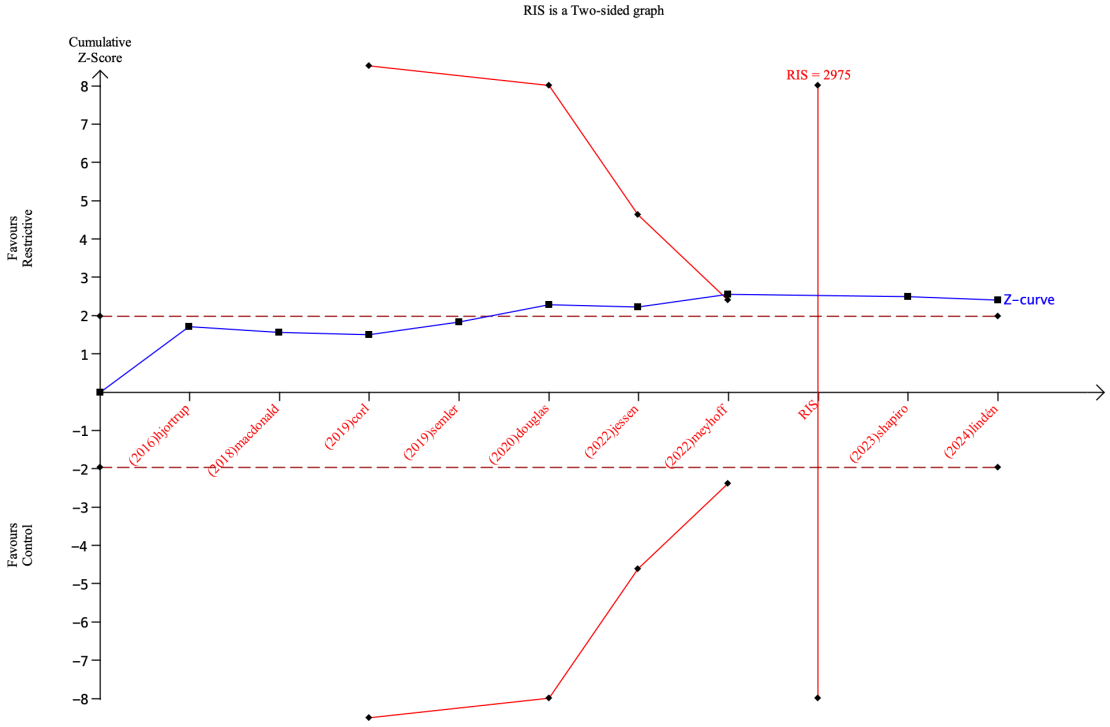

Figure 5 Trial sequential analysis (TSA). TSA showed that the diversity-adjusted required information size (RIS) was 2975. The Z-curve surpassed the conventional boundary and the trial sequential monitoring boundary both for benefit, indicating that the result was reliable and the accuracy was testified. The cumulative amount of participants met the RIS line, this positive conclusion had been confirmed.

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 (online supplemental 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. 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 (online supplemental figure 8). The result showed a p value of 0.4579 (p>0.05), meaning that no significant publication bias was detected.

DISCUSSION

This study focused on the influence of up-to-date restrictive fluid resuscitation therapy on the incidence of severe AKI in patients under such circumstance, which was a topic that little previous studies had ever discussed and we found that though restricted fluid resuscitation therapy does not 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 for more individual and specialised 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.[41] 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 42 43] 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 at the conclusion that lies with this finding. Fluid resuscitation needs to be sufficient but must be in a controlled fashion and be carried out under dynamic assessment monitoring of patients' volume situation.[44]

Volumes of intravenous resuscitation fluids directly ameliorate the tissue and organ perfusion, along with vasopressors, the treatment holds 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 oedema, thus decreasing the renal tissue perfusion. Volume overload will lead to an increase in central venous pressure, which leads to the obstruction of renal venous reflux and a decrease in 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.[45] 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[46] but also has economic benefits. High heterogeneity was found between the included three trials, which is mainly related to the Corl *et al*'s study.[36] It was likely to be concerned with less centres of the study, its more complicated septic shock inclusion criterion compared with the other two studies and higher intravenous fluid volume of the restrictive fluid group (online supplemental 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 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. Elder patients' vascular wall elasticity decreases, leading to a decrease in their ability to respond to variety of 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 stabilisation of patients' vital signs, caregivers all adapted an initial treatment before randomisation and admission into the ICU or emergency department. The treatments aimed to delay the progression of the disease. All patients included in 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[47] and gave their participants an initial fluid volume of 30 mL/kg.[14 31 35 36] One trial clearly limited the initial infusion of restricted fluid protocol to 1000 mL as long as the patients' vital signs had stabled.[29] The other four did not mention whether the intervention included an initial resuscitation fluid volume.[30 32–34] So, the amount of resuscitation fluid can be recognised as sufficient. In all nine RCTs, seven of which applied norepinephrine or to say norepinephrine,[14 29–33 35] and two were unclear.[34 36] The time frame for the intervention fluid therapy differed extremely in these trials. Three were within the first 24-hour period,[29 30 34] two were 72 hours[35 36] and the rest were 6-hour post randomisation,[33] 5 days[31] and 14 days[32] individually. The patients received the assigned intervention from the time of randomisation until they were discharged from the ICU, for a maximum of 90 days.[14] There were also differences of the 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 the number of participants and the long duration of the intervention means. The results of this meta-analysis were confirmed by various analyses, and adding other studies provided more comprehensive insights into this topic.

Results of the GRADE assessments were one with high certainty (incidence of worse AKI), three with moderate certainty (incidence of severe AKI, mortality, duration of ventilation) and one 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 issues, 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 were not included, which may lead to publication bias. There was little evidence supporting that fluid restriction strategy affects patients' mortality and ICU LOS. This could be due to differences in the initial causes of infection among all patients, making outcome comparisons complex. The risk of bias in 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 number 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 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 the fluid restriction strategy is superior to usual care when it comes to reducing the incidence of severe AKI 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.

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REFERENCES

1 Cecconi M, Evans L, Levy M, *et al*. Sepsis and septic shock. *Lancet* 2018;392:75–87.
2 Seymour CW, Rosengart MR. Septic Shock: Advances in Diagnosis and Treatment. *JAMA* 2015;314:708–17.
3 Ma S, Evans RG, Iguchi N, *et al*. Sepsis-induced acute kidney injury: A disease of the microcirculation. *Microcirculation* 2019;26:e12483.
4 Rhodes A, Evans LE, Alhazzani W, *et al*. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;43:304–77.
5 Petejova N, Martinek A, Zadrazil J, *et al*. Acute Kidney Injury in Septic Patients Treated by Selected Nephrotoxic Antibiotic Agents-Pathophysiology and Biomarkers-A Review. *Int J Mol Sci* 2020;21:7115.
6 Montomoli J, Donati A, Ince C. Acute Kidney Injury and Fluid Resuscitation in Septic Patients: Are We Protecting the Kidney? *Nephron* 2019;143:170–3.
7 Watchorn J, Huang D, Bramham K, *et al*. Decreased renal cortical perfusion, independent of changes in renal blood flow and sublingual microcirculatory impairment, is associated with the severity of acute kidney injury in patients with septic shock. *Crit Care* 2022;26:261.
8 Ronco C, Ferrari F, Ricci Z. Recovery after Acute Kidney Injury: A New Prognostic Dimension of the Syndrome. *Am J Respir Crit Care Med* 2017;195:711–4.
9 Hoste EAJ, Kellum JA, Selby NM, *et al*. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018;14:607–25.
10 Evans L, Rhodes A, Alhazzani W, *et al*. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med* 2021;49:e1063–143.
11 Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ* 2016;353:i1585.
12 Vaara ST, Ostermann M, Bitker L, *et al*. Restrictive fluid management versus usual care in acute kidney injury (REVERSE-AKI): a pilot randomized controlled feasibility trial. *Intensive Care Med* 2021;47:665–73.
13 Peters E, Antonelli M, Wittebole X, *et al*. A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit. *Crit Care* 2018;22:188.
14 Meyhoff TS, Hjortrup PB, Wetterslev J, *et al*. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. *N Engl J Med* 2022;386:2459–70.
15 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
16 Kellum JA, Lameire N, Aspelin P, *et al*. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl (2011)* 2012;2:1–138.
17 Thomas ME, Blaine C, Dawnay A, *et al*. The definition of acute kidney injury and its use in practice. *Kidney Int* 2015;87:62–73.
18 Cruz DN, Ricci Z, Ronco C. Clinical review: RIFLE and AKIN--time for reappraisal. *Crit Care* 2009;13:211.
19 Rochwerg B, Alhazzani W, Sindi A, *et al*. Fluids in Sepsis and Septic Shock Group. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med* 2014;PMID:347–55.

20 Silversides JA, Major E, Ferguson AJ, *et al*. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med* 2017;43:155–70.
21 Shi J, Luo D, Wan X, *et al*. Detecting the skewness of data from the five-number summary and its application in meta-analysis. *Stat Methods Med Res* 2023;32:1338–60.
22 Shi J, Luo D, Weng H, *et al*. Optimally estimating the sample standard deviation from the five-number summary. *Res Synth Methods* 2020;11:641–54.
23 Luo D, Wan X, Liu J, *et al*. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;27:1785–805.
24 Wan X, Wang W, Liu J, *et al*. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
25 Higgins JP, Altman DG, Gøtzsche PC, *et al*. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;PMCID:d5928.
26 Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015;44:512–25.
27 Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
28 Serpa Neto A, Veelo DP, Peireira VGM, *et al*. Fluid resuscitation with hydroxyethyl starches in patients with sepsis is associated with an increased incidence of acute kidney injury and use of renal replacement therapy: a systematic review and meta-analysis of the literature. *J Crit Care* 2014;29:185.
29 Shapiro NI, Douglas IS, Brower RG, *et al*. National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network. *N Engl J Med* 2023;PMCID:499–510.
30 Lindén A, Spångfors M, Olsen MH, *et al*. Protocolized reduction of non-resuscitation fluids versus usual care in septic shock patients (REDUSE): a randomized multicentre feasibility trial. *Crit Care* 2024;28:166.
31 Hjortrup PB, Haase N, Bundgaard H, *et al*. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med* 2016;42:1695–705.
32 Semler MW, Janz DR, Casey JD, *et al*. Conservative Fluid Management After Sepsis Resuscitation: A Pilot Randomized Trial. *J Intensive Care Med* 2020;35:1374–82.
33 Macdonald SPJ, Keijzers G, Taylor DM, *et al*. Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial. *Intensive Care Med* 2018;44:2070–8.
34 Jessen MK, Andersen LW, Thomsen M-LH, *et al*. Restrictive fluids versus standard care in adults with sepsis in the emergency department (REFACED): A multicenter, randomized feasibility trial. *Acad Emerg Med* 2022;29:1172–84.
35 Douglas IS, Alapat PM, Corl KA, *et al*. Fluid Response Evaluation in Sepsis Hypotension and Shock: A Randomized Clinical Trial. *Chest* 2020;158:1431–45.
36 Corl KA, Prodromou M, Merchant RC, *et al*. The Restrictive IV Fluid Trial in Severe Sepsis and Septic Shock (RIFTS): A Randomized Pilot Study. *Crit Care Med* 2019;47:951–9.
37 Wetterslev J, Thorlund K, Brok J, *et al*. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol* 2009;9:86.
38 Jiang L, Jiang S, Zhang M, *et al*. Albumin versus Other Fluids for Fluid Resuscitation in Patients with Sepsis: A Meta-Analysis. *PLoS ONE* 2014;9:e114666.
39 Zarbock A, Nadim MK, Pickkers P, *et al*. Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. *Nat Rev Nephrol* 2023;19:401–17.
40 Xu X, Nie S, Liu Z, *et al*. Epidemiology and Clinical Correlates of AKI in Chinese Hospitalized Adults. *Clin J Am Soc Nephrol* 2015;10:1510–8.
41 Gibbison B, López-López JA, Higgins JPT, *et al*. Corticosteroids in septic shock: a systematic review and network meta-analysis. *Crit Care* 2017;21:78.
42 Nagendran M, Russell JA, Walley KR, *et al*. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. *Intensive Care Med* 2019;45:844–55.
43 Patel A, Laffan MA, Waheed U, *et al*. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ* 2014;349:g4561.
44 Joannidis M, Druml W, Forni LG, *et al*. Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017 : Expert opinion of the Working Group on Prevention, AKI section, European Society of Intensive Care Medicine. *Intensive Care Med* 2017;43:730–49.
45 Griffin BR, Liu KD, Teixeira JP. Critical Care Nephrology: Core Curriculum 2020. *Am J Kidney Dis* 2020;75:435–52.
46 Papazian L, Klompas M, Luyt CE. Ventilator-associated pneumonia in adults: a narrative review. *Intensive Care Med* 2020;46:888–906.
47 Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med* 2018;44:925–8.