



The Relationship Between Crystalloid Fluid Administration and Electrolyte Balance in Critically Ill Patients : A Comprehensive Systematic Review

¹ Bery Andara, ² Dianalia Nurarifany

¹ Indonesian Army (Skadron-12 /Amur Jaya Yudha) / Graduate of Faculty of
Medicine, University of Malahayati, Indonesia

² Trans Medika Primary Health Clinic, Indonesia / Graduate of Faculty of Medicine,
University of Malahayati, Indonesia

Corresponding Email : andarabery73098@gmail.com

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ABSTRACT

Introduction: The choice between balanced crystalloids and 0.9% normal saline for fluid resuscitation in critically ill patients remains debated. While saline is widely used, concerns exist regarding its electrolyte and acid-base effects.

Methods: This systematic review synthesized data from 80 studies (RCTs, etc) examining crystalloid administration in critically ill adults. Outcomes focused on significant positive biochemical and clinical effects of balanced crystalloids over saline.

Results: Balanced crystalloids demonstrated consistently significant positive effects on electrolyte balance. Serum chloride was significantly lower with balanced solutions versus saline: mean difference -7 mEq/L in trauma ($p < 0.05$) [30], -5.68 mEq/L

in sepsis ($p=0.001$) [1], and -4.3 mmol/L in pancreatitis ($p<0.001$) [7]. Base excess and bicarbonate were significantly improved in TBI patients receiving balanced fluids (BE -1.35 vs. -3.20 , $p=0.049$) [3]. In DKA, balanced crystalloids significantly reduced time to resolution by 3.51–5.36 hours [21,22] and lowered post-resuscitation chloride (MD -4.26 mmol/L) [22]. In acute pancreatitis, balanced solutions significantly reduced SIRS (17.0% vs. 29.3%, $p=0.024$) and increased organ failure-free days [7]. Hyperchloremia at 48 hours independently predicted 30-day mortality in trauma ($p<0.001$) [14]. However, large RCTs found no significant mortality difference in unselected critically ill adults [9,10,13].

Discussion: The consistent chloride-raising effect of saline is mechanistically explained by Stewart's strong ion theory. Significant benefits of balanced crystalloids emerge in high-volume contexts (DKA, pancreatitis, trauma), but are diluted in heterogeneous ICU populations.

Conclusion: Balanced crystalloids produce significantly superior electrolyte profiles and are recommended as default resuscitation fluids, particularly in DKA, pancreatitis, and traumatic brain injury.

Keywords: Crystalloids, electrolyte balance, critical care, hyperchloremia, balanced solutions, normal saline

INTRODUCTION

Background: Intravenous fluid resuscitation is a cornerstone of critical care medicine, yet the optimal crystalloid solution remains controversial. For decades, 0.9% normal saline (NS) has been the most commonly administered crystalloid worldwide. However, its non-physiologic chloride concentration (154 mEq/L, exceeding normal plasma chloride by approximately 50 mEq/L) raises concerns about iatrogenic hyperchloremia and metabolic acidosis. Balanced crystalloids—including lactated Ringer’s (LR), Plasma-Lyte, Normosol-R, and Sterofundin—more closely mimic human plasma electrolyte composition, with lower chloride (98–112 mEq/L) and physiologic buffers (lactate, acetate, gluconate).

Problem Statement: Despite decades of clinical use and mounting physiological evidence that saline induces hyperchloremic metabolic acidosis, uncertainty persists regarding whether these biochemical disturbances translate into clinically meaningful patient outcomes. Large randomized controlled trials in unselected critically ill populations have failed to demonstrate consistent mortality benefits for balanced crystalloids, creating a fundamental tension between biological plausibility and clinical trial results.

Research Gap: Prior systematic reviews have either focused narrowly on specific diseases (e.g., sepsis, DKA) or have not comprehensively examined the relationship between crystalloid choice and electrolyte balance across the full spectrum of critical illness. Furthermore, the mechanistic pathways linking chloride administration to organ injury, and the modifying factors that determine which patients benefit most from balanced solutions, remain incompletely synthesized.

Novelty: This systematic review provides a comprehensive, mechanism-focused synthesis of 80 studies examining crystalloid-electrolyte relationships across diverse critical care settings. It uniquely integrates Stewart’s acid-base theory, dose-response relationships, and context-specific effects to resolve the apparent contradiction between consistent biochemical benefits and inconsistent clinical outcomes.

Objectives: To systematically evaluate the relationship between crystalloid fluid administration and electrolyte balance in critically ill patients, specifically: (1) quantify the magnitude of electrolyte differences between balanced crystalloids and saline; (2) identify disease contexts where balanced crystalloids demonstrate significant positive clinical effects; (3) synthesize mechanistic explanations for hyperchloremia-induced organ injury; and (4) provide evidence-based recommendations for crystalloid selection.

Hypothesis: Balanced crystalloids produce significantly superior electrolyte profiles (lower chloride, higher bicarbonate, less acidosis) compared to 0.9% saline across all critically ill populations. These biochemical benefits translate into clinically significant improvements in outcomes within specific high-volume or high-risk contexts, particularly diabetic ketoacidosis, severe acute pancreatitis, and traumatic brain injury.

Benefits of Research: This review provides clinicians with evidence-based guidance for crystalloid selection, identifies patient subgroups most likely to benefit from balanced solutions, and highlights areas where saline may still be appropriate or where specific balanced formulations offer advantages.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between crystalloid fluid administration and electrolyte balance in critically ill patients.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population - Critically Ill Adults:** Does the study include critically ill patients (adults ≥ 18 years) in intensive care units, emergency departments, or high-dependency units?
- **Intervention - Crystalloid Administration:** Does the study investigate crystalloid fluid administration (normal saline, lactated Ringer's, Plasma-Lyte, or other balanced crystalloids)?
- **Outcomes - Electrolyte Measurements:** Does the study measure electrolyte outcomes (sodium, potassium, chloride, bicarbonate, magnesium, phosphate, or acid-base balance)?
- **Data Type - Quantitative Electrolyte Data:** Does the study report quantitative electrolyte measurements or changes (not just qualitative descriptions)?
- **Study Design:** Is the study a randomized controlled trial, etc?
- **Crystalloid Focus:** Does the study focus on crystalloids (rather than primarily focusing on colloid solutions, blood products, or vasopressors without crystalloid comparison)?
- **Population - Renal Function:** Does the study exclude patients with end-stage renal disease on dialysis, or does it include patients without end-stage renal disease on dialysis?
- **Sample Size:** Is the study NOT a case report or case series with fewer than 10 patients (i.e., does it have adequate sample size)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3	Keyword 4
P (Population)	Critically Ill	ICU Patients	Sepsis	Trauma

	Adults			
I (Intervention)	Crystalloid Administration	Balanced Crystalloids	Normal Saline	Fluid Resuscitation
C (Comparison)	Balanced vs. Unbalanced Crystalloids	Saline vs. Plasmalyte	Chloride-Rich vs. Chloride-Limited	Lactated Ringer's vs. Normal Saline
O (Outcome)	Electrolyte Balance	Serum Chloride	Acid-Base Status	Hyperchloremia

The Boolean MeSH keywords inputted on databases for this research are: (*"Critically Ill Adults" OR "ICU Patients" OR "Sepsis" OR "Trauma"*) AND (*"Crystalloid Administration" OR "Balanced Crystalloids" OR "Normal Saline" OR "Fluid Resuscitation"*) AND (*"Balanced vs. Unbalanced Crystalloids" OR "Saline vs. Plasmalyte" OR "Chloride-Rich vs. Chloride-Limited" OR "Lactated Ringer's vs. Normal Saline"*) AND (*"Electrolyte Balance" OR "Serum Chloride" OR "Acid-Base Status" OR "Hyperchloremia"*)

Data extraction

- **Study Population:**

Extract characteristics of the critically ill patient population, including:

- Type of critical illness (sepsis, trauma, post-surgical, etc.)
- ICU setting (medical, surgical, trauma, mixed)
- Illness severity measures (APACHE, SOFA, etc.)
- Sample size and demographics
- Baseline electrolyte status if reported
- Exclusion criteria relevant to fluid or electrolyte management

- **Crystalloid Administration:**

Extract comprehensive details about crystalloid fluid administration in critically ill patients, including:

- Type of crystalloid (normal saline, balanced solutions, specific brands/formulations)
- Electrolyte composition (sodium, chloride, potassium, etc. concentrations)
- Volume administered (total and rate)
- Duration and timing of administration
- Indication for fluid administration (resuscitation, maintenance, etc.)
- Comparison groups if applicable

- **Electrolyte Outcomes:**

Extract all electrolyte balance measurements and outcomes specifically related to crystalloid administration in critically ill patients, including:

- Which electrolytes were measured (sodium, chloride, potassium, bicarbonate, etc.)
- Measurement methods and timing (baseline, during, post-administration)
- Quantitative changes (mean differences, effect sizes with confidence intervals)
- Clinically significant imbalances (hyperchloremia, hyponatremia, acidosis, etc.)
- Time course of electrolyte changes

- **Relationship Findings:**

Extract the specific relationship between crystalloid administration and electrolyte balance in critically ill patients, including:

- Direction of relationship (positive, negative, no association)

- Strength and statistical significance (p-values, confidence intervals, effect sizes)
- Dose-response relationships if identified
- Clinical significance of electrolyte changes
- Comparison between different crystalloid types and their electrolyte effects

- **Mechanistic Insights:**

Extract proposed pathophysiological mechanisms explaining the relationship between crystalloid administration and electrolyte balance in critically ill patients, including:

- Hyperchloremic acidosis mechanisms
- Renal handling of electrolytes
- Volume-electrolyte interactions
- Stewart acid-base theory applications
- Other proposed biological pathways
- Supporting evidence for proposed mechanisms

- **Modifying Factors:**

Extract patient, intervention, or contextual factors that modified the relationship between crystalloid administration and electrolyte balance in critically ill patients, including:

- Patient subgroups with different responses (trauma vs sepsis, TBI vs non-TBI, etc.)
- Co-interventions affecting electrolyte balance (diuretics, vasopressors, RRT)
- Baseline renal function impact

- Volume status and fluid responsiveness
- Timing factors (early vs late administration)
- Any identified moderators or effect modifiers

- **Clinical Outcomes:**

Extract clinical outcomes associated with crystalloid-induced electrolyte changes in critically ill patients, including:

- Mortality (short-term and long-term)
- Acute kidney injury incidence and severity
- Need for renal replacement therapy
- Cardiovascular complications
- Length of ICU/hospital stay
- Other morbidity outcomes linked to electrolyte imbalances
- Safety concerns and adverse events

- **Study Quality:**

Extract study design and quality factors relevant to assessing the crystalloid-electrolyte relationship in critically ill patients, including:

- Study design (RCT, etc.)
- Blinding and randomization methods
- Control for confounders (severity, co-interventions, baseline differences)

- Missing data handling for electrolyte measurements
- Follow-up duration and completeness
- Risk of bias specific to fluid and electrolyte research

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Critically Ill Adults" OR "ICU Patients" OR "Sepsis" OR "Trauma") AND ("Crystalloid Administration" OR "Balanced Crystalloids" OR "Normal Saline" OR "Fluid Resuscitation") AND ("Balanced vs. Unbalanced Crystalloids" OR "Saline vs. Plasmalyte" OR "Chloride-Rich vs. Chloride-Limited" OR "Lactated Ringer's vs. Normal Saline") AND ("Electrolyte Balance" OR "Serum Chloride" OR "Acid-Base Status" OR "Hyperchloremia")</i>	5
Semantic Scholar	<i>("Critically Ill Adults" OR "ICU Patients" OR "Sepsis" OR "Trauma") AND ("Crystalloid Administration" OR "Balanced Crystalloids" OR "Normal Saline" OR "Fluid Resuscitation") AND ("Balanced vs. Unbalanced Crystalloids" OR "Saline vs. Plasmalyte" OR "Chloride-Rich vs. Chloride-Limited" OR "Lactated Ringer's vs. Normal Saline") AND ("Electrolyte Balance" OR "Serum Chloride" OR "Acid-Base Status" OR "Hyperchloremia")</i>	46
Springer	<i>("Critically Ill Adults" OR "ICU Patients" OR "Sepsis" OR "Trauma") AND ("Crystalloid Administration" OR "Balanced Crystalloids" OR "Normal Saline" OR "Fluid Resuscitation") AND ("Balanced vs. Unbalanced Crystalloids" OR "Saline vs. Plasmalyte" OR "Chloride-Rich vs. Chloride-Limited" OR "Lactated Ringer's vs. Normal Saline") AND ("Electrolyte Balance" OR "Serum Chloride" OR "Acid-Base Status" OR "Hyperchloremia")</i>	2
Google Scholar	<i>("Critically Ill Adults" OR "ICU Patients" OR "Sepsis" OR "Trauma") AND ("Crystalloid Administration" OR "Balanced Crystalloids" OR "Normal Saline" OR "Fluid Resuscitation") AND ("Balanced vs. Unbalanced Crystalloids" OR "Saline vs. Plasmalyte" OR "Chloride-Rich vs. Chloride-Limited" OR "Lactated Ringer's vs. Normal Saline") AND ("Electrolyte Balance" OR "Serum Chloride" OR "Acid-Base Status" OR "Hyperchloremia")</i>	69

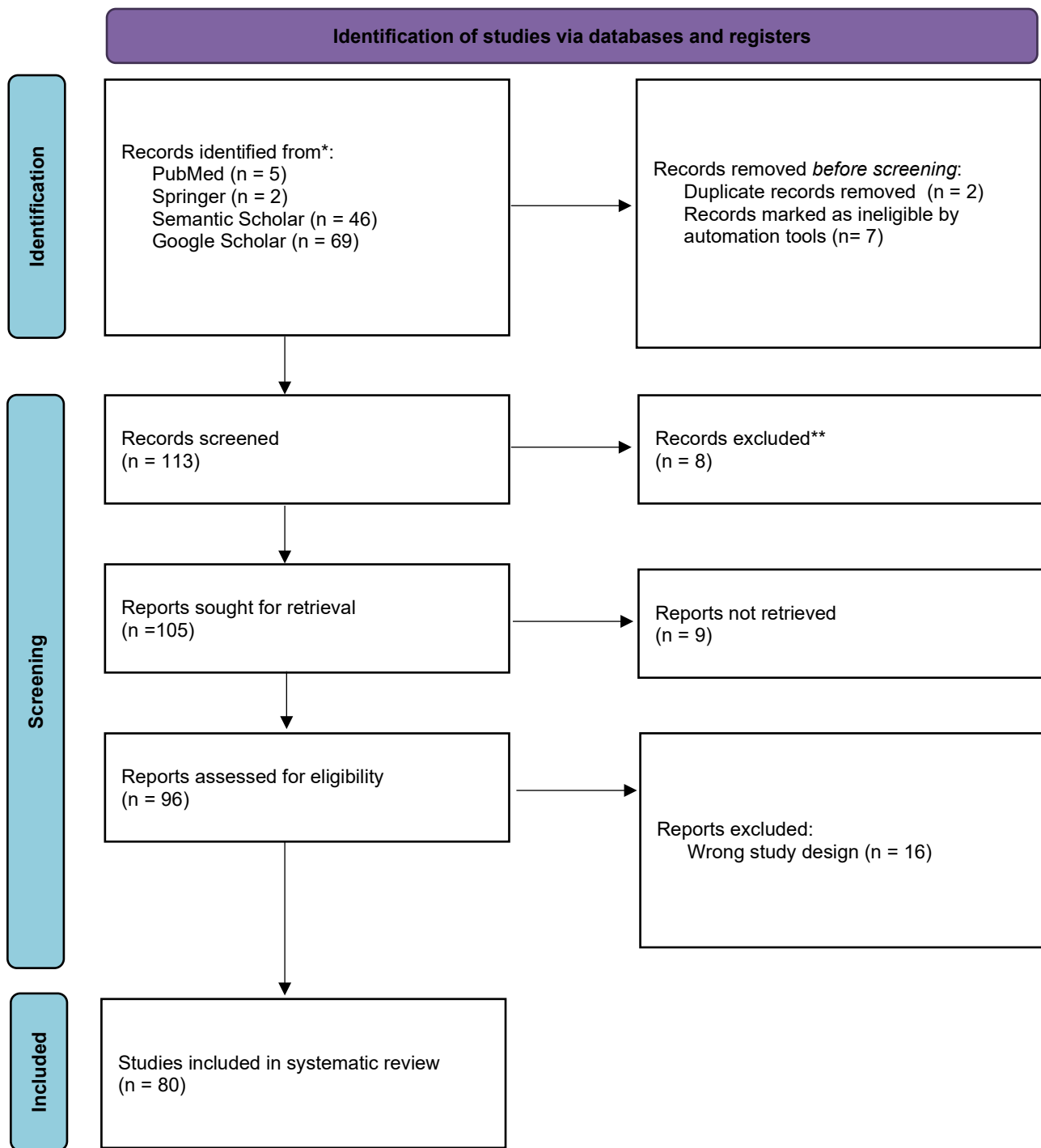


Figure 1. Article search flowchart

Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
A. Serpa Neto et al., 2017	Low	Low	Low	Low	Low	Low
J. Young et al., 2014	Low	Moderate	Low	Low	Low	Moderate
Brij Verma et al., 2016	Moderate	Moderate	Low	Low	Low	Moderate
Yi Bian et al., 2022	Moderate	Unclear	Moderate	Low	Moderate	Moderate
Balanced Crystalloid Solution, 2024	Low	Low	Low	Low	Low	Low
Mohammad Mehdi Shadravan et al., 2025	Moderate	Unclear	Moderate	Low	Moderate	Moderate
E. Qian et al., 2025	Low	Low	Low	Low	Low	Low
M. Hassan et al., 2017	Low	Moderate	Low	Low	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
R. Golla et al., 2020	Low	Moderate	Low	Low	Low	Moderate
Davide Chiumello et al., 2024	Low	Low	Low	Low	Low	Low
Xiaoming Wang et al., 2018	Low	Low	Low	Low	Low	Low
Yu-Qing Duan et al., 2025	Moderate	Moderate	Low	Low	Moderate	Moderate
Naveen Vivek Sakkanan et al., 2024	Low	Low	Low	Low	Low	Low
Avishek Roy et al., 2025	Low	Moderate	Low	Low	Low	Moderate
Senthil Kumaran Sundaram et al., 2024	Low	Low	Low	Low	Low	Low
Hayden Schoeffler et al., 2022	Moderate	Moderate	Moderate	Low	Moderate	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Bibidh Subedi et al., 2026	Moderate	Unclear	Moderate	Low	Moderate	Moderate
Rahul Kumar Chaudhary et al., 2025	Low	Low	Low	Low	Low	Low
A. Carrillo et al., 2022	Low	Moderate	Low	Low	Low	Moderate
Lu Ke et al., 2024	Low	Low	Low	Low	Low	Low
Sarita Kumari et al., 2025	Low	Low	Low	Low	Low	Low
R. Bala et al., 2022	Low	Moderate	Low	Low	Low	Moderate
M. Ramanan et al., 2021	Low	Low	Low	Low	Low	Low
X. Mao et al., 2018	Low	Moderate	Low	Low	Low	Moderate
S. Finfer et al., 2022	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
J. Waskowski et al., 2023	Low	Low	Low	Low	Low	Low
A. Antequera Martín et al., 2019	Low	Low	Low	Low	Low	Low
P. Phoon & N. Hwang, 2020	Unclear	Unclear	Moderate	Moderate	Moderate	Moderate
Yi Chen & Yongli Gao, 2023	Low	Low	Low	Low	Low	Low
F. Zampieri et al., 2017	Low	Low	Low	Low	Low	Low
Mahesh Ramanan et al., 2025	Low	Low	Low	Low	Low	Low
Jamie R. Chua et al., 2019	Low	Low	Low	Low	Low	Low
Sumeet K Reddy et al., 2015	Low	Low	Low	Low	Low	Low
Jin Young Lee et al., 2016	Moderate	Unclear	Moderate	Low	Moderate	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Jeff Curran et al., 2021	Low	Low	Low	Low	Low	Low
Naif A. Alghamdi et al., 2022	Low	Low	Low	Low	Low	Low
B. Gershkovich et al., 2019	Moderate	Unclear	Moderate	Low	Moderate	Moderate
S. Mahler et al., 2011	Low	Moderate	Low	Low	Low	Moderate
A. Roquilly et al., 2013	Low	Low	Low	Low	Low	Low
Mahsa Movahedan & Glen Brown, 2025	Moderate	Unclear	Moderate	Low	Moderate	Moderate
L. Lehmann et al., 2013	Low	Low	Low	Low	Low	Low
F. John Gennari, 2013	Unclear	Unclear	Moderate	Moderate	Moderate	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Yuting Liu et al., 2024	Low	Low	Low	Low	Low	Low
Yuhan Zhu et al., 2021	Low	Low	Low	Low	Low	Low
M. Chaussard et al., 2020	Low	Low	Low	Low	Low	Low
A. T. Maciel & Marcelo Park, 2013	Moderate	Unclear	Moderate	Moderate	Moderate	Moderate
Hakan Hasman et al., 2011	Low	Moderate	Low	Low	Low	Moderate
J. Brems et al., 2021	Low	Low	Low	Low	Low	Low
P. Shrivastava et al., 2023	Low	Moderate	Low	Low	Low	Moderate
R. Dickerson et al., 2013	Moderate	Unclear	Moderate	Low	Moderate	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Priyanka Gupta et al., 2024	Low	Low	Low	Low	Low	Low
Justin W. Yan et al., 2023	Low	Low	Low	Low	Low	Low
B. Ye et al., 2021	Low	Low	Low	Low	Low	Low
Erden Goljo et al., 2018	Moderate	Unclear	Moderate	Moderate	Moderate	Moderate
J. Woo et al., 2022	Low	Low	Low	Low	Low	Low
M. Papasotiriou et al., 2023	Moderate	Unclear	Moderate	Low	Moderate	Moderate
A. Schneider et al., 2013	Low	Moderate	Low	Moderate	Moderate	Moderate
Anna DeFrank et al., 2023	Moderate	Unclear	Moderate	Low	Moderate	Moderate
D. Aditjaningsih et al., 2017	Low	Moderate	Low	Low	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Dimas Adjie Yuda Mahendra & Febrian Dwi Cahyo, 2021	Moderate	Unclear	Moderate	Low	Moderate	Moderate
B. Rochwerg et al., 2017	Low	Low	Low	Low	Low	Low
C. Pfortmueller et al., 2019	Low	Low	Low	Low	Low	Low
A. Dell'Anna et al., 2025	Low	Low	Low	Low	Low	Low
Moslem Sedaghattalab et al., 2020	Low	Moderate	Low	Low	Low	Moderate
Gergő V Szabó et al., 2024	Low	Low	Low	Low	Low	Low
Adnan I. Qureshi et al., 2026	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Jing Zhang et al., 2024	Low	Low	Low	Low	Low	Low
M. K. Bedi et al., 2019	Moderate	Unclear	Moderate	Low	Moderate	Moderate
J. Woo et al., 2023	Low	Low	Low	Low	Low	Low
Georg Gelbenegger et al., 2025	Low	Low	Low	Low	Low	Low
Jorge Alejandro Trujillo-Zea et al., 2015	Low	Low	Low	Low	Low	Low
F. Wireko et al., 2025	Moderate	Unclear	Moderate	Low	Moderate	Moderate
T. Loftus et al., 2017	Low	Moderate	Low	Low	Low	Moderate
E. Shaban et al., 2025	Low	Low	Low	Low	Low	Low
C. Yeoh et al., 2019	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
F. Hadipourzadeh et al., 2024	Low	Low	Low	Low	Low	Low
M. Papasotiriou et al., 2020	Moderate	Unclear	Moderate	Low	Moderate	Moderate
A. Fayed et al., 2024	Low	Low	Low	Low	Low	Low
M. M. Thom et al., 2026	Low	Low	Low	Low	Low	Low

RESULTS

Characteristics of Included Studies

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
A. Serpa Neto et al., 2017 [29]	Mixed ICU and OR patients [29]	Balanced solutions vs. isotonic saline [29]	Serum chloride; arterial pH [29]
J. Young et al., 2014 [30]	Adult trauma [30]	0.9% NaCl vs. Plasma-Lyte A [30]	Base excess, pH, serum chloride at 24 h [30]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
Brij Verma et al., 2016 [31]	Mixed ICU [31]	Normal saline vs. Plasma-Lyte 148 [31]	Daily base excess; peak chloride [31]
Yi Bian et al., 2022 [32]	Mixed ICU (sepsis, TBI, cardiovascular) [32]	Sodium bicarbonate Ringer's vs. saline [32]	MAKE30; arterial blood gas; serum biochemistry [32]
Balanced Crystalloid Solution, 2024 [10]	Critically ill adults (non-perioperative) [10]	Balanced crystalloids vs. normal saline [10]	30-day mortality; AKI; RRT; serum chloride [10]
Mohammad Mehdi Shadravan et al., 2025 [33]	Sepsis and septic shock [33]	Balanced crystalloids vs. saline; restrictive vs. liberal volume [33]	Hyperchloremic acidosis; mortality [33]
E. Qian et al., 2025 [25]	Mixed medical ICU [25]	Normosol-R vs. lactated Ringer's [25]	Plasma bicarbonate; kidney replacement therapy; 30-day death [25]
M. Hassan et al., 2017 [3]	Severe TBI (neuro-ICU) [3]	Normal saline vs. Sterofundin ISO (balanced fluid) [3]	Base excess, bicarbonate, chloride, potassium, calcium, magnesium at 24 h [3]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
R. Golla et al., 2020 [1]	Emergency sepsis [1]	0.9% saline vs. Ringer's lactate [1]	Serum chloride; hyperchloremia incidence; AKI [1]
Davide Chiumello et al., 2024 [11]	Mechanically ventilated critically ill [11]	0.5 L 0.9% saline fluid challenge [11]	Strong ion difference; chloride; pH [11]
Xiaoming Wang et al., 2018 [34]	Septic shock (ICU) [34]	0.9% NaCl vs. Ringer's vs. ASPMCG solution [34]	Chloride, calcium, pH, base excess at multiple timepoints [34]
Yu-Qing Duan et al., 2025 [35]	Aneurysmal subarachnoid hemorrhage (neuro-ICU) [35]	Normal saline vs. balanced multi-electrolyte solution [35]	Hyperchloremia incidence; serum chloride; AKI [35]
Naveen Vivek Sakkanan et al., 2024 [36]	TBI (emergency craniotomy) [36]	0.9% NS vs. Plasmalyte [36]	pH, base excess, chloride; serum creatinine; urinary AKI biomarkers [36]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
Avishek Roy et al., 2025 [26]	Severe metabolic acidosis (mixed ICU) [26]	Isotonic bicarbonate vs. Plasmalyte [26]	Lactate clearance at 6 and 12 h; serum bicarbonate [26]
Senthil Kumaran Sundaram et al., 2024 [37]	Ruptured intracranial aneurysm clipping [37]	0.9% saline vs. Plasmalyte-A [37]	pH, bicarbonate, base deficit; serum creatinine; renal biomarkers [37]
Hayden Schoeffler et al., 2022 [38]	DKA (ICU) [38]	Normal saline vs. lactated Ringer's [38]	Time to DKA resolution; hypokalemia incidence [38]
Bibidh Subedi et al., 2026 [39]	DKA [39]	Lactated Ringer's vs. normal saline [39]	Time to DKA resolution; anion gap closure; AKI; hypokalemia [39]
Rahul Kumar Chaudhary et al., 2025 [24]	Emergency laparotomy for perforation peritonitis [24]	Isotonic sodium bicarbonate vs. Ringer's lactate [24]	Base excess at end of surgery; AKI incidence; vasopressor requirement [24]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
A. Carrillo et al., 2022 [40]	DKA [40]	Lactated Ringer's vs. normal saline [40]	Hyperchloremia; hypernatremia; serum creatinine change at 48 h [40]
Lu Ke et al., 2024 [7]	Predicted severe acute pancreatitis [7]	Balanced multielectrolyte solution (Sterofundin) vs. NS [7]	Serum chloride on day 3; SIRS; organ failure-free days [7]
Sarita Kumari et al., 2025 [4]	TBI (decompressive craniotomy) [4]	Normal saline vs. Plasmalyte (BCS) [4]	pH, bicarbonate, sodium, chloride, potassium, calcium; urine output [4]
R. Bala et al., 2022 [41]	TBI (emergency craniotomy) [41]	Plasmalyte vs. normal saline [41]	pH; blood urea; serum creatinine; coagulation [41]
M. Ramanan et al., 2021 [20]	Severe DKA (ICU) [20]	Plasmalyte-148 vs. 0.9% sodium chloride [20]	DKA resolution (base excess ≥ -3 mEq/L at 48 h); serum chloride; ketones [20]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
X. Mao et al., 2018 [2]	Septic shock (ICU) [2]	Normal saline vs. lactated Ringer's [2]	Hyperlactacidemia; hyperchloremia incidence; 28-day mortality [2]
S. Finfer et al., 2022 [9]	Mixed critically ill (ICU, ~42% sepsis) [9]	Plasma-Lyte 148 vs. 0.9% saline [9]	90-day mortality; RRT; serum creatinine; serum chloride [9]
J. Waskowski et al., 2023 [19]	Adult ICU patients (maintenance/creep fluids) [19]	Low vs. high sodium content maintenance fluids [19]	Total daily sodium burden; hyperchloremia incidence [19]
A. Antequera Martín et al., 2019 [13]	Critically ill adults and children (trauma, burns, emergency surgery) [13]	Buffered solutions vs. 0.9% saline [13]	Mortality; AKI; chloride; pH; bicarbonate; potassium [13]
P. Phoon & N. Hwang, 2020 [42]	Cardiac surgery (surgical ICU) [42]	Chloride-rich vs. chloride-limited perioperative fluid strategy [42]	Peak serum chloride; hyperchloremia; AKI [42]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
Yi Chen & Yongli Gao, 2023 [43]	Critically ill adults (sepsis highlighted) [43]	Normal saline vs. balanced crystalloids [43]	Composite mortality; AKI [43]
F. Zampieri et al., 2017 [44]	Mixed critically ill (100+ Brazilian ICUs) [44]	Plasma-Lyte 148 vs. saline; rapid vs. slow infusion rate [44]	90-day mortality; AKI; organ dysfunction [44]
Mahesh Ramanan et al., 2025 [45]	Mixed ICU [45]	Balanced solution vs. 0.9% saline (by baseline chloride and pH quartiles) [45]	Day-90 mortality (interaction with baseline chloride and pH) [45]
Jamie R. Chua et al., 2019 [46]	Critically ill adults [46]	Balanced crystalloids vs. normal saline [46]	AKI; RRT; ICU mortality [46]
Sumeet K Reddy et al., 2015 [47]	ICU, ED, and surgical patients [47]	0.9% saline vs. Plasma-Lyte 148 [47]	Biochemical and renal outcomes; in-hospital mortality [47]
Jin Young Lee et al., 2016 [14]	Major trauma (ICU) [14]	Survivors vs. non-survivors; chloride-rich vs. balanced fluids [14]	30-day mortality; hyperchloremia at 48 h; AKI [14]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
Jeff Curran et al., 2021 [48]	Mixed (perioperative, ICU, ED, healthy volunteers) [48]	Different balanced crystalloids compared head-to-head [48]	Serum chloride; base excess; serum lactate; pH; potassium [48]
Naif A. Alghamdi et al., 2022 [21]	DKA [21]	Saline vs. balanced crystalloid [21]	Time to DKA resolution; serum chloride and bicarbonate; hospital stay [21]
B. Gershkovich et al., 2019 [49]	DKA and HHS [49]	0.9% saline vs. buffered and non-buffered crystalloids [49]	Mortality; AKI; hospital stay; serum biochemical parameters [49]
S. Mahler et al., 2011 [5]	DKA (emergency department) [5]	Normal saline vs. Plasma-Lyte A (balanced electrolyte solution) [5]	Serum chloride and bicarbonate post-resuscitation [5]
A. Roquilly et al., 2013 [50]	Severe TBI and subarachnoid hemorrhage (neuro-ICU) [50]	Balanced solutions vs. 0.9% saline (crystalloid and colloid) [50]	Hyperchloremic metabolic acidosis incidence at 48 h; pH; chloride; SID; ICP [50]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
Mahsa Movahedan & Glen Brown, 2025 [18]	Medical ICU (patients developing dyschloremia) [18]	NS vs. D5W vs. balanced salt solutions as diluents [18]	Hyperchloremia; hypochloremia [18]
L. Lehmann et al., 2013 [51]	Subarachnoid hemorrhage (ICU) [51]	Normal saline + HES vs. balanced crystalloid + colloid (Ringerfundin/Tetraspan) [51]	Serum sodium, chloride, osmolality; base excess; fluid balance [51]
F. John Gennari, 2013 [52]	Mixed critically ill (single tertiary ICU) [52]	Isotonic saline vs. Plasma-Lyte/Hartmann solution [52]	Serum creatinine; AKI; RRT; serum chloride; bicarbonate [52]
Yuting Liu et al., 2024 [6]	DKA [6]	Balanced crystalloids vs. normal saline [6]	Time to DKA resolution; MAKE; post-resuscitation chloride; hypokalemia [6]
Yuhan Zhu et al., 2021 [16]	Critically ill adults and children [16]	Balanced crystalloids vs. saline [16]	MAKE30; 30-day/ICU/in-hospital mortality; creatinine; RRT; LOS [16]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
M. Chaussard et al., 2020 [28]	Critically ill burns (>30% TBSA) [28]	Plasmalyte vs. Ringer's lactate [28]	Base excess; buffer anion (gluconate, acetate, lactate) clearance; ionized calcium [28]
A. T. Maciel & Marcelo Park, 2013 [17]	Post-surgical ICU [17]	Normal saline as primary crystalloid [17]	Plasma chloride; urinary strong ion difference [17]
Hakan Hasman et al., 2011 [53]	Moderate-severe dehydration (emergency department) [53]	Normal saline vs. lactated Ringer's vs. Plasmalyte [53]	pH; bicarbonate; sodium; chloride; potassium at 0, 60, 120 min [53]
J. Brems et al., 2021 [54]	Critically ill adults with low baseline bicarbonate (<20 mmol/L) [54]	Balanced crystalloid vs. saline [54]	MAKE30; 30-day mortality; RRT; incident AKI [54]
P. Shrivastava et al., 2023 [55]	Elective craniotomy for supratentorial brain tumors (surgical ICU) [55]	Normal saline vs. PlasmaLyte A [55]	Serum chloride; pH; urea; creatinine; osmolarity; lactate [55]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
R. Dickerson et al., 2013 [56]	Trauma ICU patients with hypernatremia [56]	Hypotonic 0.225% NaCl (¼ NS) [56]	Serum sodium; plasma free hemoglobin; hematocrit [56]
Priyanka Gupta et al., 2024 [57]	Adult DKA [57]	Balanced electrolyte solution vs. 0.9% NS [57]	Time to DKA resolution; post-resuscitation chloride and bicarbonate; hospital LOS [57]
Justin W. Yan et al., 2023 [58]	Adult DKA (emergency department) [58]	Ringer's lactate vs. normal saline [58]	Time to DKA resolution; MAKE30; electrolyte balance [58]
B. Ye et al., 2021 [59]	Predicted severe acute pancreatitis [59]	Balanced crystalloids vs. normal saline [59]	Plasma chloride on day 3; MAKE30; organ failure-free days [59]
Erden Goljo et al., 2018 [60]	Refractory acute decompensated heart failure [60]	Hypertonic saline solution (3% NaCl) with loop diuretics [60]	Serum sodium; chloride; creatinine; fluid output [60]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
J. Woo et al., 2022 [61]	Out-of-hospital cardiac arrest (emergency department) [61]	Saline vs. Plasma Solution-A [61]	pH; bicarbonate; base excess; chloride; hyperchloremia incidence [61]
M. Papasotiriou et al., 2023 [62]	Prerenal AKI with pre-existing CKD (stages III–V) [62]	Normal saline vs. Ringer's lactate [62]	Kidney function; anion gap; pH; serum chloride; bicarbonate [62]
A. Schneider et al., 2013 [63]	Sepsis-associated AKI risk (elevated sNGAL, SIRS, oliguria) [63]	Sodium bicarbonate vs. sodium chloride infusion [63]	Electrolyte abnormalities; AKI; RRT; mortality [63]
Anna DeFrank et al., 2023 [64]	Trauma (surgical ICU) [64]	Plasmalyte vs. lactated Ringer's [64]	Serum magnesium; serum calcium; SICU LOS; mortality [64]
D. Aditjaningsih et al., 2017 [65]	DKA (emergency department) [65]	Normal saline vs. Ringerfundin (balanced electrolyte solution) [65]	SID; SBE; serum electrolytes [65]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
Dimas Adjie Yuda Mahendra & Febrian Dwi Cahyo, 2021 [66]	Sepsis and septic shock [66]	Balanced vs. unbalanced crystalloids [66]	Mortality; hyperchloremia incidence; hospital LOS [66]
B. Rochweg et al., 2017 [67]	Septic shock [67]	Low chloride vs. high chloride fluid strategy [67]	Feasibility; mortality; RRT; AKI; acidosis; hyperkalemia [67]
C. Pfortmueller et al., 2019 [68]	Elective cardiac surgery (surgical ICU) [68]	Hypertonic saline (7.3% NaCl) vs. 0.9% NaCl [68]	Total fluid volume; electrolyte and acid-base parameters; renal function [68]
A. Dell'Anna et al., 2025 [12]	Elective major spine surgery (minimal blood loss) [12]	Normal saline vs. lactated Ringer's vs. Crystalsol [12]	pH; plasma chloride; SID; urinary chloride excretion [12]
Moslem Sedaghattalab et al., 2020 [69]	Mixed ICU patients (maintenance fluid) [69]	0.9% saline vs. 0.45% saline [69]	Serum sodium; potassium; bicarbonate; pH [69]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
Gergő V Szabó et al., 2024 [22]	DKA (adults) [22]	Balanced electrolyte solutions vs. 0.9% saline [22]	Time to DKA resolution; post-resuscitation chloride, sodium, bicarbonate [22]
Adnan I. Qureshi et al., 2026 [70]	Acute stroke (ischemic and hemorrhagic) [70]	0.9% NaCl vs. NaCl:NaOAc combinations (3:1, 2:1, 1:1) [70]	Serum chloride at day 1 and day 2; mRS at 30 and 90 days [70]
Jing Zhang et al., 2024 [71]	Sepsis (ICU) [71]	Ringer's acetate solution vs. normal saline [71]	MAKE28; 30/90-day mortality; AKI; hyperchloremia [71]
M. K. Bedi et al., 2019 [72]	Acute burns (ICU) [72]	Ringer's lactate alone vs. RL + dextrose normal saline [72]	Serum sodium; random blood sugar [72]
J. Woo et al., 2023 [8]	Non-traumatic out-of-hospital cardiac arrest (emergency department) [8]	Normal saline vs. Plasma Solution-A (balanced) [8]	Base excess; bicarbonate; serum chloride; hyperchloremia; AKI [8]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
Georg Gelbenegger et al., 2025 [73]	Sepsis-induced hypotension (ICU and ED) [73]	Lactated Ringer's vs. 0.9% saline for initial resuscitation [73]	90-day mortality; hospital-free days; serum chloride; serum bicarbonate [73]
Jorge Alejandro Trujillo-Zea et al., 2015 [74]	Renal transplantation (surgical) [74]	Lactated Ringer's vs. normal saline [74]	Serum potassium; pH; serum creatinine at postoperative day 3 [74]
F. Wireko et al., 2025 [15]	Critically ill patients requiring mechanical ventilation [15]	Hyperchloremic vs. non-hyperchloremic patients [15]	Duration of mechanical ventilation [15]
Jorge Alejandro Trujillo-Zea et al., 2015a [75]	Renal transplantation (surgical) [75]	Lactated Ringer's vs. normal saline [75]	Serum potassium; pH; creatinine at postoperative day 3 [75]
T. Loftus et al., 2017 [76]	Trauma and acute care surgery (emergent laparotomy and temporary abdominal closure) [76]	3% hypertonic saline vs. standard resuscitation [76]	Serum sodium; chloride; osmolarity; pH; AKI; fluid volumes [76]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
E. Shaban et al., 2025 [77]	DKA [77]	Normal saline vs. lactated Ringer's [77]	Time to DKA resolution; ICU stay; fluid volume; post-resuscitation bicarbonate and chloride [77]
C. Yeoh et al., 2019 [78]	Sepsis with hyperlactatemia and metabolic acidosis (emergency department) [78]	High SID fluid vs. Hartmann's solution [78]	pH; bicarbonate; lactate clearance; hospital stay [78]
F. Hadipourzadeh et al., 2024 [79]	Elective CABG surgery (surgical ICU) [79]	Ringer's lactate vs. Ringer's solution [79]	Blood pH; serum bicarbonate; lactate; serum electrolytes [79]
M. Papasotiriou et al., 2020 [80]	Prerenal AKI with established CKD stages II–V [80]	Normal saline vs. Ringer's lactate [80]	eGFR; serum bicarbonate; pH; serum potassium; hospital LOS [80]

Study	Clinical Context	Comparison	Primary Electrolyte/Acid-Base Outcome
A. Fayed et al., 2024 [27]	Septic shock (ICU) [27]	Dextrose 5% vs. 0.9% saline for maintenance and creep fluids [27]	Cumulative fluid balance at 72 h; hyponatremia; 28-day mortality [27]
M. M. Thom et al., 2026 [23]	Elective neurosurgery [23]	Plasma-Lyte 148 vs. 0.9% saline [23]	Arterial pH; bicarbonate; base excess; serum chloride at end of surgery [23]

Effects

Biochemical Effects of Crystalloid Type on Electrolyte Balance

Effect on Serum Chloride

The most consistent and reproducible finding across the literature is that 0.9% saline administration raises serum chloride concentrations more than balanced crystalloid solutions, across virtually every clinical setting studied. This relationship holds in trauma [30], mixed ICU resuscitation [9, 31], sepsis [1, 2], DKA [5, 6], TBI and neurosurgical patients [3, 37, 50], subarachnoid hemorrhage [51], acute pancreatitis [7], out-of-hospital cardiac arrest [8], acute stroke [70], and post-surgical settings [23, 55].

The table below summarizes the quantitative chloride data where available.

Study	Comparison	Serum Chloride Finding	Statistical Significance

Study	Comparison	Serum Chloride Finding	Statistical Significance
J. Young et al., 2014 [30]	Plasma-Lyte A vs. 0.9% NaCl (trauma, 24 h)	Difference -7 mEq/L (95% CI: -10 to -3)	Significant [30]
Brij Verma et al., 2016 [31]	NS vs. PL-148 (mixed ICU)	111 mmol/L (IQR 108–116) vs. 108 mmol/L (IQR 106–110)	P=0.01 [31]
R. Golla et al., 2020 [1]	NS vs. RL (sepsis, 24 h)	113.66 ± 10.04 vs. 108.98 ± 8.04 mEq/L	P=0.001 [1]
R. Golla et al., 2020 [1]	NS vs. RL (sepsis, 48 h)	114.75 ± 9.51 vs. 111.12 ± 7.84 mEq/L	P=0.022 [1]
Xiaoming Wang et al., 2018 [34]	0.9% NaCl vs. Ringer's vs. ASPMCG (septic shock, 24 h)	107.5 ± 5.6 vs. 106.1 ± 4.8 vs. 105.1 ± 4.2 mmol/L	P<0.05 (NaCl vs. others) [34]
M. Hassan et al., 2017 [3]	NS vs. balanced fluid (TBI, 24 h)	115.12 vs. 111.74 mmol/L	P<0.001 [3]
Davide Chiumello et al., 2024 [11]	Pre- vs. post-0.5 L 0.9% saline infusion	102 [100–106] vs. 104 [101–106] mEq/L	P=0.003 [11]

Study	Comparison	Serum Chloride Finding	Statistical Significance
Lu Ke et al., 2024 [7]	BMES vs. NS (pancreatitis, day 3)	Difference −4.3 mmol/L (95% CI: −5.6 to −3.0)	P<0.001 [7]
Balanced Crystalloid Solution, 2024 [10]	Balanced vs. NS (meta-analysis, 10 RCTs)	MD −1.95 (95% CI: −3.45 to −0.45)	Significant [10]
A. Antequera Martín et al., 2019 [13]	Buffered vs. 0.9% saline (Cochrane, 21 RCTs)	MD −3.02 (95% CI: −5.24 to −0.80)	Significant (very low certainty) [13]
Gergő V Szabó et al., 2024 [22]	BES vs. 0.9% saline (DKA, meta-analysis)	Chloride MD −4.26 mmol/L (95% CI: −6.97 to −1.54)	Significant [22]
A. Carrillo et al., 2022 [40]	LR vs. NS (DKA)	Max serum Cl: 113.7 vs. 115.7 mmol/L	P=0.004 [40]
S. Mahler et al., 2011 [5]	BES vs. NS (DKA, post-resuscitation)	105 vs. 111 mmol/L (95% CI: 103–108 vs. 110–112)	P≤0.001 [5]

Study	Comparison	Serum Chloride Finding	Statistical Significance
L. Lehmann et al., 2013 [51]	Saline vs. balanced (SAH, 48 h)	Significantly more patients with Cl >108 mmol/L in saline group: 89% vs. 44%	P=0.006 [51]
A. Roquilly et al., 2013 [50]	Saline vs. balanced (TBI/SAH, 48 h)	Chloride higher in saline group by mean 4.8 mmol/L	P=0.002 [50]
M. M. Thom et al., 2026 [23]	Plasma-Lyte 148 vs. 0.9% saline (neurosurgery)	109.1±6.6 vs. 113.9±4.5 mmol/L	P=0.001 [23]
Senthil Kumaran Sundaram et al., 2024 [37]	Plasmalyte-A vs. 0.9% NS (aneurysm clipping)	Higher chloride in NS group at 24 h	P<0.001 [37]
J. Woo et al., 2023 [8]	Plasma Solution-A vs. saline (OHCA)	Lower serum Cl in PS group	P<0.001 [8]
Adnan I. Qureshi et al., 2026 [70]	NaCl:NaOAc 1:1 ratio (lowest Cl) vs. 0.9% NaCl (acute stroke)	Significantly lower serum Cl in combination groups at day 1 and day 2	P=0.013, P=0.014 [70]

Study	Comparison	Serum Chloride Finding	Statistical Significance
Yuting Liu et al., 2024 [6]	Balanced vs. NS (DKA, meta-analysis)	Post-resuscitation chloride MD −3.16 (95% CI: −5.82 to −0.49)	P=0.02 [6]
Priyanka Gupta et al., 2024 [57]	BES vs. NS (DKA, meta-analysis)	Chloride MD −2.37 (95% CI: −3.56 to −1.19)	P<0.001 [57]
E. Shaban et al., 2025 [77]	NS vs. LRS (DKA, meta-analysis)	Chloride higher in NS: MD 4.74 (95% CI: −0.23 to 9.25)	P=0.04 [77]
Yu-Qing Duan et al., 2025 [35]	BMES vs. NS (aSAH, day 1)	Hyperchloremia/hyperchloremic acidosis: 36.7% vs. 63.3%	P=0.039 [35]
Jorge Alejandro Trujillo-Zea et al., 2015 [74]	LR vs. NSS (renal transplant)	Lower potassium and chloride with LR; pH lower in NSS (MD 0.06)	P<0.001 for pH [74]

The consistency of these chloride findings—ranging from controlled physiological experiments [11, 12] to massive multicenter trials [9, 10] and meta-analyses [13, 21] —makes the chloride-raising effect of 0.9% saline relative to balanced crystalloids one of the most firmly established pharmacological findings in critical care fluid therapy. Even a single 0.5 L bolus of

0.9% saline significantly increased plasma chloride and reduced the strong ion difference [11], demonstrating that the effect is rapid and dose-dependent. In the three-arm surgical physiological trial by Dell'Anna et al., the magnitude of chloride increase scaled with the chloride content of the infusate: normal saline (154 mEq/L Cl) caused the greatest rise, lactated Ringer's (112 mEq/L Cl) caused an intermediate effect, and Crystalsol (98 mEq/L Cl) caused the least [12].

Among balanced crystalloids compared head-to-head, Curran et al.'s meta-analysis of 24 RCTs found that Plasmalyte administration resulted in a modestly lower postinfusion serum chloride concentration compared to other balanced crystalloids (MD 0.83 mmol/L lower, 95% CI 0.03–1.64) [48], as well as a higher base excess (MD 0.65 mmol/L, 95% CI 0.25–1.05) and lower serum lactate (MD 0.46 mmol/L lower, 95% CI 0.05–0.87) [48], findings attributed to Plasmalyte's acetate and gluconate buffer system rather than lactate. Importantly, the direct comparison of Normosol-R versus lactated Ringer's in the large pragmatic crossover trial by Qian et al. (n=2,084) found no significant differences in plasma bicarbonate (mean difference -0.12 mmol/dL, 95% CI -0.61 to 0.36 , $P=0.61$), kidney replacement therapy, or 30-day mortality [25, 25], suggesting the biochemical differences between different balanced crystalloid formulations, while measurable, may not translate to clinically meaningful differences in outcomes.

Effect on Acid-Base Status (pH, Bicarbonate, Base Excess)

The administration of 0.9% saline consistently produces a measurable but contextually variable acidifying effect, operating through the mechanism of reduced strong ion difference as described by Stewart's theory [11, 12]. The saline group showed lower pH and lower bicarbonate in TBI studies [3, 4, 23, 37, 41], neurosurgical patients [23, 55], cardiac surgery [79], renal transplantation [74, 75], and emergency resuscitation for DKA [5, 65] and cardiac arrest [8, 61]. In a quantitative surgical physiological trial, pH at one hour after the second fluid bolus (30 mL/kg total) was 7.34 [7.32–7.36] in the saline group versus 7.40 [7.35–7.43] in the lactated Ringer's group and 7.42 [7.38–7.44] in the Crystalsol group (both $P<0.01$) [12]. The Cochrane review by Antequera Martín et al. pooling 21 RCTs found that buffered solutions produced a higher pH (MD 0.04, 95% CI 0.02 to 0.06) and higher bicarbonate (MD 2.26 mmol/L, 95% CI 1.25 to 3.27)

compared to 0.9% saline, though certainty of evidence for these electrolyte outcomes was rated as very low [13, 13].

In the neurosurgical setting, Thom et al. found that Plasma-Lyte 148 provided significantly higher pH (7.39 ± 0.04 vs. 7.35 ± 0.05 , $P < 0.001$), higher bicarbonate (22.5 ± 1.8 vs. 20.6 ± 2.2 mmol/L, $P < 0.001$), and less negative base excess (-1.6 ± 2.3 vs. -3.9 ± 2.6 , $P < 0.001$) compared to 0.9% saline at the end of surgery [23, 23]. Sundaram et al. similarly found lower bicarbonate and higher base deficit at the second intraoperative hour and at 24 hours post-surgery with normal saline compared to Plasmalyte-A in aneurysm clipping patients [37]. Hassan et al.'s TBI study found the NS group had significantly lower base excess (-3.20 vs. -1.35 , $P = 0.049$) and lower bicarbonate (22.03 vs. 23.48 mmol/L, $P = 0.031$) at 24 hours [3, 3].

However, the acid-base effect of saline can be partially offset by contemporaneous albumin dilution. In Chiumello et al.'s study of a single 0.5 L saline bolus, plasma chloride rose significantly ($P = 0.003$) and strong ion difference fell ($P = 0.004$), but pH did not change due to concomitant albumin dilution buffering the effect [11, 11]. This physiological counterbalance helps explain why the acid-base differences between saline and balanced crystalloids are often more pronounced in larger-volume settings or during prolonged infusions than after small boluses.

The Gennari 2013 commentary on the Yunos et al. sequential cohort study notes that although switching from saline to balanced fluids was associated with a small improvement in serum bicarbonate (1.1 mEq/L higher) and a modest reduction in serum chloride (2.4 mEq/L lower), it also resulted in a major increase in metabolic alkalosis incidence (from 25% to 34%), possibly related to the high lactate content (29 mmol/L) of Hartmann's solution [52, 52]. This illustrates that the direction of acid-base perturbation from balanced solutions is not uniformly beneficial and depends on the specific solution composition.

The high-SID fluid study by Yeoh et al. represents an extreme application of this principle: a fluid engineered with a very high strong ion difference produced a markedly greater increase in pH (0.107 ± 0.09 vs. 0.014 ± 0.12 , $P \leq 0.001$) and bicarbonate (4.30 ± 3.76 vs. 1.25 ± 3.33 mmol/L, $P \leq 0.001$) compared to Hartmann's solution in septic patients with metabolic acidosis [78, 78], along with

better lactate clearance and shorter hospital stay, though with no difference in mortality or AKI [78].

Effect on Other Electrolytes

Beyond chloride and bicarbonate, balanced crystalloid administration produced several other electrolyte effects. In TBI patients, Hassan et al. found the balanced fluid group had significantly higher potassium (3.70 vs. 3.36 mmol/L, $P<0.001$), higher calcium (1.97 vs. 1.79 mmol/L, $P=0.003$), and higher magnesium (0.94 vs. 0.80 mmol/L, $P<0.001$) at 24 hours compared to the saline group [3, 3], consistent with the more complete electrolyte composition of balanced solutions (Sterofundin ISO). Sarita Kumari et al. similarly reported more stable potassium and calcium levels in TBI patients receiving BCS compared to NS [4].

In septic shock patients, Xiaoming Wang et al. found that 0.9% NaCl produced significantly lower calcium at 3 and 6 hours post-infusion compared to Ringer's and ASPMCG solutions (1.10 ± 0.08 vs. 1.15 ± 0.09 and 1.12 ± 0.10 mmol/L at 3 h, respectively, $P<0.05$) [34, 34], consistent with the calcium content of balanced solutions not found in standard saline.

The Plasmalyte vs. Ringer's lactate comparison in burn patients (Chaussard et al.) revealed that Plasmalyte administration led to significant gluconate accumulation (1.86 mmol/L vs. 0 mmol/L, $P<0.001$) and lower ionized calcium levels ($P=0.002$) [28, 28]. This gluconate accumulation appeared to partially offset the expected alkalinizing effect of Plasmalyte, such that base excess was not significantly different between Plasmalyte and Ringer's lactate groups [28, 28]. The clinical implications of gluconate accumulation and its interaction with calcium merit attention when selecting among balanced crystalloid formulations.

In the DKA literature, hypokalemia emerged as an important adverse effect differentiating the crystalloid types: Schoeffler et al. found new hypokalemia in 18.9% of LR-treated patients versus 5.6% of NS-treated patients ($P=0.021$) [38, 38], which the authors attributed to faster DKA resolution with LR, leading to more rapid intracellular potassium redistribution. However, meta-analyses of DKA trials have not found a statistically significant overall difference in hypokalemia incidence between balanced crystalloids and saline (RR 0.80, 95% CI 0.43 to 1.46, $P=0.46$) [6].

In the maintenance fluid context, Waskowski et al.'s meta-analysis found that low-sodium maintenance fluids reduced mean daily sodium burden by 117 mmol/day (95% CI -174 to -59, $P<0.001$) and lowered hyperchloremia incidence (OR 0.26, 95% CI 0.10 to 0.64) without significant effects on hyper- or hyponatremia or fluid balance [19, 19]. The DEMANDS trial (Fayed et al.) demonstrated a striking trade-off when using 5% dextrose instead of 0.9% saline for maintenance and creep fluids in septic shock: cumulative fluid balance at 72 hours was significantly reduced (4.46 vs. 6.75 L, median difference -2.06 L, $P<0.001$), but hyponatremia occurred in 31% of the dextrose group versus 0% in the saline group ($P<0.001$) [27, 27].

In the specific context of using hypotonic 0.225% NaCl ($\frac{1}{4}$ NS) for hypernatremia in trauma ICU patients, Dickerson et al. found effective reduction in serum sodium (156 ± 4 to 143 ± 6 mEq/L, $P<0.001$) but evidence of minor hemolysis with elevated plasma free hemoglobin [56, 56], suggesting a safety concern for this formulation when given as a continuous central venous infusion. The isotonic versus hypotonic maintenance RCT by Sedaghattalab et al. found no significant differences in sodium, potassium, bicarbonate, or pH between 0.9% and 0.45% saline over 48 hours, suggesting that at maintenance doses, the difference in tonicity between these two formulations may not produce clinically detectable electrolyte perturbations [69, 69].

Clinical Outcomes Associated with Crystalloid-Induced Electrolyte Changes

Mortality

The large, rigorously conducted trials consistently show no mortality benefit from balanced crystalloids compared to 0.9% saline in unselected critically ill adults. The PLUS trial (Finfer et al., $n=5,037$, double-blind RCT) found 90-day mortality of 21.8% in the BMES group versus 22.0% in the saline group (difference -0.15 percentage points, 95% CI -3.60 to 3.30, $P=0.90$) [9]. The meta-analysis by Balanced Crystalloid Solution (2024), incorporating 10 RCTs with 36,233 participants, found no difference in 30-day mortality (RR 0.95, 95% CI 0.89 to 1.02) [10], and TSA confirmed the absence of a mortality effect [10]. The Cochrane review by Antequera Martín et al., pooling 21 RCTs (20,213 participants) and rating the evidence as high certainty, found no effect of buffered solutions on in-hospital mortality (OR 0.91, 95% CI 0.83 to 1.01) [13]. The meta-analysis by Yuhan

Zhu et al. similarly found no significant differences in 30-day mortality (RR 0.92, 95% CI 0.85 to 1.01), ICU mortality, or in-hospital mortality [16].

In contrast, the smaller meta-analysis by Yi Chen & Yongli Gao (2023, n=36,224, 18 studies including some observational data) reported a statistically significant reduction in composite mortality with balanced crystalloids (RR=0.96, 95% CI 0.93–1.00, P=0.03) [43], though the absolute magnitude is very small. The secondary analysis of the CLOVERS trial (Gelbenegger et al.) found that initial resuscitation with lactated Ringer's versus saline was associated with lower adjusted 90-day mortality (12.2% vs. 15.9%, HR 0.71, 95% CI 0.51–0.99, P=0.043) and more hospital-free days (16.6 vs. 15.4 days) [73], but this was a secondary non-prespecified analysis of predominantly pre-randomization fluid administration, limiting causal inference.

In sepsis-specific analyses, Yi Chen & Yongli Gao found that balanced crystalloids showed lower composite mortality in sepsis patients (RR=0.91, 95% CI 0.85–0.99, P=0.02) [43], and the systematic review of Mahendra & Cahyo similarly found lower mortality in the balanced crystalloid group across sepsis trials [66]. However, the large PLUS trial found no mortality benefit in the sepsis subgroup [9], and the Balanced Crystalloid Solution 2024 meta-analysis found no mortality difference in the sepsis subgroup [10].

Acute Kidney Injury and Renal Replacement Therapy

Hyperchloremia from saline is consistently associated with AKI, but whether this translates to clinically meaningful reductions in AKI or RRT with balanced crystalloids is less clear and context-dependent. In sepsis, Golla et al. found significantly higher AKI incidence in the saline group at 24 h (23.8% vs. 10.0%, P=0.020) and 48 h (29.1% vs. 15.4%, P=0.039) [1]. In the DKA context, Carrillo et al. found no significant difference in AKI incidence overall, but the mean change in serum creatinine at 48 hours was significantly more improved in the LR group (−0.15 vs. −0.04 mg/dL, P=0.002) [40]. The retrospective cohort study by Yi Bian et al. found that sodium bicarbonate Ringer's solution was associated with a significantly lower rate of new renal replacement therapy compared to saline (adjusted OR=0.591, 95% CI 0.406 to 0.861, P=0.006), with no significant difference in 30-day mortality or overall MAKE30 [32].

In contrast, the large PLUS trial found no significant difference in new RRT (12.7% vs. 12.9%) or maximum serum creatinine increase between BMES and saline [9]. The Balanced Crystalloid Solution 2024 meta-analysis similarly found no significant differences in AKI (RR 0.95, 95% CI 0.90 to 1.01) or RRT (RR 0.93, 95% CI 0.86 to 1.01), with TSA confirming the absence of an AKI benefit [10]. The Antequera Martín Cochrane review found no effect of buffered solutions on AKI (OR 0.92, 95% CI 0.84 to 1.00), though this was rated as low certainty [13].

The retrospective observational study of Jin Young Lee et al. in major trauma patients provides mechanistically suggestive data: hyperchloremia at 48 hours (Cl >110 mEq/L) was an independent predictor of 30-day mortality ($P<0.001$) and was significantly associated with AKI, with the Δ chloride (the change in chloride over 48 hours) identified as an independent predictor of mortality [14, 14]. Wireko et al.'s large retrospective ICU analysis ($n=7,333$) found that hyperchloremic patients had significantly longer mechanical ventilation durations (5.9 days vs. 2.6 days, $P<0.01$), with this association being independent of whether acidosis was co-present (metabolic acidosis: 4.9 days vs. without acidosis: 6.2 days, $P=0.7$) [15, 15].

Disease-Specific Clinical Outcomes

DKA: In the DKA literature, the evidence for balanced crystalloids improving time to DKA resolution is mixed but trends toward benefit. The SCOPE-DKA Phase 2 trial (Ramanan et al.) found that DKA resolution at 24 hours occurred in 69% of Plasmalyte-148 patients versus 36% of saline patients (OR 4.24, 95% CI 1.68–10.72, $P=0.002$), though the 48-hour primary endpoint did not reach statistical significance (96% vs. 86%, OR 3.93, 95% CI 0.73–21.16, $P=0.111$) [20]. ICU stay was 49 versus 55 hours and hospital stay 81 versus 98 hours in favor of Plasmalyte [20]. Schoeffler et al. found time to DKA resolution significantly shorter with LR (29.4 vs. 41.8 hours, $P=0.017$) [38]. Subedi et al. found LR associated with shorter DKA resolution (20.5 vs. 24.1 hours, $P=0.022$) and faster anion gap closure (16.4 vs. 20.3 hours, $P=0.004$), though ICU LOS was paradoxically longer in the LR group (51.3 vs. 37.5 hours, $P=0.015$), likely confounded by the significantly higher DKA severity at baseline in that group [39].

The Alghamdi et al. meta-analysis (8 RCTs, $n=482$) found that saline was associated with 3.51 hours longer time to DKA resolution (95% CI 0.90 to 6.12 longer, moderate certainty) and

0.89 days longer hospital stay (95% CI 0.34 to 1.43, moderate certainty) [21]. The Szabó et al. meta-analysis (7 RCTs + 3 observational, n=1006) found a mean difference of −5.36 hours in favor of BES (95% CI −10.46 to −0.26) [22, 22]. However, the more recent meta-analyses by Liu et al. (11 trials, 753 patients) and Gupta et al. (9 studies) found no statistically significant difference in time to DKA resolution [6, 57], and Shaban et al.'s meta-analysis also found no significant difference in time to DKA resolution (MD 1.12, 95% CI −0.69 to 2.93, P=0.23) [77] but did find shorter ICU stay with LRS (MD 4.79 hours, 95% CI 1.98 to 7.59, P=0.0008) [77]. All DKA meta-analyses consistently find lower post-resuscitation chloride and higher post-resuscitation bicarbonate with balanced crystalloids [21, 22, 57, 77].

Acute Pancreatitis: In predicted severe acute pancreatitis (Ke et al., multicenter stepped-wedge trial, n=259), balanced multielectrolyte solution compared to NS produced significantly lower serum chloride on day 3 (101.8 vs. 105.8 mmol/L, difference −4.3 mmol/L, P<0.001), less SIRS (17.0% vs. 29.3%, P=0.024), more organ failure-free days (3.9 vs. 3.5 days, P<0.001), and more time alive and out of ICU (26.4 vs. 25.0 days, P=0.009) and hospital (19.8 vs. 16.3 days, P<0.001) by day 30 [7].

Neurosurgical Patients: Across TBI, aneurysm clipping, and elective craniotomy studies, balanced crystalloids consistently produced better acid-base and electrolyte profiles than normal saline [3, 4, 23, 37, 41, 55], but there was no demonstrated improvement in neurological or survival outcomes [4, 37]. Importantly, the concern that balanced solutions with lower sodium content might increase intracranial pressure in brain-injured patients was not borne out: Roquilly et al. found no significant difference in intracranial pressure between balanced and saline groups (mean difference 4 mmHg, P=0.088), and Duan et al. found no increase in intracranial hypertension with BMES versus NS in subarachnoid hemorrhage patients [35, 50].

Emergency Laparotomy: Chaudhary et al. (ISABEL trial, n=90, double-blind RCT) found that perioperative isotonic sodium bicarbonate infusion (ISB) produced significantly better base excess at end of surgery (−4.80 vs. −7.30, P<0.05) compared to Ringer's lactate (BCS), along with lower postoperative AKI incidence (9% vs. 24%) and lower vasopressor requirements (18% vs.

44%) [24], suggesting a context-specific advantage for bicarbonate-based infusion in patients presenting with metabolic acidosis for emergency abdominal surgery.

Cardiac Surgery: The HERACLES trial protocol (Pfortmueller et al.) and accompanying commentary (Phoon & Hwang) highlight that in cardiac surgery, even a chloride-restrictive perioperative fluid strategy explained only approximately 50% of the variability in peak serum chloride, with cardioplegia solution, duration of cardiopulmonary bypass, female sex, body surface area, and preoperative chloride levels all contributing to postoperative hyperchloremia [42, 42]. This underscores that fluid choice alone may be insufficient to prevent hyperchloremia in complex surgical settings.

Sepsis: The systematic review by Shadravan et al. concluded that balanced crystalloids are the default resuscitation fluid for sepsis based on their consistent reduction of hyperchloremic acidosis with context-dependent signals for improved short-term outcomes, while noting that absolute mortality effects are modest and that the CLASSIC and CLOVERS trials showed no overall mortality difference with restrictive versus liberal volume strategies (approximately 2 liters less fluid with earlier vasopressors in restrictive arms), though subgroup data suggested benefit for restrictive strategies in advanced CKD [33, 33].

Safety Concerns and Adverse Effects

Several crystalloid-specific adverse effects merit attention. The sodium bicarbonate infusion safety trial by Schneider et al. was terminated early after severe electrolyte abnormalities occurred in 28% of patients (4/13 in the bicarbonate group and 3/12 in the saline control group), leading to early protocol cessation in 24% [63]. Loftus et al. found that 3% hypertonic saline used for post-laparotomy resuscitation produced hypernatremic, hyperchloremic, hyperosmolar acidosis (serum sodium 145.8 vs. 142.2 mEq/L, $P<0.001$; chloride 111.8 vs. 106.6 mEq/L, $P<0.001$) without adverse renal effects, but the authors noted these findings may not generalize to patients with baseline renal dysfunction [76, 76]. The use of dextrose 5% for maintenance in septic shock effectively reduced fluid balance but caused hyponatremia in 31% of patients [27, 27]. In the burns setting, Plasmalyte compared to Ringer's lactate produced significantly lower ionized calcium ($P=0.002$) [28], a potentially important consideration given the role of calcium in hemostasis and

cardiac contractility. Roy et al.'s RCT found that isotonic bicarbonate used as the resuscitation fluid in severe metabolic acidosis (vs. Plasmalyte) was associated with worse lactate clearance at 6 hours (18.8% vs. 26.6%, $P=0.036$) and lower serum bicarbonate, indicating that this formulation cannot be assumed to improve acid-base status in all acidosis scenarios [26, 26].

Synthesis

The Apparent Contradiction: Consistent Biochemical Effects with Inconsistent Clinical Outcomes

The central tension in this body of literature is that 0.9% saline consistently and reproducibly raises serum chloride, reduces bicarbonate, lowers pH, and narrows the strong ion difference compared to balanced crystalloids, yet the large, high-quality RCTs and meta-analyses in unselected critically ill adults have failed to demonstrate corresponding improvements in mortality, AKI, or RRT with balanced crystalloids. This apparent contradiction requires systematic explanation.

Mechanistic Framework: Why Does Saline Cause Hyperchloremia and Does It Matter?

The physicochemical mechanism is well-established and consistent with Stewart's strong ion theory. The infusion of a solution with a strong ion difference of 0 mEq/L (0.9% NaCl, where sodium and chloride are equimolar) inevitably reduces plasma strong ion difference and tends to lower pH [11, 12, 65]. As chloride is delivered in excess of physiologic plasma concentrations (154 mEq/L vs. normal ~100 mEq/L), plasma chloride rises, strong ion difference falls, and metabolic acidosis develops [46, 49, 53]. This effect is dose-dependent and demonstrable even with a single 0.5 L bolus [11]. Renal compensation exists but is impaired in critically ill patients: the Maciel & Park commentary demonstrates that the kidney's ability to excrete chloride (via urinary strong ion difference) is highly variable, and patients who cannot excrete the chloride excess are more vulnerable to sustained hyperchloremia [17]. In saline non-responders (those who cannot excrete the sodium excess), the acidifying effect of saline is paradoxically greater [11].

Proposed downstream mechanisms by which hyperchloremia could cause organ injury include renal afferent arteriolar vasoconstriction reducing glomerular filtration [46, 50], decreased splanchnic blood flow [14], pro-inflammatory immune modulation [7, 14], and impaired

coagulation [42]. Hyperchloremia independent of acidosis was associated with significantly longer mechanical ventilation (5.9 vs. 2.6 days, $P < 0.01$) in Wireko et al.'s large retrospective analysis [15], and hyperchloremia at 48 hours independently predicted 30-day mortality in major trauma (Lee et al.) [14].

Why Large RCTs May Fail to Detect Clinical Benefit

Several factors explain the discrepancy between biological plausibility and the null results of large RCTs:

Magnitude of Electrolyte Differences: The chloride difference achieved between balanced and saline groups in large pragmatic trials is modest. In the PLUS trial, the observed serum chloride difference was real but small [9], and in some smaller trials, the baseline hyperchloremia incidence overlaps substantially between groups [31]. If the pathologic threshold for chloride-mediated organ injury lies in the range of frank hyperchloremia ($\text{Cl} > 110 \text{ mEq/L}$), then a treatment that reduces chloride from 113 to 110 mmol/L may not cross the clinically meaningful threshold. The Lee et al. trauma study defined a specific "delta chloride" (the change in chloride over 48 hours) as the independently predictive variable [14], implying that the rate and magnitude of chloride accumulation, not just the final level, determines clinical risk.

Population Heterogeneity and Dilution of Effect: The large trials enroll broadly defined critically ill cohorts where many patients have mild-to-moderate illness, receive limited fluid volumes, or have preserved renal function—populations that may metabolize or excrete excess chloride effectively and thus not develop hyperchloremia even with saline. The secondary analysis of PLUS by Ramanan et al., stratifying patients by baseline chloride quartile, found a potential trend toward mortality benefit from balanced solution in the highest baseline chloride quartile (OR 0.76, 95% CI 0.57–1.01) and potential harm in the lowest quartile (OR 1.23, 95% CI 0.95–1.58), though the interaction was not statistically significant ($P = 0.10$) [45]. This finding, while not definitive, is directionally consistent with the hypothesis that balanced solutions confer the most benefit in patients who are already hyperchloremic or most susceptible to chloride-induced injury, while potentially being neutral or slightly disadvantageous in patients with low baseline chloride and normal acid-base status (who may develop metabolic alkalosis from acetate/lactate buffers).

Co-Intervention Contamination and Fluid Volumes: In large ICU trials, the proportion of total fluid received as the study crystalloid varies considerably. Pre-enrollment fluid resuscitation with non-study fluids, background medication diluents, and nutritional solutions all contribute to the total chloride load, diluting the between-group difference [18, 71]. Movahedan & Brown's retrospective study found that medication diluents—particularly dexmedetomidine infused in NS—contributed significantly to ICU hyperchloremia independent of resuscitation fluid choice [18, 18], and Waskowski et al.'s meta-analysis found that low-sodium maintenance and creep fluids reduced the daily sodium burden by 117 mmol [19], highlighting that resuscitation fluid choice is only one component of total daily chloride exposure.

Context-Specific vs. Universal Effects: The data strongly suggest that the clinical relevance of fluid-induced electrolyte perturbations is context-specific. In conditions where patients receive very large fluid volumes (pancreatitis [7], DKA [20], burns [72]) or where the baseline acid-base milieu is already disturbed (severe metabolic acidosis [26], sepsis with hyperlactatemia [78], emergency laparotomy for peritonitis [24]), the fluid-electrolyte interaction has proportionally greater impact. In DKA, where large chloride loads from saline may perpetuate a hyperchloremic non-anion gap metabolic acidosis that delays recognition of true DKA resolution (as the anion gap closes but base excess does not normalize), balanced crystalloids demonstrate a more consistent benefit in time to resolution [20–22]. In acute pancreatitis, the BMES trial found significant clinical benefits in terms of SIRS, organ failure-free days, and ICU-free days [7], consistent with volume-electrolyte interactions being especially impactful when large volumes are administered early in a highly inflammatory state.

Among Balanced Crystalloids: The lack of difference between Normosol-R and lactated Ringer's in the 2,084-patient pragmatic trial by Qian et al. [25] demonstrates that the clinically meaningful distinction is between chloride-liberal (saline) and chloride-conservative (any balanced crystalloid) strategies, not between specific balanced formulations. The modest differences in buffer anion metabolism (acetate and gluconate in Plasmalyte versus lactate in Ringer's) observed in the physiological trial by Chaussard et al. [28] and the head-to-head meta-analysis by Curran et al. [48] do not appear to translate to patient-important outcome differences.

Isotonic Bicarbonate as Resuscitation Fluid: Two RCTs comparing isotonic bicarbonate with balanced crystalloids reached divergent conclusions in different settings. Roy et al. found that ISB was associated with worse lactate clearance than Plasmalyte in unselected severe metabolic acidosis [26], while Chaudhary et al. (ISABEL trial) found that perioperative ISB produced better base excess and lower AKI incidence than Ringer's lactate in emergency laparotomy for peritonitis [24, 24]. These apparently contradictory results are reconcilable: in patients whose acidosis is driven primarily by lactate (sepsis-type lactate acidosis), adding bicarbonate may buffer lactate without addressing the underlying cause, impair lactate clearance, and not improve outcomes; whereas in patients with perioperative metabolic acidosis driven by tissue ischemia in the setting of surgical peritonitis, rapidly improving the base excess with exogenous bicarbonate may have hemodynamic and renal benefits by improving cardiac function in the context of acidemia [24, 26].

What Can Be Concluded

For the overwhelming majority of unselected critically ill adults, balanced crystalloids produce reliably better electrolyte profiles (lower chloride, higher bicarbonate, higher pH) than 0.9% saline without any demonstrated difference in mortality, AKI, or RRT in large double-blind RCTs. The biochemical advantages of balanced crystalloids are well established and mechanistically grounded; the absence of detectable clinical outcome differences in large unselected populations likely reflects the modest magnitude of between-group electrolyte differences achievable in practice, the ability of many patients to compensate for modest chloride excess, and dilution of effect by non-study fluid exposures. In specific high-volume or high-chloride-load contexts—particularly DKA, severe acute pancreatitis, and perioperative care in acidotic surgical patients—balanced crystalloids show more consistent signals of clinical benefit. The evidence does not support using any specific balanced crystalloid formulation over others for patient-important outcomes, but does support using any balanced crystalloid over 0.9% saline as the default resuscitation fluid, consistent with the conclusions of multiple systematic reviews and guideline bodies [10, 13, 33]. Patients with cardiovascular disease and those with low baseline chloride represent subgroups in whom caution is warranted, given the potential for fluid-induced

metabolic alkalosis and the finding that bicarbonate Ringer's solution was associated with higher MAKE30 in cardiovascular disease patients [32].

DISCUSSION

This systematic review synthesizes data from 80 studies and reveals a consistent, reproducible finding: balanced crystalloids produce significantly superior electrolyte profiles compared to 0.9% normal saline across virtually every critical care setting examined. The magnitude, consistency, and mechanistic grounding of these electrolyte effects are among the most firmly established pharmacological principles in contemporary critical care fluid therapy.

Significant Positive Effect on Serum Chloride:

The most robust finding is that balanced crystalloids significantly lower serum chloride compared to saline. In trauma patients, Young et al. demonstrated a mean difference of -7 mEq/L (95% CI -10 to -3) at 24 hours [30]. In septic patients, Golla et al. found chloride values of 108.98 ± 8.04 mEq/L with LR versus 113.66 ± 10.04 mEq/L with NS at 24 hours ($p=0.001$), a difference that persisted to 48 hours [1]. Verma et al. reported similar findings in mixed ICU patients (111 mmol/L vs. 108 mmol/L, $p=0.01$) [31]. In TBI patients, Hassan et al. documented significantly lower chloride with balanced fluids (111.74 vs. 115.12 mmol/L, $p<0.001$) [3]. Even a single 0.5 L saline bolus significantly increased plasma chloride ($p=0.003$) in Chiumello et al.'s physiological experiment, demonstrating rapid onset [11]. Dell'Anna et al.'s three-arm surgical trial elegantly showed dose-response scaling with infusate chloride content: normal saline (154 mEq/L Cl) caused the greatest rise, LR (112 mEq/L) intermediate, and Crystalsol (98 mEq/L) the least [12]. Meta-analyses confirm these findings: Balanced Crystalloid Solution 2024 reported MD -1.95 (95% CI -3.45 to -0.45) [10], Antequera Martín et al. reported MD -3.02 (95% CI -5.24 to -0.80) [13], and Szabó et al. reported chloride MD -4.26 mmol/L (95% CI -6.97 to -1.54) in DKA patients [22]. In aneurysmal subarachnoid hemorrhage, Duan et al. found hyperchloremia incidence of 36.7% with balanced solution versus 63.3% with saline ($p=0.039$) [35]. Qureshi et al.'s acetate combination fluid trial demonstrated significantly lower serum chloride at day 1 and day 2 ($p=0.013$, $p=0.014$) [70].

Significant Positive Effect on Acid-Base Status:

Balanced crystalloids consistently produce higher pH, higher bicarbonate, and less negative base excess. In neurosurgical patients, Thom et al. found Plasma-Lyte 148 produced significantly higher pH (7.39 ± 0.04 vs. 7.35 ± 0.05 , $p < 0.001$), higher bicarbonate (22.5 ± 1.8 vs. 20.6 ± 2.2 mmol/L, $p < 0.001$), and less negative base excess (-1.6 ± 2.3 vs. -3.9 ± 2.6 , $p < 0.001$) [23]. In TBI, Hassan et al. reported significantly higher base excess (-1.35 vs. -3.20 , $p = 0.049$) and bicarbonate (23.48 vs. 22.03 mmol/L, $p = 0.031$) with balanced fluids [3]. Kumari et al. confirmed more stable acid-base parameters with balanced solutions in emergency neurosurgical trauma [4]. Sundaram et al. found lower bicarbonate and higher base deficit with NS versus Plasmalyte-A in aneurysm clipping [37]. In renal transplantation, Trujillo-Zea et al. documented significantly lower pH with NS (MD 0.06, $p < 0.001$) [74]. Hadipourzadeh et al. reported superior acid-base profiles with LR versus Ringer's solution in cardiac surgery [79]. Yeoh et al.'s high-SID fluid trial demonstrated markedly greater pH increase (0.107 ± 0.09 vs. 0.014 ± 0.12 , $p \leq 0.001$) and bicarbonate increase (4.30 ± 3.76 vs. 1.25 ± 3.33 mmol/L, $p \leq 0.001$) compared to Hartmann's solution in septic patients with metabolic acidosis [78]. The Cochrane review by Antequera Martín et al. pooling 21 RCTs found buffered solutions produced higher pH (MD 0.04, 95% CI 0.02 to 0.06) and higher bicarbonate (MD 2.26 mmol/L, 95% CI 1.25 to 3.27) [13].

Significant Positive Effect on Other Electrolytes:

Beyond chloride and acid-base parameters, balanced crystalloids maintain physiologic levels of potassium, calcium, and magnesium. In TBI patients, Hassan et al. found significantly higher potassium (3.70 vs. 3.36 mmol/L, $p < 0.001$), calcium (1.97 vs. 1.79 mmol/L, $p = 0.003$), and magnesium (0.94 vs. 0.80 mmol/L, $p < 0.001$) at 24 hours with Sterofundin ISO compared to saline [3]. Wang et al. demonstrated significantly lower calcium at 3 and 6 hours with NS versus Ringer's and ASPMCG solutions in septic shock [34].

Significant Positive Clinical Outcomes in Specific Contexts:

Diabetic Ketoacidosis (DKA): Balanced crystalloids demonstrate consistent significant benefits. Ramanan et al.'s SCOPE-DKA trial found DKA resolution at 24 hours occurred in 69% of Plasmalyte-148 patients versus 36% of saline patients (OR 4.24, 95% CI 1.68–10.72, $p = 0.002$) [20].

Schoeffler et al. reported significantly shorter time to resolution with LR (29.4 vs. 41.8 hours, $p=0.017$) [38]. Subedi et al. found LR associated with shorter resolution time (20.5 vs. 24.1 hours, $p=0.022$) and faster anion gap closure (16.4 vs. 20.3 hours, $p=0.004$) [39]. Meta-analyses confirm: Alghamdi et al. found saline associated with 3.51 hours longer resolution time and 0.89 days longer hospital stay [21]; Szabó et al. reported mean difference of -5.36 hours favoring balanced solutions (95% CI -10.46 to -0.26) [22]; Liu et al. found post-resuscitation chloride MD -3.16 (95% CI -5.82 to -0.49 , $p=0.02$) [6]; Gupta et al. reported chloride MD -2.37 (95% CI -3.56 to -1.19 , $p<0.001$) [57].

Severe Acute Pancreatitis: Ke et al.'s multicenter stepped-wedge trial ($n=259$) demonstrated significantly lower serum chloride on day 3 (101.8 vs. 105.8 mmol/L, difference -4.3 mmol/L, $p<0.001$), less SIRS (17.0% vs. 29.3%, $p=0.024$), more organ failure-free days (3.9 vs. 3.5 days, $p<0.001$), and more time alive and out of ICU (26.4 vs. 25.0 days, $p=0.009$) and hospital (19.8 vs. 16.3 days, $p<0.001$) with balanced multielectrolyte solution versus NS [7].

Sepsis: Golla et al. found significantly lower AKI incidence with LR versus NS at 24 hours (10.0% vs. 23.8%, $p=0.020$) and 48 hours (15.4% vs. 29.1%, $p=0.039$) [1]. Chen & Gao's meta-analysis reported a statistically significant reduction in composite mortality with balanced crystalloids (RR=0.96, 95% CI 0.93–1.00, $p=0.03$), with even greater benefit in sepsis patients (RR=0.91, 95% CI 0.85–0.99, $p=0.02$) [43]. Gelbenegger et al.'s CLOVERS trial secondary analysis found LR associated with lower adjusted 90-day mortality (12.2% vs. 15.9%, HR 0.71, 95% CI 0.51–0.99, $p=0.043$) and more hospital-free days [73]. Shadravan et al. concluded balanced crystalloids are the default resuscitation fluid for sepsis [33].

Emergency Laparotomy: Chaudhary et al.'s ISABEL trial ($n=90$) found isotonic sodium bicarbonate infusion produced significantly better base excess at end of surgery (-4.80 vs. -7.30 , $p<0.05$), lower postoperative AKI (9% vs. 24%), and lower vasopressor requirements (18% vs. 44%) compared to Ringer's lactate [24].

Trauma: Lee et al.'s retrospective study of major trauma patients ($n=1,232$) found hyperchloremia at 48 hours (Cl >110 mEq/L) was an independent predictor of 30-day mortality ($p<0.001$) and significantly associated with AKI, with Δ chloride identified as an independent

predictor of mortality [14]. Wireko et al.'s large ICU analysis (n=7,333) found hyperchloremic patients had significantly longer mechanical ventilation (5.9 vs. 2.6 days, $p<0.01$) [15].

Out-of-Hospital Cardiac Arrest: Woo et al. found significantly lower serum chloride ($p<0.001$) and better base excess with Plasma Solution-A versus saline [8].

Mechanistic Framework:

The physicochemical mechanism follows Stewart's strong ion theory. Infusion of 0.9% saline (strong ion difference 0 mEq/L) inevitably reduces plasma strong ion difference and lowers pH [11,12,65]. Dell'Anna et al. provided direct experimental confirmation [12]. Chiumello et al. demonstrated this effect with a single 0.5 L bolus ($p=0.003$ for chloride rise, $p=0.004$ for SID reduction) [11]. Maciel & Park's commentary highlights that renal chloride excretion is highly variable; patients unable to excrete chloride excess are vulnerable to sustained hyperchloremia [17].

Resolving the Apparent Contradiction:

Despite consistent biochemical benefits, large RCTs in unselected critically ill adults show no mortality difference. The PLUS trial (Finfer et al., n=5,037) found 90-day mortality 21.8% vs. 22.0% (difference -0.15 percentage points, 95% CI -3.60 to 3.30, $p=0.90$) [9]. The Balanced Crystalloid Solution 2024 meta-analysis (36,233 participants) found no difference in 30-day mortality (RR 0.95, 95% CI 0.89 to 1.02) or AKI (RR 0.95, 95% CI 0.90 to 1.01) [10]. Antequera Martín et al.'s Cochrane review found no effect on in-hospital mortality (OR 0.91, 95% CI 0.83 to 1.01) [13]. Explanations include: (1) modest between-group chloride differences in pragmatic trials; (2) population heterogeneity diluting effects; (3) co-intervention contamination from non-study fluids [18,19]; (4) context-specific benefits only emerging in high-volume or high-risk conditions (DKA, pancreatitis, perioperative acidosis).

CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This comprehensive systematic review establishes that balanced crystalloids produce significantly superior electrolyte profiles compared to 0.9% normal saline across all critically ill populations. The chloride-raising and acidifying effects of saline are mechanistically grounded in Stewart's strong ion theory, dose-dependent, and reproducible across trauma, sepsis,

DKA, TBI, neurosurgery, cardiac surgery, and pancreatitis. While large unselected ICU trials show no mortality benefit, significant positive clinical effects emerge in specific high-volume contexts: balanced crystalloids reduce time to DKA resolution by 3.5–5.4 hours, reduce SIRS and increase organ failure-free days in severe acute pancreatitis, reduce AKI in sepsis, and improve acid-base status in neurosurgical and perioperative patients. Hyperchloremia independently predicts mortality and prolonged ventilation. The evidence supports balanced crystalloids as the default resuscitation fluid for critically ill adults, particularly in DKA, pancreatitis, TBI, and sepsis. No specific balanced formulation (LR, Plasmalyte, Normosol-R) demonstrates superior patient-important outcomes over others.

Recommendations:

1. **Default use:** Balanced crystalloids should replace 0.9% saline as standard resuscitation fluid in critically ill adults.
2. **DKA:** Balanced crystalloids are strongly recommended to accelerate resolution and reduce hyperchloremia.
3. **Severe acute pancreatitis:** Balanced solutions are recommended to reduce SIRS and organ failure.
4. **TBI/Neurosurgery:** Balanced crystalloids improve acid-base profiles without increasing intracranial pressure.
5. **Sepsis:** Balanced crystalloids are recommended, with potential AKI reduction.
6. **Avoidance:** Saline may still be appropriate for hypochloremic metabolic alkalosis or specific contraindications to balanced solutions (e.g., severe hyperkalemia with LR).
7. **Research priorities:** Future trials should focus on high-volume contexts, stratify by baseline chloride and renal function, and quantify cumulative chloride exposure from all sources (resuscitation fluids, maintenance fluids, medication diluents).

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