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Resuscitation Fluids for Patients at High Risk of Multiple Organ Dysfunction Syndromes: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Intravenous fluid therapy is one of the most common interventions in critically ill patients. Normal saline is frequently used, but there have been some concerns about hyperchloremia. Due to closer to plasma composition, crystalloids have been used as alternatives to normal saline. However, the optimal choice of resuscitative fluids remains controversial. **Methods:** MEDLINE, EMBASE, and CENTRAL were comprehensively searched until July 2021 to compare balanced crystalloids with normal saline in critically ill patients with the risk factors for multiple organ dysfunction syndromes (MODS).The primary endpoint was composite mortality. Secondary outcomes were acute kidney injury (AKI)/acute renal failure (ARF), and new receipt of renal replacement therapy (RRT). **Results:** A total of 1,240 studies were searched, and finally, 8 randomized controlled trials and 5 cohort studies were included. In the meta-analysis of composite mortality of 30,710 patients, balanced crystalloids compared to normal saline were significantly associated with reduced mortality (OR 0.80, 95% CI 0.68-0.95). In AKI/ARF, balanced crystalloids had a lower risk than normal saline (OR 0.91, 95% CI 0.84-0.99). There was no difference between balanced crystalloids and normal saline in risk of new receipt of RRT (OR 0.91, 95% CI 0.80-1.04). **Conclusion:** In fluid resuscitation for patients at high risk of MODS, the use of balanced crystalloids showed a significantly lower incidence of mortality compared to normal saline.

KEYWORDS: Balanced crystalloids, fluid resuscitation, critically ill patients, multiple organ dysfunction syndrome, mortality

According to the fluid resuscitation guidelines published in 2013 and updated in 2017 by the National Institute for Health and Care Excellence, UK, crystalloids containing 130-154 mmol/L sodium are the first choice for patients requiring emergency fluid resuscitation.[1)] Normal saline, which has a composition of 154 mmol/L for both sodium and chloride, is crystalloid and meets this criterion but, contains more chloride than normal plasma.[2)] In various animal experiments, hyperchloremia exacerbates hemodynamic instability and inflammatory markers.[3-6)] In addition, various clinical trials in intensive care unit (ICU) patients have demonstrated that chloride-rich fluids are associated with higher mortality.[7-10)] Because fluid resuscitation therapy requires aggressive administration of normal saline, there have been constant concerns about hyperchloremia, which leads to metabolic acidosis, acute kidney injury, and death.[11)] Balanced crystalloids were considered an optimal alternative to normal saline because the electrolyte composition is similar to that of normal plasma, and various clinical trials and cohort studies have been conducted to evaluate the significant benefits.[12-16)] For fluid resuscitation, balanced crystalloids are probably the best choice, but the evidence was inconclusive.

In 2018, results were published from the SMART trial, a large randomized controlled trial involving 15,802 ICU

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patients. This randomized clinical trial found no significant difference in outcomes between normal saline and balanced crystalloids except for major adverse kidney events within 30 days and renal replacement therapy (RRT)-free days.[13] However, the SMART trial included patients with various severity, indications, and demographic characteristics, although it did not show statistical significance in mortality, it demonstrated relatively close to statistical significance.

In critical patients, fluid resuscitation is administered in various situations, such as endothelial dysfunction of the kidney, shock, sepsis, pancreatitis, severe anemia, and care for geriatric patients.[17-20] In particular, shock is associated with high mortality in severely ill patients, and very high mortality of 50% or greater is observed in septic shock.[21] Shock is a condition in which peripheral tissues or organs fail to maintain necessary perfusion for proper function due to sepsis, traumatic injury, burn injury, impairment of cardiac contractility, and type 1 hypersensitivity.[22-25] In the clinical field, when shock occurs in critically ill patients, it leads to multiple organ failure, which is associated with the acutely failing liver, cardiovascular system, and respiratory systems. The multiple organ dysfunction syndrome (MODS) can be characterized by reversible physiological abnormalities with the dysfunction of two or more organs leading to ICU admission, and in severe conditions, results in higher mortality.[26] Aggressive fluid resuscitation therapy is administered to prevent the progression of MODS by maintaining tissue and organ perfusion.[27-28]

Although large-scale randomized controlled clinical trials and observational studies with a similar topic have been conducted in critically ill patients, they couldn't reach significant generalizable conclusions due to the diversity of disease severity and indications of study populations.[13,29]

Therefore, we classified the critically ill patients by more specific severity descriptors and aimed to identify optimal fluid for resuscitation in critically ill patients with the risk factors of MODS by comparing the effects of normal saline and balanced crystalloids using a meta-analysis.

Methods

Search strategies

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews as recommended by the Cochrane Collaboration.[30] Two researchers separately searched PubMed, EMBASE, and CENTRAL for studies, published until July 2021 to compare balanced crystalloids with normal saline in critically ill patients. After removing duplicates, we independently screened the titles and abstracts of all records to identify potentially eligible studies. To identify the patients with risk factors for MODS, we also searched for terms for shock, mechanical ventilator, vasopressor, multiple organ failure, multiple organ dysfunction syndrome, Acute Physiology and Chronic Health Evaluation score, Simplified Acute Physiology Score II, and Sequential Organ Failure Assessment score.[31-33] Then, a full-text review was performed to determine the final inclusion according to eligibility criteria. In cases of disagreement, they were included based on mutual agreement. There were no restrictions on the starting point of the publication date, or the type of literature. Studies were included only original studies published in peer-reviewed journals. Studies conducted on non-adult patients under 18 years or patients with preeclampsia were excluded. Studies where crystalloids were administered for reasons other than fluid resuscitation, such as postoperative fluid management, and studies that did not report primary outcome data were also excluded.

Data extraction

Data extraction categories were determined by dividing the basic information of studies, clinical information of the patients, and outcome of the studies. We investigated author information, the study design, the types of balanced crystalloids administered, and the number of study participants as basic information. Demographic characteristics and clinical information including disease severity were described. We extracted mortality as the primary outcome and the incidence of AKI and ARF, and new receipt of RRT as secondary outcomes of the study. The mortality confirmed in each study was extracted and composite mortality was defined as all-cause mortality for the total follow up periods of each study. The definitions of AKI and ARF included in the secondary outcome were based on the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease criteria; the Acute Kidney Injury Network classification; and Kidney Disease: Improving Global Outcomes guideline.[34-36]

Quality Assessment

To evaluate the methodological quality, we used the tools

recommended by the Cochrane Association for bias assessments. Risk of Bias by Non-Randomized Studies (RoBANS) in cohort studies and Cochrane's assessment of the risk of bias (RoB) in randomized controlled trials were used (Supplementary Figure 1).

Data synthesis and analysis

We analyzed the odds ratio (OR) and 95% confidence interval (95% CI) for mortality, AKI or ARF incidence rates, and new receipt of RRT. The heterogeneity between studies was evaluated by Higgin's I squared (I^2) statistics and a random-effect model was applied to control the heterogeneity.[37,38] Subgroup analysis was conducted per patients' diagnosis. All statistical analyses were performed using RevMan (Review manager version 5.4, Copenhagen).

Results

A total of 1,240 articles were retrieved from three databases and 241 duplicate articles, 45 systematic reviews and meta-analyses were excluded. After 831 studies during title and abstract screening, 123 were selected for full text review. A total of 110 studies were excluded for the following reasons: inappropriate types of articles (n=23), articles that did not meet the target population group (n=16), studies with inappropriate interventions (n=3), articles where primary outcomes could not be extracted (n=20), irrelevant articles (n=23), overlapping clinical trial studies (n=21), articles that were not published in English (n=4). Finally, 13 articles were included in this study.[13-16,29,39-46] The extracted data from Jackson KE's study[46] was only included for subgroup

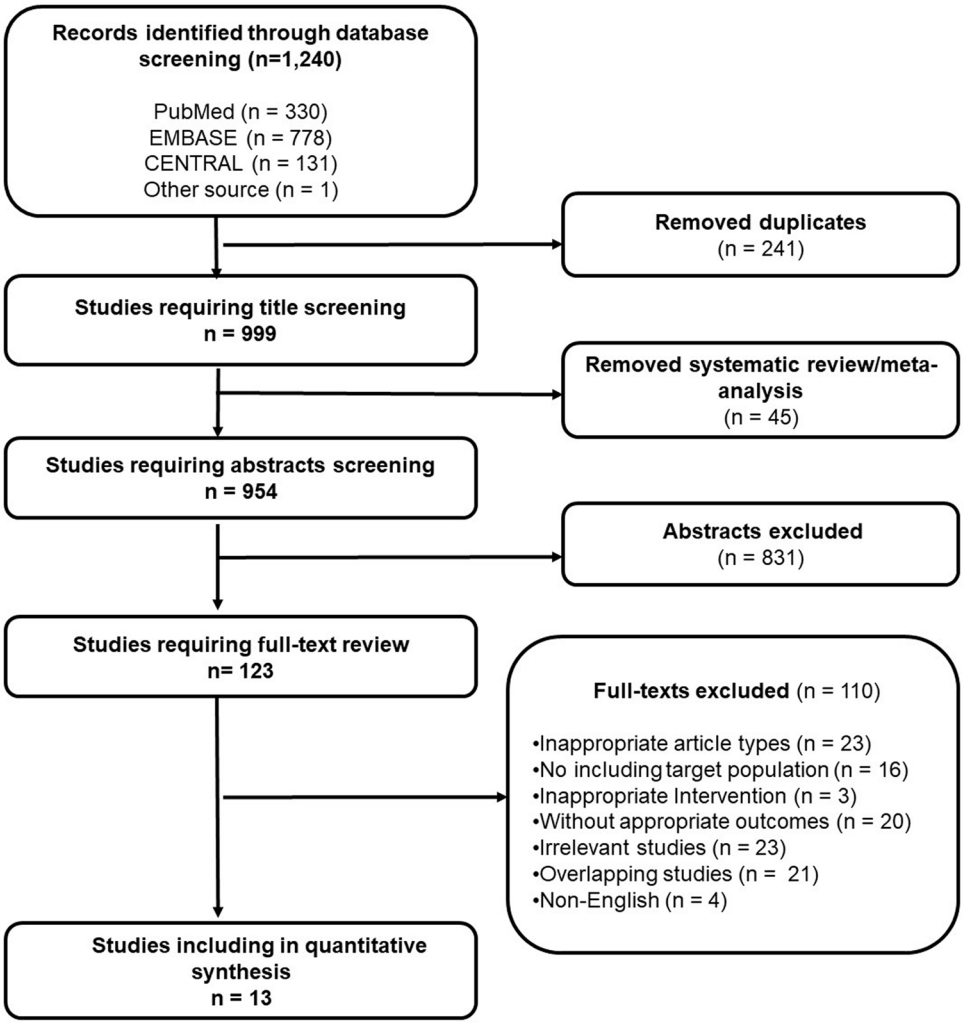

Fig. 1. Flow diagram for study selection

Table 1. Characteristics of included studies

Study name	Study design	Sample size	Intervention fluids	Gender Male (%)	median Age (years) Intervention vs Control	Diagnosis	Disease severity assessment Intervention vs Control	MV (%) Intervention vs Control
Wu BU 2011[42]	Randomized controlled study	40	LR	55.0	50(40-73) vs 54(40-60)	Acute pancreatitis	SIRS: 32% vs 19% BISAP : 0 vs 1 median APACHE II: 3 vs 3	NA
Young P 2015[44]	Double-blind, cluster randomized, double-crossover trial	2,262	PL 148	65.6	60.10(16.79) vs 60.95(16.25)	Sepsis, Trauma, Brain Injury, Operative admission (ICU)	mean APACHE II: 14.1 vs 14.1	67.0% vs 66.0%
Verma B 2016[41]	Randomized controlled pilot study	67	PL 148	62.7	62(45-70) vs 64(46-72)	Sepsis,Trauma, Operative admission (ICU)	median APACHE III: 55 vs 64 Vasopressor use: 45.5% vs 32.4%	57.6% vs 55.9%
Semler MW 2017[39]	Cluster-randomized, multiple-crossover trial	974	LR PL 148	52.8	57(44-68) vs 58(46-70)	Sepsis, Pneumonia, Respiratory failure, GI bleeding, Liver failure, Ingestion, Malignancy, DKA, AKI (ICU)	Vasopressor use: 21.9 % vs 24.4 % Stage 2 AKI 18.5% vs 19.2%	33.5% vs 34.1 %
Semler MW 2018[13]	Randomized controlled study	15,802	LR PL 148	57.6	58(44-69) vs 58(44-69)	Sepsis,Trauma, Brain Injury (ICU)	Vasopressor use: 26.4 % vs 26.2 % Stage 2 AKI 8.6% vs 8.2%	34.3% vs 34.7 %
de-Madaria E 2018[14]	Randomized controlled study	40	LR	47.5	61.4(15.5)† vs 63.8(19.1)†	Acute pancreatitis	SIRS criteria ≥2 47.4 % vs 66.7%	NA
Golla R 2020[40]	Open label RCT	160	LR	53.1	43.46(17.99)† vs 42.44(19.37)†	Sepsis (ED)	mean SOFA: 7.63 vs 7.64	NA
Jackson KE 2021[46]	Secondary analysis of SMART trial (Semler MW, 2018)	1,641	LR PL 148	54.7	59 (45-69) vs 59 (46-69)	Sepsis (ICU)	Vasopressor use: 41.9% vs 40.4% Stage 2 AKI 25.1% vs 25.5%	39.3% vs 40.8%
Raghunathan K 2014[29]	Cohort study	6,730	LR Normosol PL 148	48.5	64(53-77) vs 64(52-76)	Sepsis (ICU)	Renal failure: 20.8 % vs 20.5%	44.7% vs 43.3%
Duffy RA 2019 [15]	Cohort study	1,218	Normosol	47.7	60.6(18.7)* † vs 64.3(18.6)* †	Sepsis (ED)	mean qSOFA: 0.70 vs 0.68	NA
Shaw AD 2015[45]	Cohort study	3,116	Normosol PL 148	42.8	NA	SIRS (SIRS criteria)	SIRS: 100 % of total population	NA
Lipinski M 2015[16]	Cohort study	103	LR	66.0	49.2(18.0)† vs 52.5(17.6)†	Acute pancreatitis	BISAP ≥3: 20.0% vs 12.7%	NA
Aboelsoud MM 2016[43]	Cohort study	198	LR	50.3	63(52-74)* vs 56(44-72)*	Acute pancreatitis (ICU)	BISAP ≥3: 32.3% vs 26.9%* median SAPS-II: 33 vs 35	NA

AKI=acute kidney injury, AP=acute pancreatitis, APACHE=Acute Physiology and Chronic Health Evaluation, BISAP=Bedside index of severity in acute pancreatitis, DKA=diabetic ketoacidosis, ED=emergency department, GI=gastrointestinal, ICU=intensive care unit, LR=Lactated Ringer's solution, MV=mechanical ventilator, NA=not available, PL 148=Plasma-Lyte 148, SAPS=Simplified Acute Physiology Score, SIRS=systemic inflammatory response syndrome, SOFA=sequential organ failure assessment

*p<0.05 †mean (standard deviation)

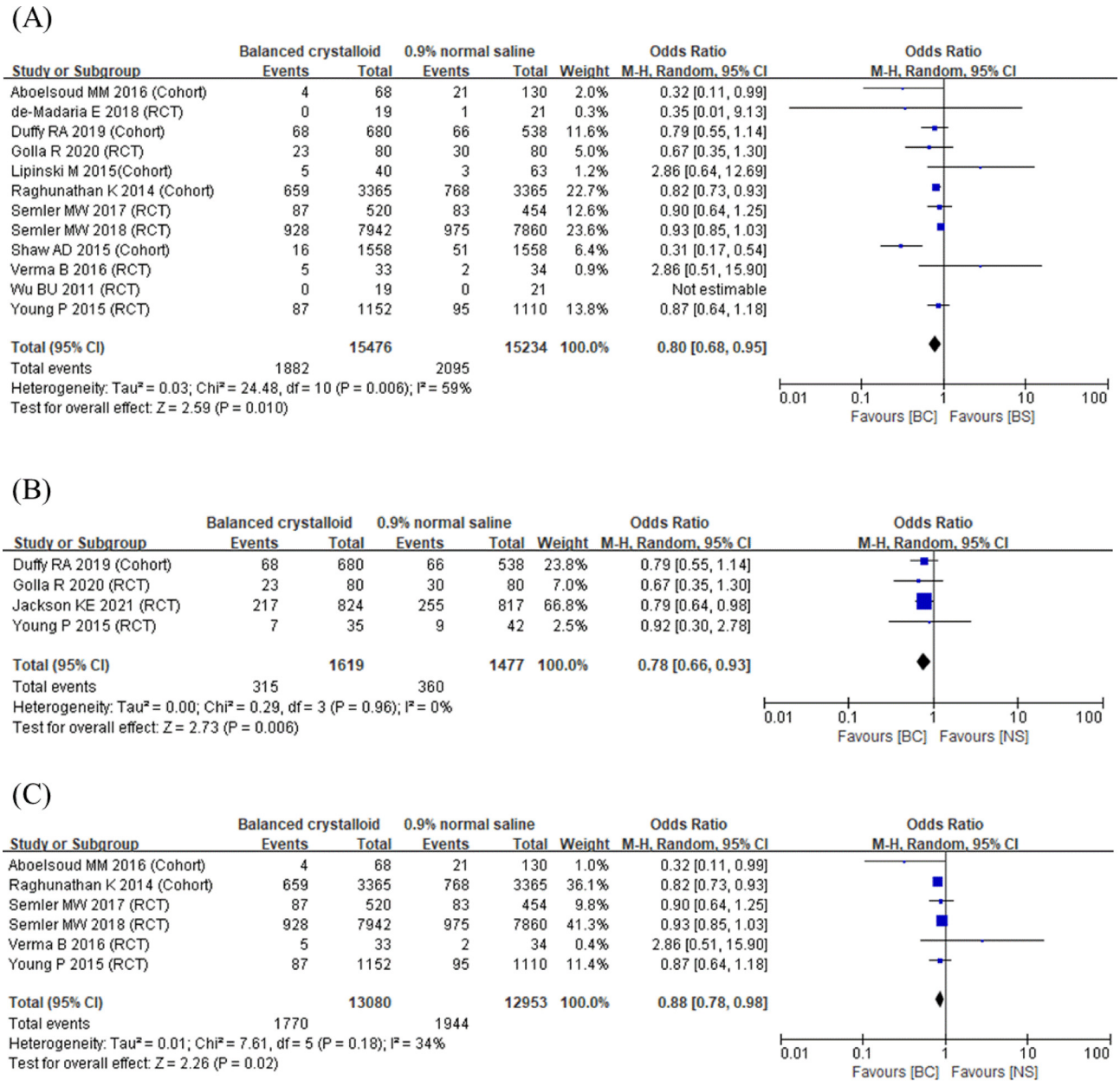

Fig. 2. Forest plots for composite mortality (A) Total composite mortality (B) Composite mortality for patients with sepsis (C) Composite mortality for patients admitted to the intensive care unit (ICU).

analysis due to overlapping results with Samler's study[13] (Fig. 1).

All articles included in the study were published during 2011-2021, of which 5 were cohort studies and 8 were randomized controlled trials. The characteristics of included studies are shown in Table 1. Publication bias was assessed using Egger's graphical method. The funnel plot did not show any publication bias.

The numbers of patients were 15,476 in the intervention and 15,234 in the control group. The balanced crystalloids included Ringer's lactate, Plasma-Lyte 148, and Normosol. Composite mortality from 12 studies was statistically significantly lower in the balanced crystalloid group than in the normal saline group (OR 0.80, 95% CI 0.68-0.95). 30-day mortality was extracted from three studies (Golla R 2020, Semler 2017, and Semler 2018), and a similar low OR was observed in the balanced crystalloid group (OR 0.91, 95% CI 0.83-0.99). For subgroup analysis, the ORs of composite

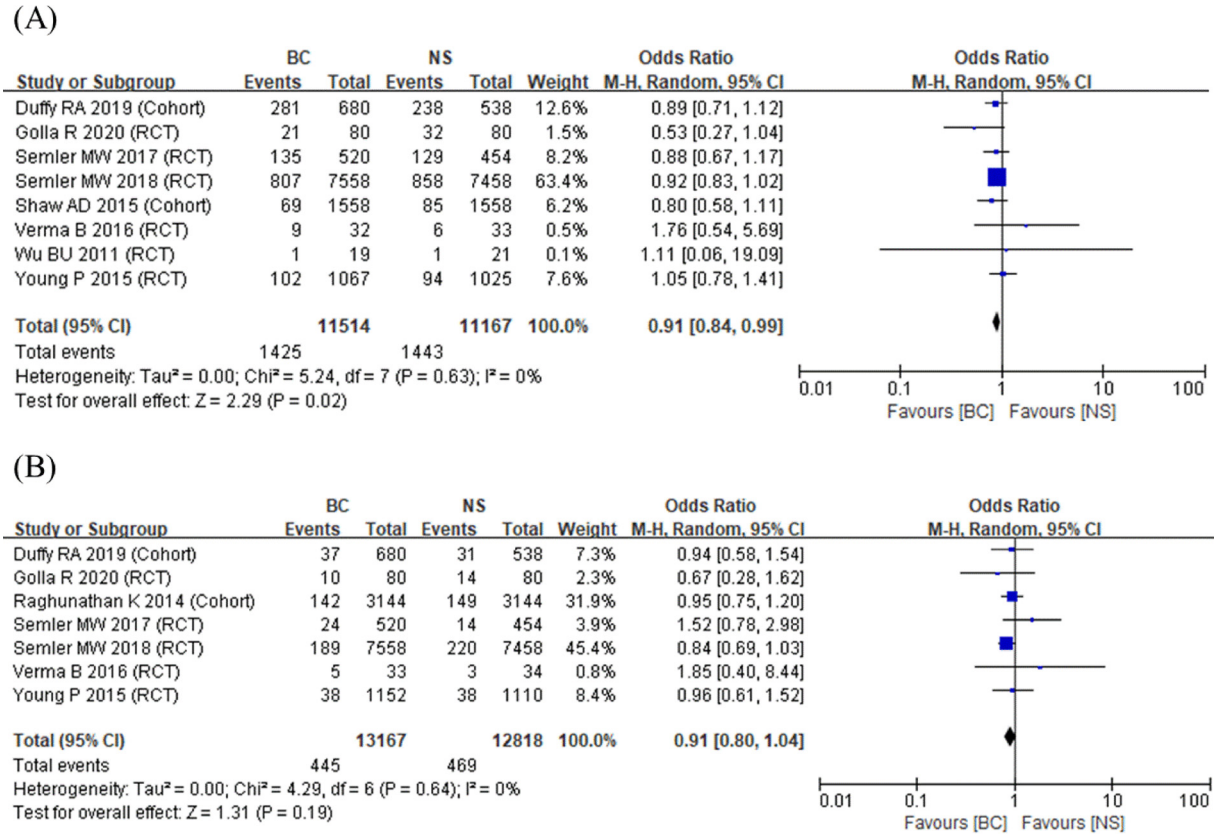

Fig. 3. Forest plots for progression of renal failure (A) Incidence of acute kidney injury /acute renal failure (B) Incidence of renal replacement therapy

mortality of patients with sepsis from 5 studies, and patients with ICU stay from 6 studies were 0.81 (95% CI 0.74-0.89, I^2 0%) and 0.88 (95% CI 0.78-0.98, I^2 34%), respectively (Fig. 2).

The AKI or ARF outcome were analyzed in 22,681 patients from 6 randomized controlled trials and 2 cohort studies. The odds ratios for AKI or ARF were statistically significantly lower in balanced crystalloids than in normal saline (OR 0.91, 95% CI 0.84-0.99, I^2 0%). New receipt of RRT was analyzed in 25,985 patients included in 5 randomized controlled trials and 2 cohort studies. The balanced crystalloids group had a lower OR for new receipt of RRT compared to normal saline, but the difference was not statistically significant (OR 0.91, 95% CI 0.80-1.04, I^2 0%) (Fig. 3).

Discussion

This study directly compares the effects of normal saline and balanced crystalloids on mortality in critically ill patients with the risk factors of MODS. The findings in this meta-analysis may assist in resolving the controversy surrounding the optimal choice of resuscitative fluids according to severity of illness. In the combined results of the meta-analysis, balanced crystalloids showed significant benefits in reducing the risk of mortality and AKI/ARF.

Several large-scale randomized controlled clinical trials for critically ill patients have been conducted.[13,47] In balanced solution versus saline in intensive care study (BaSICS trial), which is a large-scale randomized clinical trial from 75 ICUs in Brazil and 90-day mortality as the primary endpoint, a lower hazard ratio was observed in patients receiving Plasma-Lyte 148 than in patients receiving normal saline, but it was not statistically significant.[47] The BaSICS trial included a large number of patients admitted to the ICU for scheduled surgery and no significant conclusions according to disease severity were found in patients admitted the ICU. Additionally, when we included the BaSICS trial in our meta-analysis, there was no change in the results (composite mortality OR 0.85, 95% CI 0.74-0.96). A meta-analysis of eight studies, including patients with trauma, sepsis, and ICU stay, found no

statistically significant difference in mortality between the balanced crystalloids and normal saline.[48] As the result of a meta-analysis focusing on the specific population, a significantly lower 28-day mortality was found in the balanced crystalloid group than the normal saline group in patients with septic shock (RR=0.89, 95% CI=0.80-0.97).[49] However, there was no significant difference in 90-day mortality due to the difference in available studies. Another network meta-analysis study reported that significantly lower mortality was observed in the balanced crystalloid arm than the normal saline arm in sepsis patients (OR 0.84, 95% CI 0.74-0.95).[50] These are consistent with the subgroup analysis results of this study.

In a study by Tseng *et al*.,[51] administration of balanced crystalloids to a patient group with chronic pulmonary disease showed a lower mortality rate than that of normal saline, while there was no significant difference in patients with comorbidities such as cerebral disease. The authors explain that the effects of balanced crystalloids might be more important in patients prone to respiratory acidosis. It suggested that the administration of balanced crystalloids for fluid resuscitation may have a difference in mortality depending on comorbidities. In critically ill patients with risk factors for MODS, the functions of various organs, such as the kidneys, lung, and liver, would not be adequately maintained, and it becomes more difficult to compensate for hyperchloremia caused by a large volume of normal saline.[52] Therefore, it might be more appropriate to research the optimal choice of resuscitative fluid in a critically ill patients group at high risk for MODS. This meta-analysis was performed on a large number of 30,710 patients, even though the population was limited to critically ill patients with risk factors for MODS. Patients with AP, SIRS, and sepsis, known risk factors for MODS,[26-28] were included, and detailed information on the risk scores of each study population was provided using the severity assessment tools. Therefore, this study could suggest a new clinical research direction for obtaining generalized finding. The main cause of heterogeneity in composite mortality was Shaw's cohort study of only SIRS patients and Aboelsoud's cohort study, which included patients with severe AP and a BISAP score of 3 or higher. Remarkably low ORs were observed in these two studies. This result is similar to the conclusion of the present study, that fluid resuscitation with balanced crystalloids can have an advantage in patients with a high risk of MODS. Additional systematic randomized clinical studies are needed to confirm this

In this study, a favorable benefit was found with balanced crystalloid solution compared to normal saline in AKI/ARF, but there was no difference in the new receipt of RRT. Potential explanations include the following. Although the diagnostic criteria for AKI/ARF are clear, RRT is initiated based on clinician decisions, which could create treatment bias.

There are some limitations that should be considered when interpreting the result. First, it was difficult to quantify and find the severity threshold using the clinical severity assessment tools applied to each study. Second, it was not evaluated the best option of three types of balanced crystalloids such as Lactated Ringer's solution, Plasma-Lyte-148, or Normosol.

Conclusion

In fluid resuscitation for patients at high risk of MODS, balanced crystalloids have significant benefits compared to normal saline in composite mortality and AKI/ARF. This study showed that balanced crystalloid is the optimal fluid for fluid resuscitation in patients with high severity. A prospective randomized clinical trial study in patients stratified by standardized severity tools is needed.

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Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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