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Balanced crystalloids versus normal saline for trauma resuscitation: A systematic review and meta-analysis

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ABSTRACT

Background: Fluid resuscitation is a key element for the management of critical care patients. However, it is uncertain whether balanced crystalloids may be preferred over normal saline (NS) in trauma patients. Therefore, the current meta-analysis compared the efficacy and safety of balanced crystalloids with NS in trauma resuscitation.

Methods: The online search for articles relevant to our study objective was conducted in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus. This search was limited to randomized controlled trials (RCTs) available in English language. The primary outcome of our study was all-cause mortality, and secondary outcomes were incidence of acute kidney injury (AKI), length of intensive care unit (ICU) stay, ventilator-free days, need for renal replacement therapy (RRT), and base deficit. The statistical analyses were performed using RevMan 5.4.1, and bias assessment was performed using the Cochrane risk of bias tool (ROB-2).

Results: Six distinct RCTs involving 1950 trauma patients were included. The pooled analyses revealed that NS was associated with decreased mortality in traumatic brain injury (TBI) patients (OR: 1.35; 95 % CI: 1.06 to 1.72; $p = 0.02$), but not in trauma patients without TBI (OR: 1.17; 95 % CI: 0.47 to 2.90; $p = 0.74$). Similarly, more ventilator-free days were observed in the NS group than in the balanced crystalloids group among TBI patients (MD: −0.67 days; 95 % CI: −0.86 to −0.48; $p < 0.00001$), but not in trauma patients without TBI (MD: 3.0 days; 95 % CI: −3.36 to 9.36; $p = 0.36$). On the other hand, no significant difference was observed in total volume of study fluid administered, AKI incidence and length of ICU stay among patients with or without TBI.

Conclusions: In trauma patients with TBI, NS was associated with lower mortality and more ventilator-free days than balanced crystalloids, whereas no significant difference was noted in trauma populations without TBI. Moreover, there was no significant difference between NS and balanced crystalloids in terms of AKI incidence, need for RRT, and ICU stay, suggesting that balanced crystalloids remain a safe and reasonable option for trauma resuscitation.

1. Introduction

Trauma is one of the leading causes of morbidity and mortality globally [1], with the World Health Organization (WHO) reporting 4.4 million deaths annually due to unintentional or violence-related injuries [2]. Trauma patients often present with hemorrhagic and hypovolemic shock, which are the most preventable causes of early trauma-related deaths, and can promptly be managed using fluid resuscitation. However, the choice for fluid resuscitation has been a matter of long-standing debate. Historically, 0.9 % sodium chloride (normal saline) has been the most commonly administered resuscitation fluid, with research suggesting that over 200 million liters are prescribed in the United States alone every year [3-5]. Nevertheless, growing evidence has questioned its physiologic neutrality and safety profile. Indeed, human studies have reported that normal saline (NS) infusion is associated with acidosis, reduced renal cortical blood flow, delayed and decreased urine output, gastrointestinal dysfunction, increased infections, and acute kidney injury (AKI) [6-11].

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Over the last two decades, a number of randomized and observational studies have investigated the efficacy of NS and balanced crystalloids in critically ill populations. An observational study by Rowell and colleagues reported that prehospital Lactated Ringer's solution (LRS) was associated with increased mortality compared to NS in patients with traumatic brain injury (TBI) [12]. In contrast, the SALT and SPLIT randomized clinical trials (RCTs) found no significant difference between Plasm-Lyte solution and NS in terms of AKI development, need for renal replacement therapy (RRT), and in-hospital mortality [13,14]. Findings from other studies indicate that balanced crystalloids are associated with better electrolyte and acid-base balance in patients receiving kidney transplant [15], undergoing elective neurosurgery [16], and post-operative severe TBI [17]. Notably, a double-blind RCT of 42 patients with severe TBI reported that the use of balanced crystalloid (Isofundin) resulted in the reduced incidence of hyperchloremic acidosis compared with NS, but no difference in intracranial pressure (ICP) was observed [18].

Despite the investigation of NS and balanced crystalloids in critically ill patients, it is uncertain whether the findings in this population can directly be extrapolated to trauma patients. Therefore, the current systematic review and meta-analysis evaluated the efficacy and safety of NS compared with balanced crystalloids in trauma resuscitation.

2. Methods

2.1. Literature search and information sources

We conducted a comprehensive search for relevant studies across multiple electronic databases, including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus. The search included all RCTs published from inception to October 2025, but was limited to records authored in English. The search strategy through the electronic databases used a range of keywords and phrases, including “Fluid resuscitation,” “Trauma,” “Traumatic brain injury,” “balanced crystalloids,” “Lactated Ringer,” “Normal saline,” and “Plasma-Lyte.” We also screened the reference lists of included studies, grey literature, and previously published review articles to identify additional studies. The complete search strategy in each electronic database is provided in Appendix A.

2.2. Eligibility criteria

Studies were included in this meta-analysis if they satisfied the PICOS criteria provided in Table 1. Furthermore, we only included studies enrolling more than 10 participants in each intervention group.

2.3. Data extraction and data items

Two review authors screened the included studies and extracted the data required to undertake this meta-analysis in a standardized Excel spreadsheet. The following data were extracted: The first author, publication year, study design, study location (country), patient demographics (total number of trauma patients, sex distribution, mean/median age of patients, mean injury severity score, and injury mechanism), follow-up period, intervention details, and the reported outcomes. Differences in the extracted data were harmonized via discussion between the two reviewers or by enquiring the view of a third reviewer.

The primary outcome of our study was all-cause mortality, which encompassed ICU mortality, in-hospital mortality, or mortality at the final follow-up of each study. Secondary outcomes were incidence of AKI, length of ICU stay, ventilator-free days, total volume of study fluid administered, need for RRT, and base deficit.

2.4. Quality assessment

The methodological quality of included trials was assessed using the Cochrane Risk of Bias tool, which is incorporated into the Review Manager software (RevMan version 5.4.1; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). With this tool, we graded the bias of each RCT across seven different domains, specifically random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Other bias was evaluated by determining whether the studies were conducted in single or multiple medical institutions.

2.5. Data synthesis

Statistical analyses in the current study were accomplished using the RevMan version 5.4.1. software. Dichotomous data (mortality and AKI incidence) were pooled using odds ratio (OR), while continuous variables, such as ICU stay and ventilator-free days, were analyzed using mean difference (MD). These pooled outcomes were provided with their corresponding 95 % confidence intervals (CIs). Interstudy heterogeneity was determined using the I^2 statistic, with values between 0 and 25, 26–75 %, and >75 % indicating low, moderate, and high heterogeneity, respectively [19,20]. A fixed-effect model was applied for low heterogeneity, while a random-effect model was applied for moderate or high heterogeneity. Subgroup analysis was conducted according to the patient population (trauma patients with or without TBI) for each pooled outcome. For studies where continuous data were reported as median and interquartile range or range, the mean and standard deviation were estimated using the formula provided by Wan and colleagues [21].

3. Results

3.1. Search results

We identified 575 potential studies from the online search. These studies were critically screened manually or using the Covidence software, of which 322 duplicates were eliminated. The titles and abstracts

Table 1
Inclusion and exclusion criteria.

Criterion	Included	Excluded
Participants (P)	Adults or pediatric patients in prehospital, emergency department, operating room, or ICU presenting with traumatic injuries requiring fluid resuscitation.	Non-traumatic patients or studies mixing trauma with other populations, but do not provide separate data for trauma patients.
Intervention (I)	Balanced crystalloids, including but not limited to Plasma-Lyte, Lactated Ringer's, and Hartmann's solution.	Non-balanced crystalloids, blood products, or colloids.
Comparison (C)	Normal saline (0.9% sodium chloride)	Other fluid therapies, e.g., colloids, hypertonic saline etc.
Outcomes (O)	At least one of the following outcomes: All-cause mortality, total volume of study fluid administered, incidence of AKI, need for RRT, length of hospital or ICU stay, or acid-base status.	–
Study design (S)	Randomized controlled trials (RCTs)	Observational studies, case reports, conference/meeting abstracts, case series, narrative reviews, editorials, commentaries, or meta-analyses.

of the remaining 253 unique articles were screened, of which 234 were deemed irrelevant to our study objective and were excluded. Finally, we included 6 RCTs and excluded another 13 for the following reasons: 1 was an observational study, 10 included critically ill patients but did not separate the data for trauma patients, and 2 were non-English records (Fig. 1).

3.2. Characteristics of the included studies

Six RCTs involving 1950 trauma patients were included in the analysis [14,18,22-25]. These trials were published between 2013 and 2024, and were conducted in several countries, including the United States ($n = 2$), Brazil ($n = 1$), New Zealand (n = 1), Malaysia (n = 1), and France (n = 1). Moreover, several balanced crystalloids, such as Lactated Ringer's, Plasma Lyte, Isofundin, and Sterofundin were used for trauma resuscitation (Table 2).

3.3. Primary outcome

All the included trials were used in the mortality analysis. In a subgroup of trauma patients with TBI, the pooled results showed significantly lower mortality in patients receiving NS compared to those receiving balanced crystalloids (OR: 1.35; 95 % CI: 1.06 to 1.72; $p = 0.02$). However, no statistically significant difference in mortality was observed between the balanced crystalloid and NS groups among trauma patients without TBI (OR: 1.17; 95 % CI: 0.47 to 2.90; $p = 0.74$) (Fig. 2).

3.4. Secondary outcomes

The secondary outcomes are displayed in Figs. 3–6. A subgroup analysis according to the patient population revealed no significant difference in the incidence of AKI among trauma patients with (OR: 1.14; 95 % CI: 0.07 to 19.42; $p = 0.93$) and without TBI (OR: 0.47; 95 % CI: 0.13 to 1.69; $p = 0.25$) (Fig. 3). Similarly, the pooled results demonstrated no statistically significant difference between NS and balanced crystalloid in terms of length of ICU stay among trauma patients with (MD: −0.83 days; 95 % CI: −5.47 to 3.82; $p = 0.73$) and without TBI (MD: −1.66 days; 95 % CI: −6.02 to 2.70; $p = 0.46$) (Fig. 4). Regarding ventilator-free days, the balanced crystalloid group demonstrated significantly fewer days without ventilation compared to the NS group in patients with TBI (MD: −0.67 days; 95 % CI: −0.86 to −0.48; $p < 0.00001$), but no statistically significant difference in patients without TBI (MD: 3.0 days; 95 % CI: −3.36 to 9.36; $p = 0.36$) (Fig. 5). The amount of study fluids administered between the two groups was statistically similar among trauma patients with TBI (MD: 26.13 mL; 95 % CI: −275.81 to 328.07; $p = 0.87$) and those without TBI (MD: 1.30 L; 95 % CI: −2.20 to 4.80; $p = 0.47$) (Fig. 6).

Due to insufficient data, meta-analyses on the need for RRT and acid-base balance were not conducted. Nevertheless, Poh and colleagues

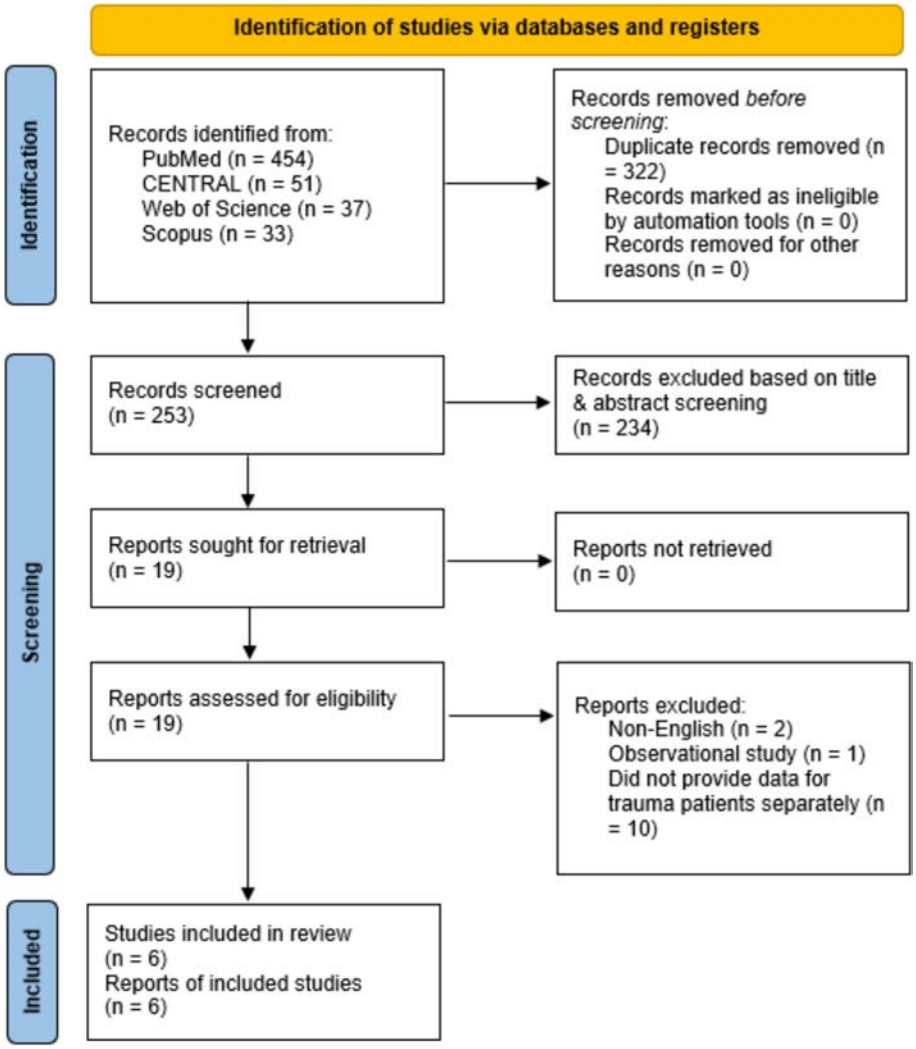

Fig. 1. PRISMA flow chart for study selection.

Table 2
Summary of study characteristics.

Author ID	Study Design	Country	Patient demographics					Intervention (Balanced crystalloids)	Comparator (Normal saline)	Reported Outcomes
			Sample size	M/F	Age (years)	Injury Mechanism	ISS			
Roquilly et al.2013 [18]	Single-center, double-blind RCT	France	36	29/7	IG: 49 CG: 47	NR	NR	Isofundin containing Na 140 mmol/L, K 4 mmol/L, Ca 2.5 mmol/L, Mg 1 mmol/L, Cl 127 mmol/L, Acetate 24 mmol/L, and Malate 5 mmol/L.	0.9 % NaCl containing Na 153 mmol/L and Cl 153 mmol/L	Length of ICU stay and ICU mortality
Zampieri et al.2021 [22]	Double-blind factorial RCT	Brazil	483	NR	NR	NR	NR	Plasma-Lyte solution containing Na 140 mmol/L, K 5 mmol/L, Mg 1.5 mmol/L, Cl 98 mmol/L, acetate 27 mmol/L, and Gluconate 23 mmol/L.	0.9 % NaCl containing Na 154 mmol/L and Cl 154 mmol/L	90-day mortality
Poh et al.2024 [23]	Double-blind RCT	Malaysia	70	66/4	IG: 28.5 CG: 27.5	Motor vehicle collision (52) Fall from height (11) Others (7)	IG: 39.5 (34.0–44.5) CG: 34 (28.0–43.0)	Sterofundin containing Na 145 mmol/L, K 4 mmol/L, Mg 1.0 mmol/L, Ca 2.5 mmol/L, Cl 127 mmol/L, acetate 24 mmol/L and malate 5 mmol/L.	0.9 % NaCl containing Na 154 mmol/L and Cl 154 mmol/L	In-hospital mortality, 6-month mortality, ventilator-free days, and AKI incidence.
Lombardo et al.2022 [24]	Pragmatic, unblinded, cluster-randomized, multiple-crossover RCT	United States	1157	744/413	IG: 51 CG: 52	Penetrating (43) Blunt (1114)	IG: 19.3 (10.2) CG: 18.6 (9.7)	Lactated Ringer's or Plasma-Lyte A	0.9 % NaCl	In-hospital mortality, ventilator-free days, need for RRT, and length of ICU stay
Young et al.2014 [25]	Double-blind, parallel-group RCT	United States	46	35/11	IG: 38 CG: 39	Penetrating (20) Blunt (26)	IG: 24 ± 18 CG: 22 ± 14	Plasma-Lyte A	0.9% NaCl	In-hospital mortality, ventilator-free days, length of ICU stay, and AKI incidence
Young et al.2015 [14]	Double-blind, cluster-randomized, double-crossover RCT	New Zealand	158	NR	NR	NR	NR	Plasma-Lyte 148	0.9 % NaCl	In-hospital mortality and incidence of AKI.

Note: RCT: Randomized controlled trial, NR: Not reported, IG: Intervention group (Balanced crystalloids), CG: Control group (Normal saline), AKI: Acute kidney injury, ICU: Intensive care unit.

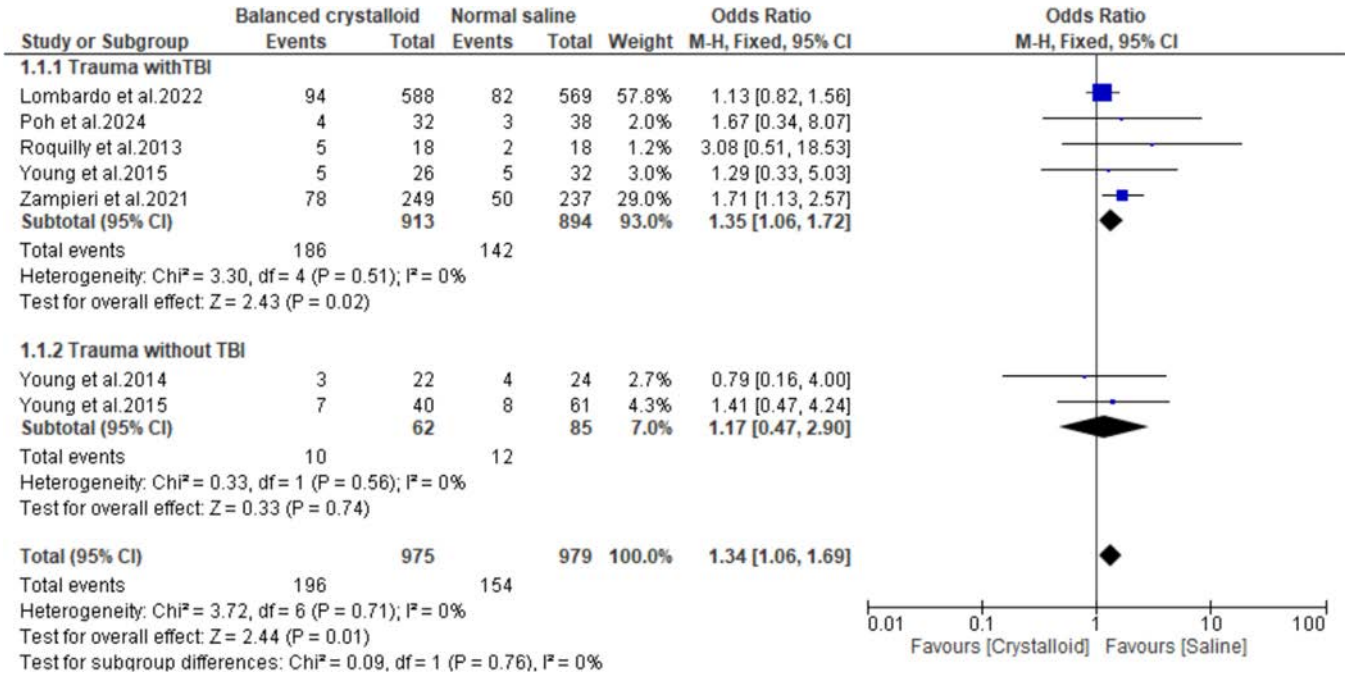

Fig. 2. Mortality rate in trauma patients receiving balanced crystalloids or normal saline.

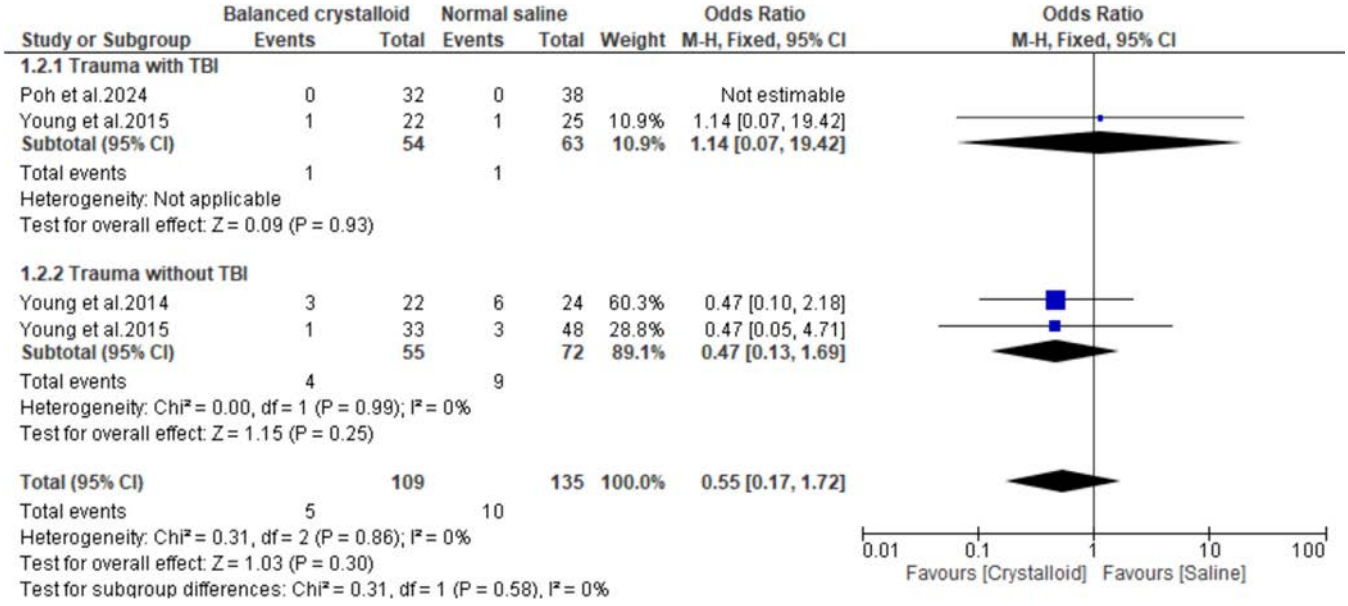

Fig. 3. Incidence of acute kidney injury in trauma patients receiving balanced crystalloids or normal saline.

reported that none of 70 patients with TBI required RRT after receiving NS or balanced crystalloid solution [23]. On the other hand, a secondary analysis of the SMART clinical trial found that of the 1157 patients with TBI, two patients, both of whom received balanced crystalloid, required new RRT during their hospitalization [24].

Regarding acid-base balance, Young et al. [25] found that Plasma-Lyte A, when compared to NS in the resuscitation of acutely injured trauma patients, resulted in a more rapid and sustained clearance of base deficit (Change in base excess at 24 h: 7.5 vs 4.4 mmol/L, respectively). Similarly, Poh et al. [23] observed a significant difference in base deficit among TBI patients on day 1, with NS demonstrating a higher base deficit than Sterofundin (2.9 vs. 3.90 mmol/L; $p < 0.05$). However, this significant difference was not recorded on subsequent days.

3.5. Risk of bias outcomes

Fig. 7 shows a summary of the risk of bias outcomes. Only one RCT was unblinded, meaning it had a high risk of performance and detection bias. Furthermore, three studies were conducted in in single center; thus, they were assigned a high risk of other bias.

4. Discussion

The present meta-analysis compared the impacts of balanced crystalloids and NS in the resuscitation of trauma patients, with the focus being on patients with and without TBI. Our analysis revealed that NS was associated with a significantly lower mortality rate and more days without ventilation than balanced crystalloid in TBI patients. However, no significant difference was observed in the incidence of AKI and the length of ICU stay. The analysis also revealed no significant difference between the two treatment groups among trauma patients without TBI in terms of mortality, incidence of AKI, the length of ICU stay, and ventilator-free days.

Previous meta-analyses on the impact of balanced crystalloids and NS on mortality rates among TBI patients have yielded similar results. A meta-analysis by Dong et al. [26] reported that mortality rates were significantly higher in TBI patients receiving balanced crystalloid solutions. A 2023 network meta-analysis evaluating the fluid choice in critically ill patients also found that NS could be preferable for TBI patients [27]. Furthermore, a more recent meta-analysis found that in patients with TBI, balanced solutions resulted in higher mortality than NS [28]. The reason for this negative impact of balanced crystalloids on mortality

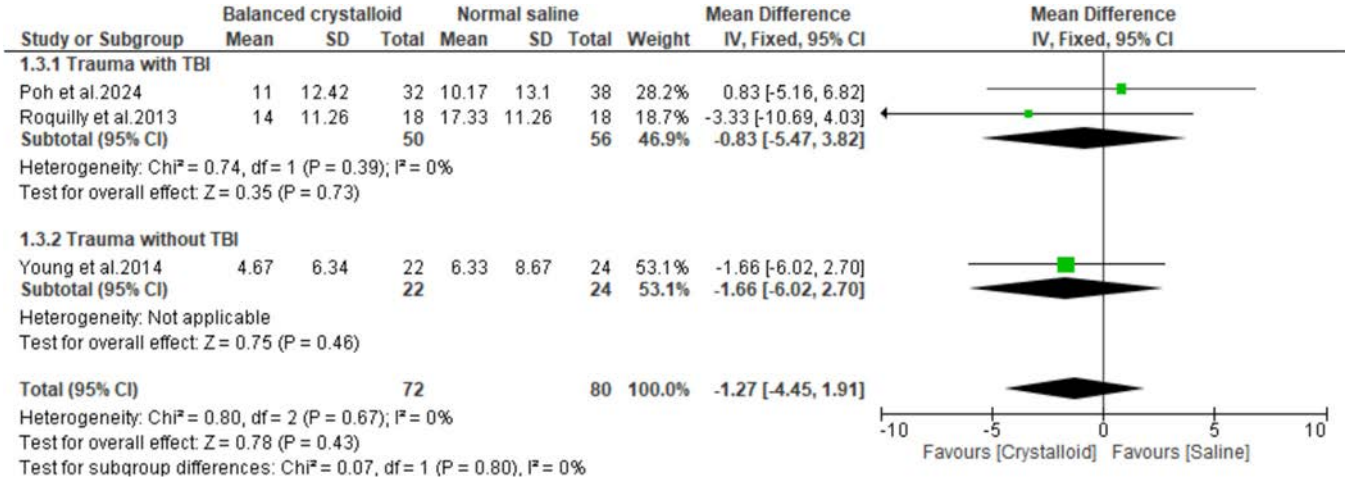

Fig. 4. Length of ICU stay for trauma patients receiving balanced crystalloids or normal saline.

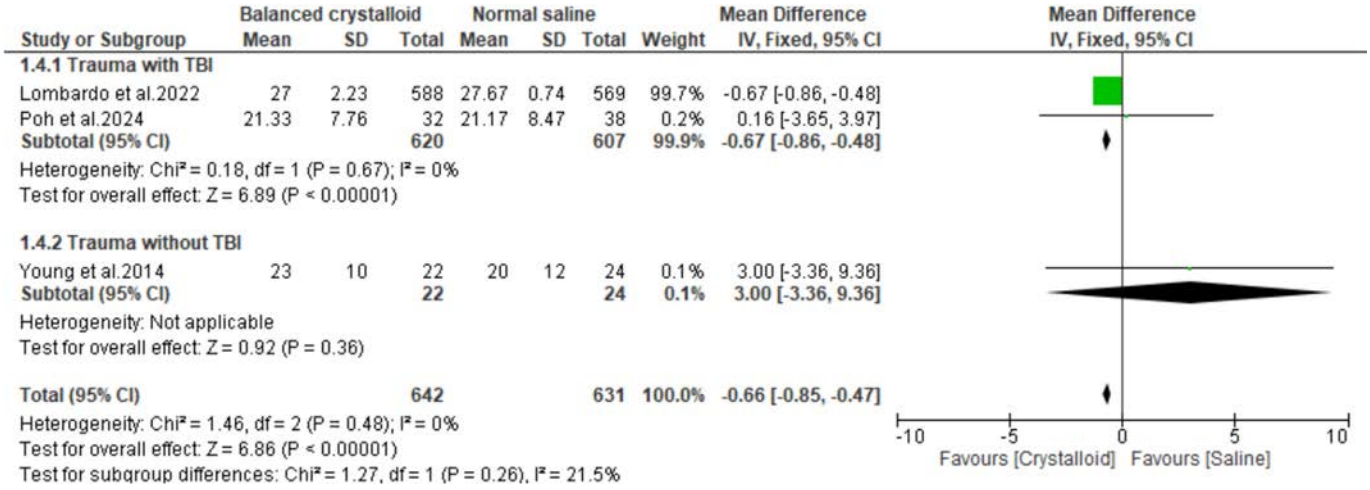

Fig. 5. Ventilator-free days for trauma patients receiving balanced crystalloids or normal saline.

is not entirely clear, but it can be attributed to several factors. Generally, balanced crystalloids have lower tonicity than NS, which might predispose TBI patients to developing or worsening cerebral edema, increasing mortality risk, or functional impairment sufficient to outweigh the potential benefits of balanced crystalloids. Indeed, several animal studies have shown that large volumes of balanced crystalloids can lower serum osmolarity, resulting in increased cerebral edema through the passage of water across the blood-brain barrier. A comparative study of dogs subjected to 30 min of sustained hypovolemic shock found that LRS contributed to increased intracranial pressure (ICP) compared to hypertonic saline [29]. Similarly, a study investigating the effects of LRS and 6 % hetastarch solutions in anesthetized rabbits using a model of isovolemic hemodilution reported a mild increase in ICP after LR infusion that dissipated within 4 h [30].

Another possible explanation for the difference in mortality rate among TBI patients is the difference in sodium concentration between NS and balanced crystalloids. NS generally contains a higher concentration of sodium than balanced solutions. Therefore, it can be beneficial in TBI patients since even a small drop of serum sodium can increase brain swelling and ICP, increasing the risk of mortality. Finally, many patients with TBI receive hyperosmolar therapies, such as hypertonic saline or mannitol, to try and minimize cerebral edema. These therapies can obviate the potential benefits of slightly hyperosmolar solutions, such as balanced crystalloids. Nevertheless, it is essential to note that of the five clinical trials evaluating mortality risk in TBI patients, only the BaSICS trial demonstrated a significantly lower mortality rate in the NS group [22]. Therefore, further research in large-sample prospective trials, exclusively focusing on TBI patients, is needed to confirm whether NS truly improves the survival of TBI patients compared to balanced crystalloids.

Our study also found no significant difference between NS and balanced crystalloids in the incidence of AKI among trauma patients with or without TBI. These findings are consistent with a previous meta-analysis, which recorded no significant difference in the incidence of AKI among critically ill patients receiving NS or balanced crystalloids (RR: 0.94; $p = 0.06$) [31]. In contrast, prior studies involving other populations suggest that saline is associated with increased risk of AKI. A prospective, open-label observational study of critically ill patients found that chloride-rich fluids, such as 0.9 % saline, were associated with increased risk for AKI after adjusting for sex, APACHE III score, diagnosis, operative status, baseline creatinine level, and admission type [6]. Furthermore, a pragmatic RCT of critically ill patients found that major adverse kidney events were significantly higher in the saline group compared to the balanced crystalloids group [13]. These contradictory findings highlight the need for further clinical studies involving exclusively trauma patients to support the findings presented in this meta-analysis.

Interestingly, a narrative synthesis of data from two clinical trials [23,25] suggested that NS is associated with a higher base deficit compared to balanced crystalloids within the first 24 h. This finding is

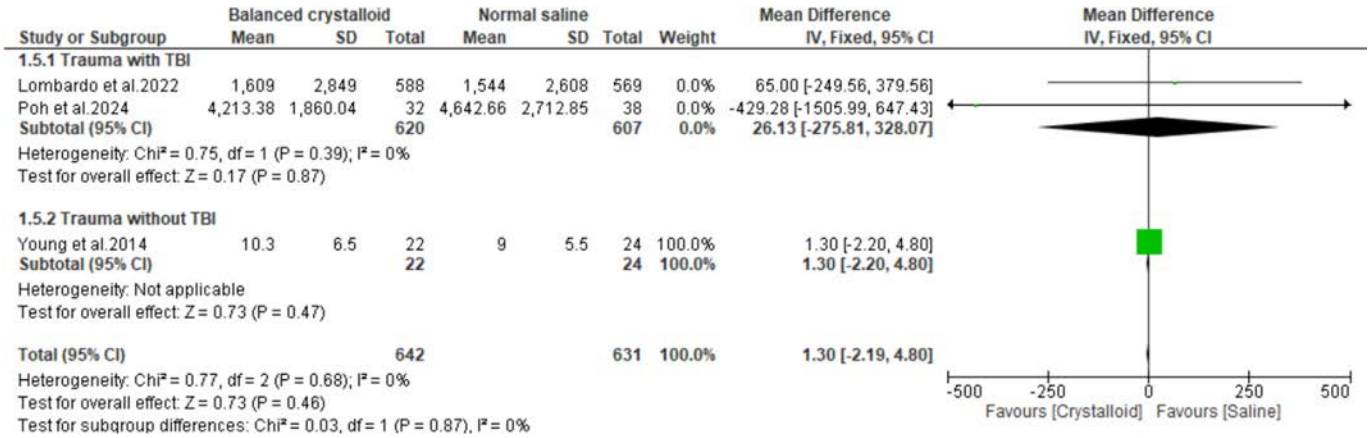

Fig. 6. Total volume of study fluid administered between patients receiving balanced crystalloid and normal saline.

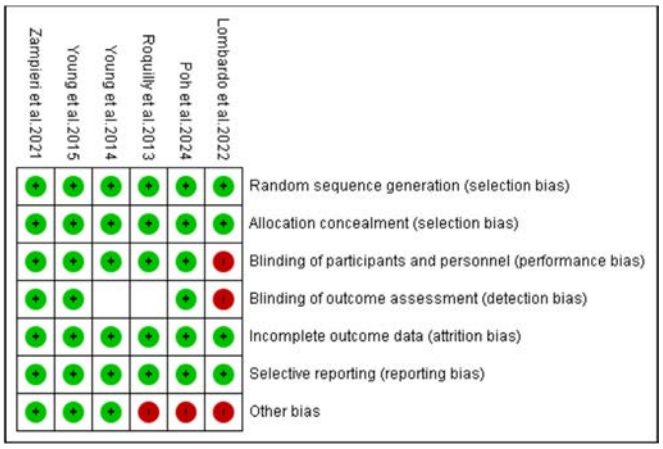

Fig. 7. Risk of bias summary.

comparable to a 2017 study of 63 patients with postoperative TBI, which reported a significantly lower base excess in the NS group than in the balanced crystalloid group (−3.20 vs. −1.35; $p = 0.049$) [17]. This high base deficit in patients receiving NS can be explained by various factors. First, NS has a higher concentration of chloride; thus, when it is infused in large volumes, the excess chloride causes a decrease in plasma strong ion difference, leading to metabolic acidosis (high base deficit) [32]. Second, the high concentration of chloride in NS dilutes the concentration of plasma bicarbonate, thus increasing the base deficit [6]. Finally, the high base deficit following NS infusion might be attributed to hyperchloremia, which worsens metabolic acidosis and delays the correction of base deficit. Nonetheless, evidence suggests that the difference in base deficit does not persist beyond 24 h. Moreover, the two clinical trials have shown that NS and balanced crystalloids maintain the pH, bicarbonate, lactate, and base deficit levels within the physiological range, suggesting that both resuscitation fluids adequately preserve acid-base balance.

Notably, only one included trial [18] reported the rate of intracranial hypertension (ICH) in TBI patients, with the results demonstrating no significant difference between the NS and balanced crystalloid groups. This finding could be attributed to the effect of balanced solutions on chloraemia, which is a key regulator of cell volume. According to the findings of this clinical trial, the balanced crystalloid group demonstrated lower chloraemia than the NS group. This lower rate of chloraemia might have increased the chloride ion efflux phenomenon, which has been reported to prevent brain swelling in hypotonic solutions. Moreover, previous studies have reported that sodium lactate-based hyperosmolar solutions are associated with significantly lower ICP than equivalent osmotic load of chloride-rich solutions.

4.1. Limitations

The current meta-analysis has several limitations that warrant attention. First, the evidence provided in this meta-analysis was based on RCTs only, meaning the generalizability of the results in real-world settings is limited, as patients enrolled in the RCTs are usually carefully selected. Therefore, future meta-analyses should strive to pool data from observational studies to determine whether the findings reported in this meta-analysis are also reflected in real-world settings. Second, our study might have some selection bias since we only included RCTs that were authored in English. Third, despite not assessing publication bias due to the limited number of studies, we cannot rule out the possibility of publication bias, since smaller RCTs with negative outcomes might not have been published. Fourth, the patients included in each RCT had varying degrees of trauma severity, which might have influenced the statistical power of our meta-analysis. Fifth, due to inconsistent reporting of anatomic and physiologic injury severity, we could not perform any meaningful subgroup analyses to investigate whether the effect of fluid resuscitation on mortality is modified by baseline injury severity. Sixth, although mortality risk in TBI patients may vary depending on the TBI subtype, none of the studies stratified mortality outcomes according to the TBI subtypes. As a result, we were unable to evaluate whether the mortality benefit of normal saline over balanced crystalloids in TBI patients is affected by the type of TBI. This represents an important research gap that should be addressed in future trials. Finally, most subgroup analyses, specifically those involving trauma patients without TBI, included a small number of studies. This limited number of studies might have hindered our results from demonstrating statistical significance across the pooled outcomes.

5. Conclusion

In summary, the present meta-analysis suggests that NS is associated with decreased mortality in trauma patients with TBI, but no significant difference was observed in trauma patients without TBI. However, most evidence reveals no significant difference in mortality between NS and balanced crystalloids in TBI patients. Additionally, our results have shown no significant difference between NS and balanced crystalloids regarding AKI incidence, need for RRT, and ICU stay. Furthermore, evidence has shown that both NS and balanced crystalloids maintain the pH, bicarbonate, lactate, and base deficit levels within the physiological range, suggesting that both resuscitation fluids are adequate in preserving acid-base balance. Taken together, our findings indicate that NS and balanced crystalloids are acceptable and safe options for early trauma resuscitation. However, since it is not possible to determine whether a patient has a head injury or not at the beginning of resuscitation, initial fluid selection cannot be based on TBI status. As a result, normal saline remains a safe and widely utilized standardized option for trauma resuscitation.

CRediT authorship contribution statement

Hany A. Zaki: Validation, Supervision, Conceptualization. **Hussam Elmelliti:** Writing – review & editing, Writing – original draft, Data curation. **Amira Shaban:** Methodology, Data curation. **Ahmed Shaban:** Software, Methodology, Data curation. **Ali Elkandow:** Software, Methodology, Formal analysis. **Mohamed Gafar Abdelrahim:** Writing – original draft. **Wadah Musaed:** Data curation. **Eman E. Shaban:** Methodology, Formal analysis.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2025.12.030.

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