



Balanced crystalloids versus normal saline for fluid resuscitation in critically ill patients: A systematic review and meta-analysis with trial sequential analysis



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ABSTRACT

Introduction: Fluid resuscitation is a fundamental component of the management of critically ill patients, but whether choice of crystalloid affects patient outcomes remains controversial. Therefore, we performed this meta-analysis to compare the efficacy and safety of balanced crystalloids with normal saline. **Methods:** We searched the MEDLINE, Cochrane Central and EMBASE up to October 2018 to identify randomized controlled trials (RCTs) that compared balanced crystalloids versus normal saline in critically ill patients. The primary outcome was mortality. The secondary results were the incidence of acute kidney injury (AKI) and risk of receiving renal replacement therapy (RRT). Two authors independently screened articles based on the inclusion and exclusion criteria. The meta-analysis was conducted using Revman 5.3, trial sequential analysis (TSA) 0.9 and STATA 12.0.

Results: Nine RCTs were identified. The pooled analyses showed that there were no significant differences in mortality (relative risk (RR) = 0.93, 95% confidence interval (CI) = 0.86, 1.01, P = 0.08), incidence of AKI (RR 0.94, 95% CI 0.88, 1.00, P = 0.06) or RRT use rate (RR 0.94, 95% CI 0.69, 1.27, P = 0.67) between balanced crystalloids and normal saline groups. However, TSA did not provide conclusive evidence.

Conclusions: Among critically ill patients receiving crystalloid fluid therapy, use of a balanced crystalloid compared with normal saline did not reduce the mortality, risk of severe AKI or RRT use rate. Further large randomized clinical trials are needed to confirm or refute this finding.

Trial registration: A protocol of this meta-analysis has been registered on PROSPERO (registration number: CRD42018094857).

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1. Introduction

Fluid resuscitation is a fundamental component of the management of critically ill patients, but whether choice of crystalloid affects patient outcomes remains controversial [1,2]. Currently, normal saline is the most commonly used resuscitation fluid. How-

ever, concern has focused on the hypothesis that the high chloride content of saline contributes to the development of acute kidney injury (AKI) [3,4]. Alternatives to normal saline include crystalloids with electrolyte compositions that more closely resemble that of plasma, such as Lactated Ringer's solution, Hartmann solution, or Plasma-Lyte [5,6]. Although observational data suggest that those balanced crystalloids may be associated with a decreased risk of severe AKI, this advantage of balanced crystalloids was not found in a recent RCT of critically ill patients [6].

Our previous network meta-analysis [7], which focused on fluid resuscitation in critically ill patients, found that balanced crystalloids, especially Plasma-Lyte, are presumably the best choice for

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most critically ill patients who need fluid resuscitation. However, the evidence was not conclusive.

Recently, three RCTs [8–10] have been published that provide new evidence on this topic, but the findings are not entirely consistent with each other. To provide the most recent available evidence, we conducted this meta-analysis to evaluate the efficacy and safety of balanced crystalloids versus normal saline for fluid resuscitation in critically ill patients, and we further used trial sequential analysis (TSA) to determine whether the current evidence was robust and conclusive.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used to perform this meta-analysis [11].

2.1. Search strategy

A literature search of MEDLINE, Cochrane Central and EMBASE databases from database inception to October 2018 was performed. The search terms used were “normal saline” or “isotonic saline” or “sodium chloride” compared with “lactated ringer” or “Hartmann” or “Plasma-Lyte” or “buffered crystalloid” or “balanced crystalloids” and “randomized” or “randomized”. The searches were limited to published studies in human subjects. There were no language restrictions. We also hand-searched conference proceedings and the reference lists of review articles (Appendix A).

2.2. Eligibility criteria

The inclusion criteria were as follows: 1) population: critically ill patients (≥ 18 years old) requiring fluid resuscitation, the length of follow up was according to the included studies; 2) intervention: balanced crystalloids (contains Lactated Ringer’s, Hartmann and Plasma-Lyte); 3) comparison: normal saline; 4) outcome measure: the primary outcome was mortality. The secondary outcomes were incidences requiring RRT and the incidence of AKI (AKI of stage 2 or higher (according to the Kidney Disease: Improving Global Outcomes plasma creatinine criteria) and injury or higher (according to the RIFLE categories)); 5) study design: RCT.

The exclusion criteria were as follows: 1) patients with pre-existing chronic renal failure; 2) patients younger than 18 years old; 3) repeated data; 4) fluids used as maintenance rather than resuscitation.

2.3. Study selection

Two independent investigators performed the study selection. Disagreements between two investigators were resolved in meetings or adjudicated by a third reviewer.

2.4. Data extraction

Two independent reviewers (CL and GML) performed the data extraction using a standardized form. The following data on study characteristics were collected: first author, publication year, study design, number of patients, mean age of patients, patient characteristics, and balanced crystalloids type. The other two independent reviewers (DW and JH) checked the data to make sure it was correct. The methodological quality of included trials was assessed by two reviewers according to the Cochrane Risk of Bias Tool.

2.5. Grading the quality of evidence

Two reviewers evaluated the quality of evidence according to the Grading of Recommendations Assessment, Development and

Evaluation (GRADE) methodology. Based on risk of bias, indirectness, imprecision, inconsistency and publication bias, the quality of the evidence was classified as high, moderate, low or very low. The software of GRADE Pro version 3.6 was used for this analysis.

2.6. Statistical analysis

Dichotomous outcomes were expressed as relative risks (RRs) with 95% confidence intervals (CI), and continuous outcomes were expressed as the mean difference (MD) with 95% CI. Statistical heterogeneity across studies was analyzed by using the I^2 statistic. An $I^2 > 50\%$ indicated significant heterogeneity [12]. The fixed-effect model was used to analyze results with acceptable or no heterogeneity, and the random-effect model was used to analyze results with significant heterogeneity. Subgroup and sensitivity analyses were performed to investigate potential between-study heterogeneities and estimate other potentially confounding factors. Statistical analyses were performed using Review Manager, version 5.3 (RevMan, The Cochrane Collaboration, Oxford, UK). The Begg and Egger tests were employed using STATA 12.0 (Stata Corporation, College Station, TX, USA). A P value < 0.05 was considered a statistically significant.

2.7. Trial sequential analysis

To determine whether the evidence from a meta-analysis is reliable and conclusive and to reduce the risk of reaching a false-positive or false-negative conclusion, the trial sequential analysis (TSA) was used [13]. This method, which combines an a priori information size calculation with the adaptation of monitoring boundaries, can be used to control the P value and widen the confidence intervals [14]. When the cumulative z-curve enters the futility area or crosses the trial sequential monitoring boundary, the anticipated intervention effect may reach a sufficient level of evidence. If the z-curve does not cross any of the boundaries and

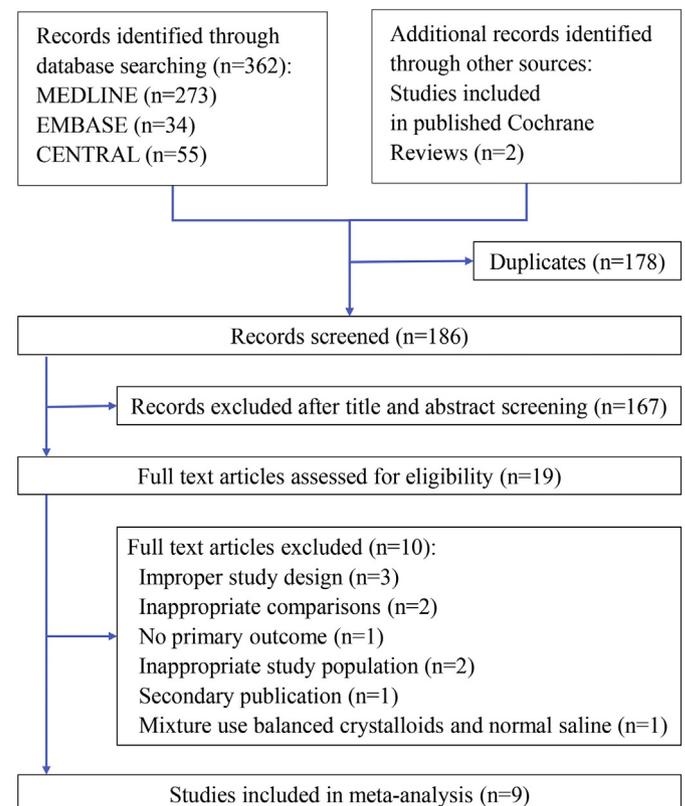


Fig. 1. Flow chart of the study selection.

the required information size has not been reached, the evidence is inadequate to reach a conclusion [15]. We calculated the required information size based on a relative risk reduction of 10%. The type I error (α) and power ($1-\beta$) were set as 0.05 and 0.90, respectively. The control event rates were calculated from the normal saline group. The TSA was conducted with the use of TSA version 0.9 beta software (<http://www.ctu.dk/tsa>).

3. Results

3.1. Search results and study characteristics

The process of study selection is outlined in Fig. 1. In total, nine studies [6,8–10,16–20] met the inclusion criteria. The main characteristics of the included studies are summarized in Table 1. These studies were published between 2011 and 2018. Six studies [6,8–10,17,20] focused on patients in ICU, two studies [18,19] focused on patients with acute pancreatitis and one study [16] included trauma patients.

3.2. Risk of bias and grades of evidence

The risk of bias is summarized in Fig. 2. Randomized sequence generation and allocation concealment were reported adequately in most studies. Three studies were high-quality studies with low risk of bias in all items. The GRADE Working Group grade of evidence was moderate for mortality, incidence of AKI and incidence of RRT use.

3.3. Primary outcome: mortality

Eight studies reported mortality, and no statistically significant difference was found between the balanced crystalloids and normal saline groups (RR = 0.93, 95% CI = 0.86, 1.01, $P = 0.08$, $I^2 = 0\%$; Fig. 3a). The fixed effects model was used to conduct TSA, and the cumulative Z-curve did not enter the futility area and did not cross the conventional boundary (Fig. 3b). Sensitivity analyses were performed to compare Plasma-Lyte with normal saline and compare Lactated Ringer's with normal saline. Similarly, no differences were found (Table 2).

3.4. Secondary outcomes

3.4.1. Incidence of AKI

Seven studies reported the incidence of AKI. There was no significant difference between the two groups (RR 0.94, 95% CI 0.88, 1.00, $P = 0.06$, $I^2 = 0\%$; Fig. 4a). Due to the low heterogeneity, the fixed-effect model was used for TSA, and the results showed that the cumulative Z-curve did not enter the futility area and did not cross the conventional boundary (Fig. 4b). Sensitivity analyses were performed to compare Plasma-Lyte with normal saline and compare Lactated Ringer's with normal saline. Similarly, no differences were found (Table 2).

3.4.2. RRT use rate

Only five studies reported the RRT use rate, and no significant difference was found between the two groups (RR 0.94, 95% CI 0.69, 1.27, $P = 0.67$, $I^2 = 39\%$; Table 2). Sensitivity analyses were

Table 1
Characteristics of included studies.

Study	Setting	Population	No. of patients (M/F)	Mean age (years)	Severity	Balanced crystalloids type	Fluid volume (24 h)
Annane D [17] (2013; multi-country)	57 participating ICUs	Sepsis, trauma, or hypovolemic shock without sepsis or trauma	BC: 72 (NR) NS: 1035 (NR)	63 (50–75)	SAPSII: 50 (36–65) ^b	Lactated ringer's	NR
Young JB [16] (2014; United States)	Level 1 trauma center	Adult trauma patients (≥ 18 years) requiring blood transfusion, intubation, or operation within 60 min	BC: 22 (16/6) NS: 24 (19/5)	BC: 38 ± 19^a NS: 39 ± 14^a	BC: 24 ± 18 (ISS) ^a NS: 22 ± 14 (ISS) ^a	Plasma-Lyte A	BC: 9000 ± 5500^a NS: 10300 ± 6500^a
Young P [6] (2015; Australian and New Zealand)	Four tertiary ICUs	ICU patients receiving crystalloid fluid therapy as clinically indicated	BC: 1152 (739/413) NS: 1110 (746/364)	BC: 60.1 ± 16.8^a NS: 61.0 ± 16.3^a	BC: 14.1 ± 6.9 (APACHEII) ^a NS: 14.1 ± 6.7 (APACHEII) ^a	Plasma-Lyte 148	NR
Verma B [9] (2016; Australia)	Three multidisciplinary ICUs	ICU patients (≥ 18 years) receiving crystalloid fluid resuscitation	BC: 33 (21/12) NS: 34 (21/13)	BC: 62 (45–70) ^b NS: 64 (46–72) ^b	BC: 55 (44–81) (APACHEIII) ^b NS: 64 (48–73) (APACHEIII) ^b	Plasma-Lyte 148	BC: 1090 (620–2500) ^b NS: 1275 (435–2243) ^b
Semler MW [8] (2016; United States)	A tertiary medical ICU	ICU patients receiving crystalloid fluid therapy	BC: 520 (268/252) NS: 454 (246/208)	BC: 57 (44–68) ^b NS: 58 (46–70) ^b	NR	Lactated ringer's solution and Plasma-Lyte A	BC: 1424 (500–3377) ^b NS: 1617 (500–3628) ^b
Semler MW [10] (2018; United States)	Five ICU at an academic center	Patients (≥ 18 years) who were admitted to a participating ICU	BC: 7942 (4540/3402) NS: 7860 (4557/3303)	BC: 58 (44–69) ^b NS: 58 (44–69) ^b	NR	Lactated ringer's solution and Plasma-Lyte A	BC: 1000 (0–3210) ^b NS: 1020 (0–3500) ^b
Ratanarat R [20] (2017; Thailand)	ICU	NR	BC: 88 (NR) NS: 93 (NR)	NR	NR	NR	NR
Wu BU [19] 2011;	A 777-bed tertiary care center	Patients (≥ 18 years) with acute pancreatitis	BC: 19 (8/11) NS: 21 (14/7)	BC: 50 (40–73) ^b NS: 54 (40–60) ^b	BC: 3 (0–6) (APACHEIII) ^b NS: 3 (1–5) (APACHEIII) ^b	Lactated ringer's	NR
Choosakul S [18] 2018;	A 1200-bed tertiary care center and pancreatic center	Patients (18–80 years old) with acute pancreatitis	BC: 23 (12/11) NS: 24 (17/7)	BC: 54.8 ± 20.4^a NS: 48.3 ± 13.6^a	BC: 1 (0–2) (SIRS) ^b NS: 1 (0–2) (SIRS) ^b	Lactated ringer's	BC: 4929.6 ± 1265.6^a NS: 5374.2 ± 768.8^a

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BC: Balanced crystalloids; NR, not report; NS: Normal saline; SAPS, Simplified Acute Physiology II score.

^a Mean \pm standard error.

^b Median (interquartile range).

performed to compare the Plasma-Lyte and normal saline. Similarly, no differences were found (Table 2).

3.4.3. ICU length of stays

Six studies reported the results for ICU length of stay, and no significant difference was found between the two groups (RR - 0.31 95% CI -1.60,0.97, P = 0.47, I² = 100%; Table 2).

3.4.4. Publication bias

Assessment of publication bias using Egger and Begg tests showed that there was no potential publication bias among the included trials (Egger's test, P = 0.25; Begg's test, P = 0.06).

4. Discussion

This systematic review and meta-analysis of nine RCTs evaluated the efficacy and safety of balanced crystalloids versus normal saline for fluid resuscitation in critically ill patients. The present meta-analysis suggests that there is no difference in mortality, AKI morbidity and RRT use rate. However, the subsequent TSA did not reach a definitive conclusion. Therefore, further high quality RCTs are needed to confirm or refute this finding.

An earlier study focused on this topic, which included six RCTs with 19,332 patients, showed no difference on various clinical outcomes including in-hospital mortality, AKI, overall ICU mortality, and new RRT between balanced crystalloids and isotonic saline [21]. Our study included more studies and we further used the TSA analysis to determine whether the evidence from this meta-analysis is reliable and conclusive and to reduce the risk of reaching a false-positive or false-negative conclusion.

The different fluid types have difference effects on different diseases, populations and genders. For example, patients with sepsis may more sensitive to metabolic acidosis and may suffer more AKI or increased mortality [22,23]. The patients included in this analysis come from different sources, but with the limited studies included in this meta-analysis, we could not perform more subgroup or sensitivity analyses. Therefore, more studies are needed to evaluate the effect of different fluids on different patients and diseases. Meanwhile, individualized treatments are necessary for each critically ill patient.

Normal saline is still the most commonly used crystalloid worldwide [5,24]. Many observational studies have shown that the use of normal saline is most likely associated with an increased incidence of AKI, hyperchloremic acidosis, coagulation disturbances, hemodynamic instability and mortality [25–27]. The balanced crystalloids in this meta-analysis contain Lactated Ringer's and Plasma-Lyte. Lactated Ringer's solution is a hypotonic solution (sodium concentration, 130 mmol/L) [28] and may lead to hyponatremia when use for resuscitation in critically ill patients [29]. Hyponatremia is also an independent predictor for hospital mortality [30]. The electrolyte composition of Plasma-Lyte closely mimics human plasma in its content of electrolytes, osmolality, and pH [31]. Therefore, we performed sensitivity analysis to compare Plasma-Lyte with normal saline and compare Lactated Ringer's with normal saline. However, no significant differences were found.

In this meta-analysis we only evaluated mortality, AKI morbidity, RRT use rate and ICU length of stay. However, we did not find any difference between the two groups. Therefore, whether the Plasma-Lyte is more effective than normal saline or Lactated Ringer's needs to be further evaluated. Further studies should also examine other outcomes, such as the incidence of hyponatremia or hospitalization cost.

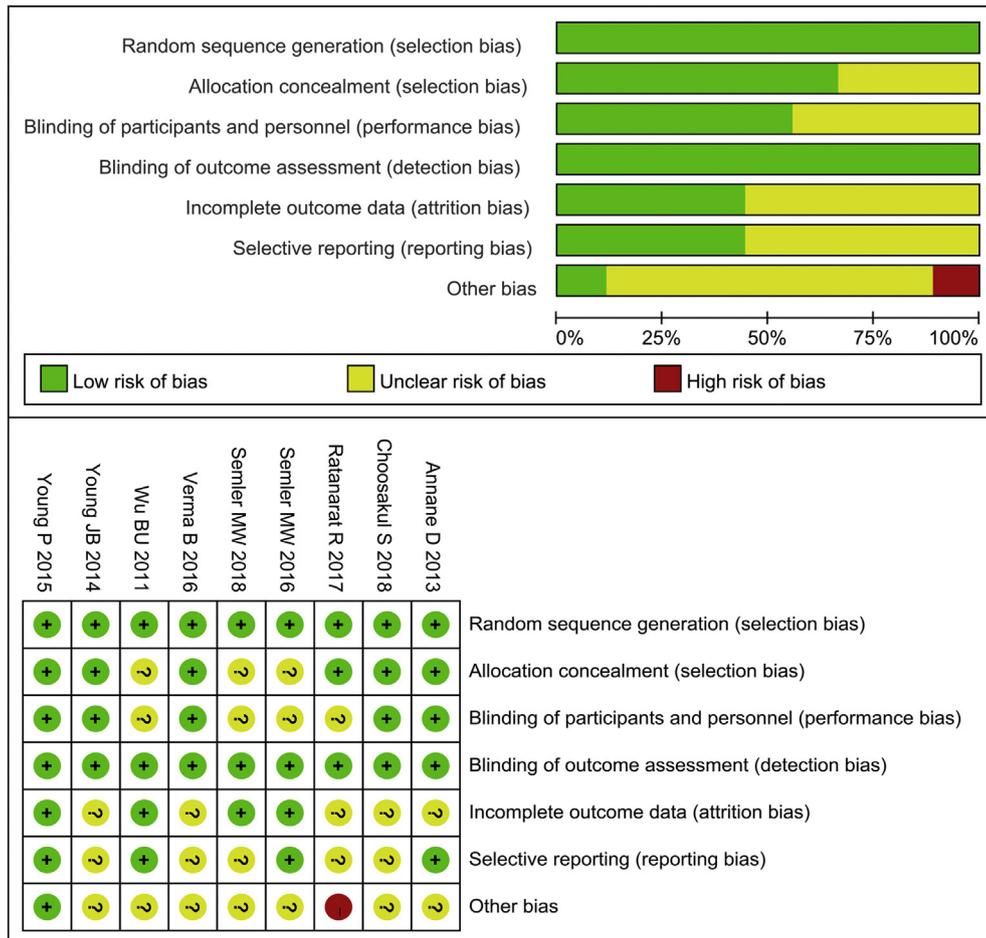


Fig. 2. Assessment for risk of bias.

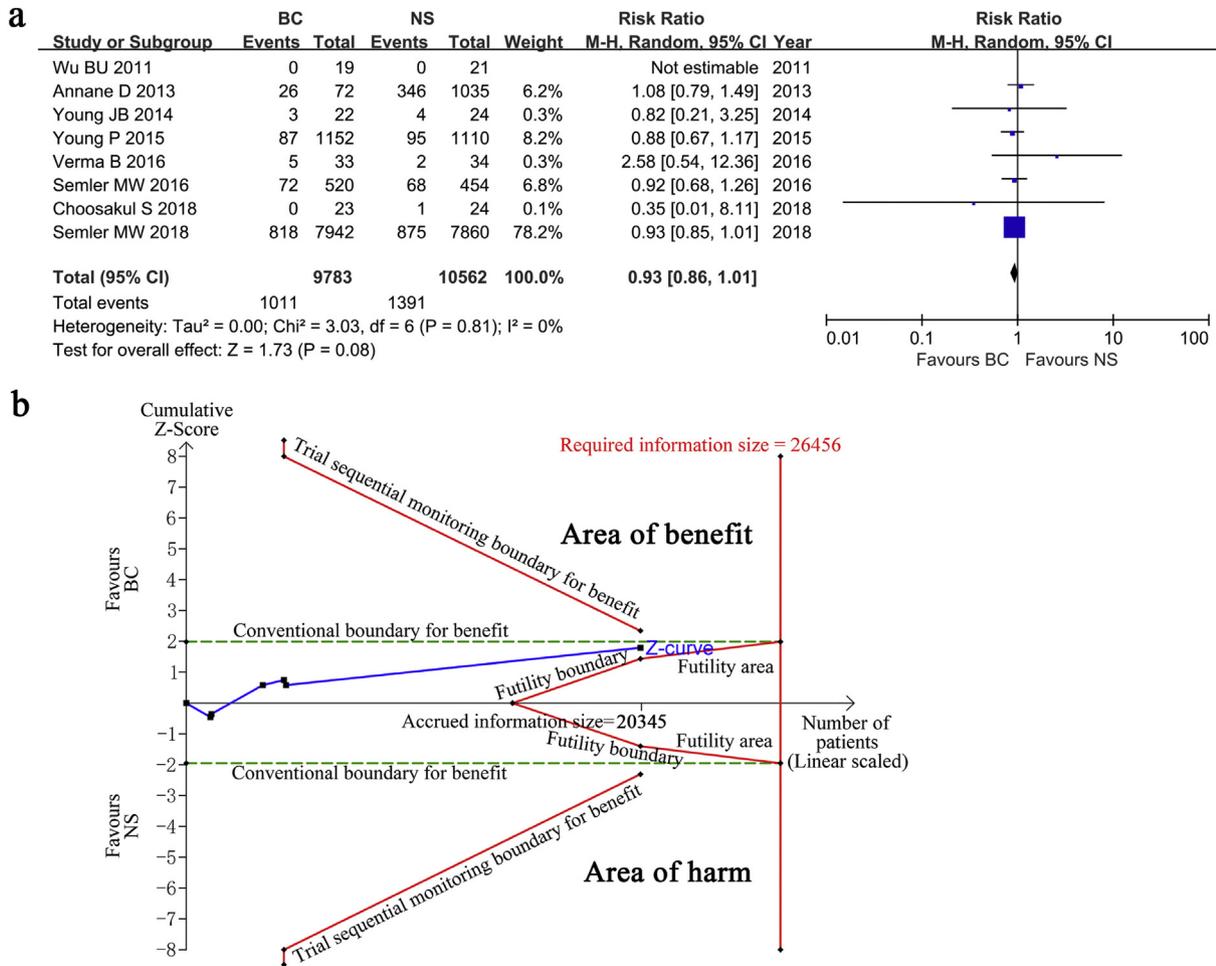


Fig. 3. Effect of balanced crystalloids versus normal saline on mortality. a. Forest plot of mortality. b. Trial sequential analysis of mortality. A diversity-adjusted information size of 26,456 participants calculated on the basis of a mortality rate of 13.2% in the normal saline group, relative risk reduction 10%, $\alpha = 5\%$ (two sided), $\beta = 10\%$, and $I^2 = 0\%$. The solid blue line represents the cumulative Z-curve, which did not cross the trial sequential monitoring boundary and did not reach the futility area. BC, balanced crystalloids; NS, normal saline; M-H, Mantel-Haenszel. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fluid overload frequently occurs in critically ill patients and many studies report its significant association with higher mortality and more RRT [33–36]. Several studies have shown that normal saline (due to its high sodium content) may result in more fluid overload [27,37]. In this meta-analysis, the fluid volume had a significant diversity between each study, but whether a patient's exposure to a positive or negative fluid balance is detrimental remains controversial. Therefore, when a patient needs fluid resuscitation, we should not only consider the fluid type but also consider the fluid responsiveness [38].

Our meta-analysis has several potential limitations. First, due to the limited data, it was difficult to perform more subgroup or sensitivity analyses. Second, patients included in this meta-analysis had varying degrees of severity (trauma, sepsis or acute pancreati-

tis), which will have caused heterogeneity and reduced the stability of the results. Third, the hyperchloremia, hyponatremia and fluid overload were all independent factors related to higher mortality. However, we could acquire sufficient evidence to perform comprehensive analyses; therefore, more studies focused on those issues are urgently needed. Fourth, there was the potential for incomplete retrieval of identified research studies, which could have introduced publication bias.

5. Conclusions

Among critically ill patients receiving crystalloid fluid therapy, use of a balanced crystalloid compared with normal saline did not reduce the mortality, the risk of AKI or the RRT use rate. Further

Table 2
Other outcomes.

Outcomes	Comparison	Number of studies	Risk ratio (95%CI)	Test for effect (P value)	Heterogeneity I ² (P value)
Mortality	PL vs NS	3 (6,9,16)	0.91 (0.69, 1.19)	0.48	0% (0.41)
	LR vs NS	3 (17,18,19)	1.07 (0.78, 1.47)	0.69	0% (0.48)
AKI morbidity	PL vs NS	2 (6, 9)	1.08 (0.83, 1.39)	0.58	0% (0.42)
	LR vs NS	3 (18,19,20)	0.94 (0.54, 1.62)	0.82	0% (0.73)
RRT use rate	BC vs NS	5 (6,8,9,10,20)	0.94 (0.69, 1.27)	0.67	39% (0.16)
	PL vs NS	2 (6, 9)	1.02 (0.67, 1.55)	0.93	0% (0.42)
	LR vs NS	1 (20)	0.35 (0.12, 1.05)	0.06	NA
ICU length of stay	BC vs NS	6 (6,8,9,16,18,19)	-0.31 (-1.60,0.97)	0.47	100% (<0.01)

Abbreviations: AKI, Acute kidney injury; BC, Balanced crystalloids; ICU, Intensive care medicine; LR, Lactated ringer's; NA, Not applicable; NS, Normal saline; PL, Plasma-Lyte; RRT, Renal replacement therapy.

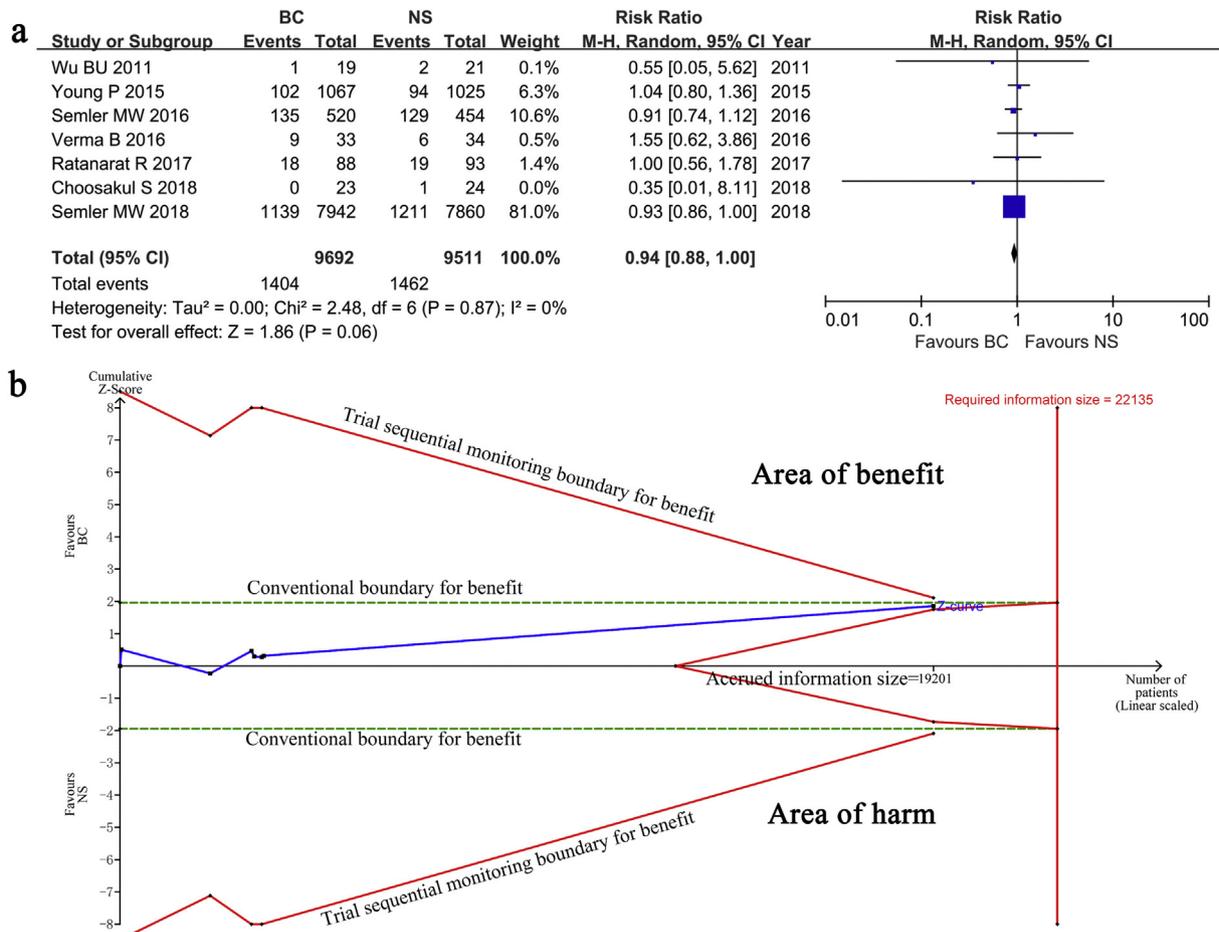


Fig. 4. Effect of balanced crystalloids versus normal saline on AKI incident. a. Forest plot of severe AKI incident. b. Trial sequential analysis of AKI incident. A diversity-adjusted information size of 22,135 participants calculated on the basis of a mortality rate of 15.4% in the normal saline group, relative risk reduction 10%, $\alpha = 5\%$ (two sided), $\beta = 10\%$, $I^2 = 0\%$. The solid blue line represents cumulative Z-curve, which did not cross the trial sequential monitoring boundary and did not reach the futility area. AKI, acute kidney injury; BC, balanced crystalloids; M-H, Mantel-Haenszel; NS, normal saline. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

large randomized clinical trials are needed to confirm or refute this finding.

Abbreviations

AKI	acute kidney injury
CI	confidence interval
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
MD	mean difference
ICU	intensive care unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RR	relative risk
RRT	renal replacement therapy
TSA	trial sequential analysis

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contribution

CL, GML and DW contributed equally to this work. CL, GML and DW conceived the study, participated in the design, collected the data, performed statistical analyses and drafted the manuscript. YL, ZM and PH performed statistical analyses and helped to draft the manuscript. JH, RL and DH collected the data and revised the manuscript critically for important intellectual content. FHZ collected the data, performed statistical analyses and helped to revise the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Not applicable.

Appendix A

Table 1

Conferences searches.

American Association for the Surgeons of Trauma (2008–2018)
American College of Chest Physicians (2010–2018)
American Society of Anaesthesiology (2009–2018)
American Thoracic Society (2009–2018)
Canadian Anesthesiologists' Society (2008–2018)
European Society of Intensive Care Medicine (2008–2018)
Society of Critical Care Medicine (2008–2018)

Table 2

Search strategy.

	n
1 Target terms for literature search: ("normal saline" OR "isotonic saline" OR "sodium chloride" OR "lactated ringer" OR "Hartmann" OR "Plasma-Lyte" OR "buffered crystalloid" OR "balanced crystalloids") and ("sepsis" OR "infection" OR "septic shock" OR "severe sepsis" OR "shock" OR "systemic inflammatory response syndrome" OR "SIRS" OR "injury" OR "trauma" OR "hemorrhage" OR "toxic shock syndrome" OR "burns" OR "acute pancreatitis" OR "critical ill" OR "critical illness" OR "intensive care unit" OR "intensive care" OR "critical care" OR "ICU")	2245
2 Limit 1 to clinical trial Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]	788
3 Limit 2 to humans	364

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