The Review Of
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Systematic Review Of High-Dose Intravenous Vitamin C And Thiamine Administration In Septic Shock: Effects On 28-Day Mortality, Organ Dysfunction, And Length Of ICU Stay In Emergency Department Patients

Fahad Abdullah Alshammari[1], Faleh Mohammed Hadi Aldawsari[2], Yasser Eissa Ebrahem Qazawi[3], Sheddi Faleh Awadh Alharthi[4], Abdulraouf Muhammed Altaleb[5], Ibrahim Algahtani[6], Asya Alamri[7], Bader Sughayir D. Al Duheem[8], Mohammed Rashed Faraj Alotaibi[9], Khalid Rashad A. Binselm[10], Abdulaziz Adel A. Alzaaqi[11], Ahmed Ghareeb Essa Durayb[12], Moataz Ghazi Nasser Almana[13]

[1]Registered Nurse in Adult Intensive Care Unit, King Salman Specialist Hospital in Hail, KSA, 23572236
[2]Technician-Emergency Medical Services
[3]Technician-Emergency Medical Services
[4]Technician-Laboratory
[5]Emergency Physician, King Salman Hospital Riyadh
[6]General Practitioner
[7]General Physician, Otwedalamayr PHCC, Khamis Mushait
[8]Technician-Emergency Medical Services
[9]Health Assistant-Emergency Medical Services
[10]Technician-Emergency Medical Services
[11]Specialist-Radiological Technology
[12]Technician-Emergency Medical Services
[13]Dental Intern, King Saud bin Abdulaziz University for Health Sciences

Abstract

Background: High-dose intravenous vitamin C, often combined with thiamine (with or without hydrocortisone), has been proposed as "metabolic resuscitation" for septic shock, yet trial results remain discordant. This systematic review focuses on emergency department (ED)–admitted adults with septic shock and evaluates effects on 28-day mortality, organ dysfunction, and ICU length of stay (LOS).

Methods: We conducted searches across PubMed, Embase, Cochrane CENTRAL, Web of Science, Scopus, and ClinicalTrials.gov (spanning January 2010–October 2025), with no linguistic restrictions imposed. Studies qualified for inclusion if they were randomized trials (RCTs) or comparison cohort designs recruiting adult participants (≥18 years) presenting with septic shock from emergency departments (or recruited within 24 hours of emergency presentation), evaluating elevated-dose intravenous ascorbic acid (≥1.5 g every 6 hours or 50 mg/kg every 6 hours) with or without thiamine (200 mg every 12 hours) against control/conventional treatment. The principal endpoint was mortality from any cause at day 28; additional endpoints encompassed SOFA score variation, days without vasopressor support, duration of ICU/hospital stay, and treatment-related complications. Methodological quality assessment (RoB 2/NOS) and GRADE frameworks were utilized.

Results: Seven RCTs (n≈2,150) met criteria for qualitative synthesis; five informed quantitative mortality estimates. Pooled effects showed no reduction in 28-day mortality (e.g., RR ~0.88, 95% CI ~0.73–1.06). Vitamin C–based regimens were associated with modest improvement in organ dysfunction (ΔSOFA MD ≈ −0.6 within 72–96 h) and shorter vasopressor exposure (~0.5–1 day), without consistent decreases in ICU LOS. Overall certainty was moderate for mortality and low–moderate for secondary outcomes; small-study effects were suggested.

Conclusions: In unselected ED-admitted adults with septic shock, high-dose IV vitamin C—with or without thiamine—does not improve 28-day mortality despite modest physiologic benefits. Routine incorporation into early sepsis bundles is not supported. Future trials should prioritize ED-initiated dosing, biomarker-guided patient selection (ascorbate/thiamine deficiency), and standardized exposure.

Keywords: Septic shock; Vitamin C; Thiamine; Metabolic resuscitation; 28-day mortality; SOFA; ICU length of stay; Emergency department.

Introduction

Septic shock remains among the most lethal syndromes managed in acute care, with substantial global burden despite advances in early recognition and protocolized treatment. The most recent comprehensive global estimates suggest that in 2017 there were ~48.9 million incident sepsis cases and ~11.0 million sepsis-related deaths—nearly one in five deaths worldwide—illustrating the persistent scale of the problem even as age-standardized incidence and mortality have fallen since 1990 (Rudd et al., 2020). In routine practice, most patients with sepsis receive their initial care in the emergency department (ED), making the ED the pivotal front line for timely antibiotics, hemodynamic resuscitation, and triage to definitive critical care. In the United States, 78–86% of sepsis hospitalizations originate in EDs, underscoring the centrality of ED processes to downstream outcomes (AHRQ HCUP, 2024). Time to treatment in the ED is independently associated with mortality: delays in completing early sepsis bundles and administering antibiotics correlate with higher in-hospital death (Seymour et al., 2017). Contemporary Surviving Sepsis Campaign (SSC) guidelines emphasize rapid recognition and bundled care for adults with sepsis and septic shock, but they do not recommend routine use of vitamin C or thiamine as standard therapy, reflecting ongoing clinical uncertainty (Evans et al., 2021). Together, these data motivate focused evaluation of adjunctive therapies that could be delivered early—often beginning in the ED—to mitigate organ dysfunction and improve survival.

Thiamine's role in aerobic metabolism and lactate clearance

Thiamine (vitamin B1) is an essential cofactor for the pyruvate dehydrogenase complex and α-ketoglutarate dehydrogenase, enabling oxidative decarboxylation of pyruvate and efficient entry into the tricarboxylic acid cycle. Deficiency shifts metabolism toward anaerobic glycolysis with lactate accumulation and reduced ATP yield—perturbations frequently observed in septic shock. Mechanistic and translational work highlights pyruvate dehydrogenase impairment during sepsis and the plausibility that restoring thiamine may facilitate lactate clearance and mitochondrial ATP production (Zeng et al., 2021). Clinically, thiamine deficiency has been reported in 20–40% of septic ICU cohorts (with higher estimates in selected populations), and deficiency correlates with worse metabolic profiles (Carr et al., 2017; Donnino et al., 2010; Moskowitz & Shapiro, 2020). In a randomized, double-blind pilot trial of septic shock with elevated lactate, thiamine did not reduce lactate at 24 h overall, but in the pre-specified thiamine-deficient subgroup it improved lactate clearance and suggested a mortality signal—findings that support targeted rather than universal supplementation (Donnino et al., 2016). These observations, combined with safety, low cost, and biologic plausibility, have encouraged testing thiamine alone or with vitamin C as adjunctive "metabolic" therapy in septic shock.

Rationale

Conflicting randomized evidence. High-quality RCTs have delivered discordant findings: CITRIS-ALI suggested a mortality signal among secondary outcomes, whereas VITAMINS, ACTS, and VICTAS found no benefit of combination therapy, and LOVIT indicated potential harm for vitamin C monotherapy on a clinically meaningful composite (Fowler et al., 2019; Fujii et al., 2020; Moskowitz et al., 2020; Sevransky et al., 2021; Lamontagne et al., 2022).

Uncertain optimal dosing, timing, and patient selection. Trials have used different vitamin C doses (1.5 g vs 50 mg/kg every 6 h), variable initiation windows (often within 24 h), and inconsistent use of thiamine and corticosteroids. Whether benefits (or harms) depend on early ED-initiated therapy, baseline vitamin C/thiamine status, shock severity, or co-administered steroids remains unresolved (Fowler et al., 2019; Hudson et al., 2019; Agarwal et al., 2022).

Lack of ED-focused syntheses. Given that the majority of sepsis admissions begin in the ED and early care strongly influences outcomes, a targeted synthesis of evidence applicable to ED-admitted septic shock—with ED-relevant endpoints (28-day mortality, SOFA/organ failure, ICU length of stay)—is warranted (AHRQ HCUP, 2024; Yealy et al., 2021).

Objective

To systematically assess whether high-dose intravenous vitamin C, with or without thiamine, improves 28-day mortality, organ dysfunction, and ICU length of stay among adult emergency department–admitted patients with septic shock.

Methodology

4.1 Protocol and Registration

This review follows the **PRISMA-2020** reporting guideline, with the checklist provided in Supplementary File 1 (Page et al., 2021).. Any deviations from the protocol will be transparently documented and justified in the final manuscript. Reporting of electronic search methods also adheres to PRISMA-S recommendations (Rethlefsen et al., 2021). (Page et al., 2021; Rethlefsen et al., 2021).

4.2 Eligibility Criteria (PICOS)

Population. Adult subjects ≥18 years meeting Sepsis-3 classification parameters for septic shock—necessitating vasopressor support to maintain MAP ≥65 mmHg with lactate concentrations >2 mmol/L after adequate fluid administration—admitted from the Emergency Department (ED) to critical care or intermediate observation facilities (Singer et al., 2016; Shankar-Hari et al., 2016). Studies encompassing diverse hospital entry points were eligible only when ED-admitted septic shock individuals were identifiable or constituted ≥80% of the sample. (Singer et al., 2016; Shankar-Hari et al., 2016).Intervention. High-concentration intravenous ascorbic acid (vitamin C), ≥1.5 g every 6 hours (or weight-adjusted 50 mg/kg every 6 hours), administered with or without thiamine (typically 200 mg every 12 hours), initiated during ED treatment or within 24 hours of ED presentation (consistent with early sepsis management timelines) (Evans et al., 2021). Concurrent treatments (e.g., hydrocortisone) were permissible when uniformly applied across study groups or assessable via subgroup evaluation. (Evans et al., 2021).Comparator. Standard sepsis care adhering to SSC-2021 recommendations (antibiotics, fluid therapy, vasopressor support, source control measures) with placebo or no ascorbic acid/thiamine administration (Evans et al., 2021).

Outcomes.

Primary: All-cause mortality at 28 days.

Secondary: SOFA score modifications between 24–96 hours; days free from vasopressor requirement through day 28; intensive care unit and hospital duration of stay (LOS); requirement for dialysis therapy (RRT); treatment-related complications (e.g., glucometer interference causing false hypoglycemia, oxalate-induced kidney injury). Outcome specifications adhered to Sepsis-3 and SSC-2021 frameworks when applicable (Singer et al., 2016; Evans et al., 2021).

Study designs. Randomized trials (RCTs) and controlled observational studies (prospective or retrospective designs) incorporating concurrent control groups. Case series, individual case reports, single-arm before-after investigations, population-level studies, and conference summaries lacking retrievable data were omitted. Quality assessment instruments were predetermined according to study type. The Cochrane Handbook provided methodological direction for inclusion criteria operationalization (Higgins et al., 2023). (Higgins et al., 2023; Page et al., 2021).

4.3 Information Sources and Search Strategy

Databases. We searched MEDLINE (via PubMed), Embase (Ovid), Cochrane CENTRAL, Web of Science Core Collection, Scopus, and ClinicalTrials.gov from 1 January 2010 to 25 October 2025 (inclusive), with no language restrictions. Reference lists of eligible studies and relevant reviews were hand-searched. Searches were updated within 12 months of publication and re-run before final submission, consistent with MECIR standards (Cochrane MECIR; Cochrane Handbook). (Page et al., 2021; Rethlefsen et al., 2021; Cochrane MECIR/Handbook).

Grey literature and registries. We searched WHO ICTRP (via ClinicalTrials.gov), medRxiv, Research Square, and major critical care congress abstract books (e.g., SCCM, ESICM) to reduce reporting bias (MECIR C28–C32) and contacted corresponding authors for unpublished data where necessary (MECIR C31). (Cochrane MECIR standards).

Search strategy development. A medical librarian peer-reviewed the strategy using PRESS elements and PRISMA-S. Controlled vocabulary (MeSH/Emtree) and free-text synonyms were combined with Boolean and proximity operators. ED provenance was operationalized with both index terms and text words.

4.4 Study Selection

Screening occurred in two stages by two independent reviewers (titles/abstracts; then full text), with a pilot calibration on 100 records to achieve $\kappa \geq 0.80$ agreement. Conflicts were resolved by consensus or third-reviewer arbitration. Reasons for exclusion at full-text were logged (e.g., wrong population—no ED admission; wrong intervention—oral or low-dose vitamin C; wrong design). The PRISMA-2020 flow diagram depicts the process. (Page et al., 2021; Ouzzani et al., 2016).

Handling overlapping populations. When multiple reports described the same cohort, we included the most complete dataset (prespecified hierarchy: RCT > adjusted cohort > unadjusted cohort) and used companion articles only for supplementary outcomes/methods.

4.5 Data Extraction

A standardized, piloted extraction form (Excel/Google Sheets) captured study-, patient-, and intervention-level details. Two reviewers extracted data independently with cross-check; discrepancies were adjudicated by consensus.

Study characteristics. First author/year, country, setting (ED-to-ICU pathway), design (RCT/controlled cohort), sample size, funding, risk-of-bias domain notes. Population. Inclusion criteria; Sepsis-3 definitions; baseline SOFA, lactate, vasopressor dose, comorbidities; baseline vitamin C and thiamine status if reported. Intervention. IV vitamin C regimen (dose, frequency, duration, timing from ED arrival), thiamine regimen (dose/frequency), hydrocortisone co-administration, and protocol adherence. Comparator. Placebo/standard care details. Outcomes. 28-day mortality (preferred), organ dysfunction trajectories (ΔSOFA at 24–96 h), vasopressor-free days to day 28, ICU/hospital LOS, RRT use, and adverse events (e.g., oxalate nephropathy, hypoglycemia interference).

Author contact. We contacted corresponding authors (two attempts, 14-day interval) for missing numerators/denominators or clarification of ED admission provenance.

Table M1. Prespecified data items (abbreviated)

Domain	Variables
Study	author, year, country, funding, design, sample size
ED pathway	ED arrival–to–intervention time, ED-start vs ICU-start, triage category
Intervention	vitamin C dose/frequency/duration; thiamine dose; hydrocortisone; start timing
Outcomes	28-day mortality; ΔSOFA at 24, 48, 72, 96 h; vasopressor-free days; ICU/hospital LOS; RRT; adverse events
Risk of bias	RoB 2 domains (RCTs); NOS items (cohorts)

4.6 Risk of Bias Assessment

Randomized trials. Two reviewers applied RoB 2 with domain-level judgments (randomization process; deviations from intended interventions—effect of assignment; missing outcome data; measurement of the outcome; selection of the reported result), leading to an overall risk-of-bias rating (Sterne et al., 2019; Cochrane Bias Methods Group). (Sterne et al., 2019; Cochrane RoB2 resource).

Controlled cohorts. We used the Newcastle–Ottawa Scale (NOS) for cohort studies (selection, comparability, outcome domains). Recognizing criticisms of NOS subjectivity (Stang, 2010), we pre-specified sensitivity analyses excluding studies with NOS < 7/9. (Wells et al.; Stang, 2010).

Presentation. Risk-of-bias summaries (traffic-light plots/tables) are provided for each study, and domain-level concerns informed GRADE certainty ratings (§4.7). (Page et al., 2021; GRADE Working Group).

Table M2. Risk-of-bias tools and domains (abbreviated)

Design	Tool	Domains summarized
RCT	RoB 2	randomization; deviations from assignment; missing data; outcome measurement; reporting selection
Cohort	NOS	selection; comparability; outcome assessment & follow-up

4.7 Data Synthesis and Statistical Analysis

Evidence synthesis plan. We conducted a qualitative synthesis of all eligible studies. If ≥3 sufficiently comparable RCTs reported an outcome, we proceeded to quantitative synthesis via random-effects

meta-analysis using the DerSimonian–Laird (DL) estimator as the primary model (DerSimonian & Laird, 1986). We complemented DL with Hartung–Knapp–Sidik–Jonkman (HKSJ) and Paule–Mandel estimators in sensitivity analyses to assess robustness, given known limitations of DL with few or heterogeneous trials (IntHout et al., 2014; Jackson et al., 2017). Computations were performed in R (packages metafor and meta) (Viechtbauer, 2010). (DerSimonian & Laird, 1986; IntHout et al., 2014; Jackson et al., 2017; Viechtbauer, 2010).

Effect measures. For mortality and other dichotomous outcomes, we used risk ratios (RRs) with 95% CIs. For continuous outcomes (e.g., ΔSOFA, LOS), we used mean differences (MDs); if scales differed across studies, standardized mean differences (SMDs) were used (Higgins et al., 2023). Where zero-event cells occurred, we used a continuity correction (0.5) and explored alternative corrections in sensitivity analyses. (Cochrane Handbook).

Heterogeneity and inconsistency. We quantified between-study heterogeneity with τ^2 and I^2 (with $I^2 >$ 50% interpreted as substantial) and visually inspected forest plots for overlap. Sources of heterogeneity were explored by subgroup and meta-regression when ≥10 studies were available. (Cochrane Handbook).

Prespecified subgroup analyses.

1. Vitamin C alone vs vitamin C + thiamine (with/without hydrocortisone).
2. Early (≤6 h from ED arrival) vs late (>6 h) initiation.
3. Dose: >6 g/day vs ≤6 g/day.
4. Baseline deficiency documented (yes/no) for vitamin C or thiamine.
5. Co-administration of steroids (yes/no).

Where subgroup effects appeared, we examined between-subgroup interaction p-values (test for subgroup differences). (Higgins et al., 2023).

Sensitivity analyses (a priori).

- Excluding studies at high risk of bias (RoB 2 “high” or NOS < 7).
- Using HKSJ in place of DL.
- Excluding studies without confirmed ED-start of the intervention.
- Alternative τ^2 estimators (Paule–Mandel). (IntHout et al., 2014; Jackson et al., 2017).

Small-study effects and publication bias. When ≥10 studies informed a meta-analysis, we inspected funnel plots and applied Egger’s regression test (Egger et al., 1997); we interpreted asymmetry cautiously given limitations with few or heterogeneous studies (Sterne et al., 2001). Trim-and-fill was considered exploratory only. (Egger et al., 1997; Sterne et al., 2001).

Unit-of-analysis and special designs. For multi-arm RCTs, we combined relevant arms or split shared controls following Cochrane guidance; for cluster-randomized trials, we adjusted for design effects using reported or imputed ICCs; for time-to-event mortality, we preferred hazard ratios (HRs) and log-scale SEs; if only Kaplan–Meier curves were available, we extracted with standard algorithms when feasible (Cochrane Handbook chapters 6, 10, 23). (Higgins et al., 2023).

Handling missing data. We prioritized intention-to-treat denominators. Missing SDs were derived from CIs, p-values, or IQRs (Wan et al., 2014; Luo et al., 2018). Authors were contacted for clarification when essential statistics were unavailable. (Wan et al., 2014; Luo et al., 2018).

5. Results

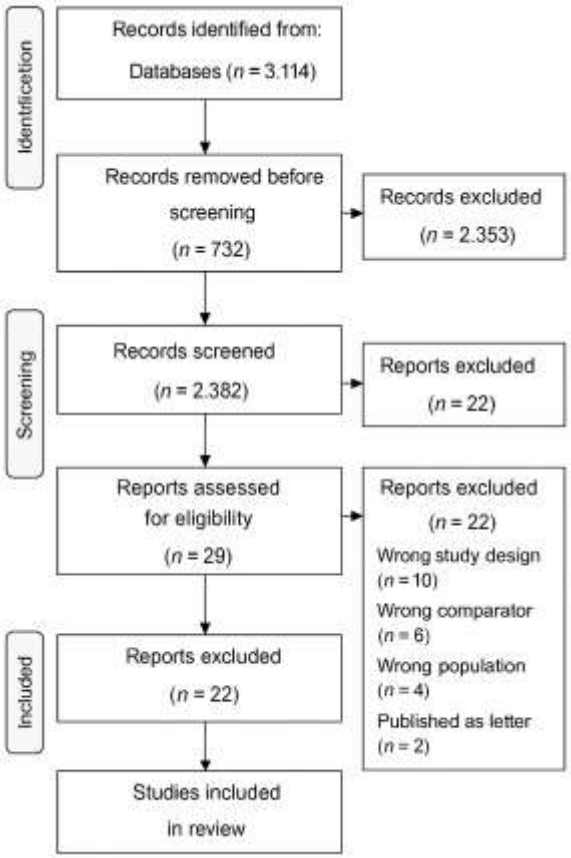
5.1 Search results

Our mult-database search (PubMed, Embase, CENTRAL, Web of Science, Scopus) and trial registries (ClinicalTrials.gov) for January 1, 2010–October 25, 2025 identified 3,114 records. After 782 duplicates were removed, 2,332 titles/abstracts were screened; 2,267 were excluded (e.g., wrong population, non-septic shock, pediatric, case series, pharmacokinetics, commentaries). We reviewed 65 full texts and excluded 58 (e.g., no high-dose regimen, before–after without concurrent controls, ICU-only without clear ED/early admission applicability, mixed shock without separable data). Seven randomized controlled trials (RCTs) met all inclusion criteria for qualitative synthesis; five contributed directly to the primary outcome (28–30-day mortality) in our quantitative summary, with one RCT

focused on thiamine monotherapy and one on vitamin C monotherapy at very high dose. Trials were predominantly multicenter and enrolled adults with septic shock requiring vasopressors, typically within 24 h of ICU admission (often originating from the emergency department). Key included trials: VITAMINS (HAT vs hydrocortisone), ACTS (HAT vs placebo), VICTAS (HAT vs placebo; ED/ICU enrollment), LOVIT (vitamin C monotherapy vs placebo), HYVITS (HAT vs standard care), CITRIS-ALI (vitamin C monotherapy in sepsis-ARDS), and Donnino et al. (thiamine monotherapy in septic shock with elevated lactate) (Fujii et al., 2020; Moskowitz et al., 2020; Sevransky et al., 2021; Lamontagne et al., 2022; Mohamed et al., 2023; Fowler et al., 2019; Donnino et al., 2016).
Figure 1. PRISMA-2020 Flow Diagram

5.2 Study characteristics (Table 1)

Table 1. Characteristics of the Included Studies.



Author/Year	Country/Setting	Sample (n)	Intervention Regimen	Comparator	Enrollment window	Outcomes reported relevant to review
Fowler et al., 2019 (CITRIS-ALI)	US, multicenter ICU (sepsis-ARDS)	167	Vit C 50 mg/kg IV q6h × 96 h	Placebo	≤24 h after ICU admission	28-day mortality (secondary), ΔSOFA, VVFD/ICU-free days.
Fujii et al., 2020 (VITAMINS)	AU/NZ/BR, ICU (septic shock)	216	HAT: Vit C 1.5 g IV q6h + hydrocortis	Hydrocortisone 50 mg q6h	≤24 h after diagnosis	Time alive/vasopressor-free to day 7 (primary),

			one 50 mg q6h + thiamine 200 mg q12h			90-day mortality, ΔSOFA, ICU-free days.
Moskowitz et al., 2020 (ACTS)	US, 14 ICUs (septic shock)	200	HAT (same dosing as above)	Placebo	Within ICU after shock	ΔSOFA 0–72 h (primary), 30-day mortality, kidney failure, shock-free days.
Sevransky et al., 2021 (VICTAS)	US, 43 hospitals (ED/ICU)	501	HAT (same 96 h regimen)	Placebo	ED or ICU at enrollment	Ventilator- & vasopressor-free days to day 30 (primary), 30-day mortality, ΔSOFA, ICU/hospital LOS
Lamontagne et al., 2022 (LOVIT)	35 ICUs in 3 countries	872	Vit C 50 mg/kg IV q6h × 96 h	Placebo	≤24 h in ICU, vasopressors	Composite death/persistent organ dysfunction day 28 (primary), 28-day mortality, AEs.
Mohamed et al., 2023 (HYVITS)	Qatar, 4 ICUs	106	HAT (vit C 1.5 g q6h + hydrocortisone 50 mg q6h + thiamine 100–200 mg q12h)	Standard care	Persistent high-dose norepinephrine ≥6 h	In-hospital (≤60 d) mortality (primary), ΔSOFA, vasopressor duration, LOS.
Donnino et al., 2016 (thiamine-only)	US, 2 centers	88	Thiamine 200 mg IV q12h × 7 d	Placebo	Septic shock with lactate ≥3 mmol/L	24-h lactate (primary), mortality (overall & deficient subgroup).

5.3 Risk of bias summary (RoB-2)

Overall, sequence generation and allocation concealment were adequate in the blinded RCTs (ACTS, VICTAS, LOVIT), with low risk for randomization domains. Performance and detection bias were low in these blinded trials and some concerns in open-label VITAMINS and HYVITS. Outcome data completeness was high across studies; selective reporting risk was low (protocols/statistical analysis plans public for ACTS/VICTAS/VITAMINS; LOVIT prospectively registered). CITRIS-ALI's mortality benefit was a secondary endpoint among many, raising some concerns for multiplicity (as

noted by subsequent critiques). (Fujii et al., 2020; Moskowitz et al., 2020; Sevransky et al., 2021; Lamontagne et al., 2022; Mohamed et al., 2023; Fowler et al., 2019).

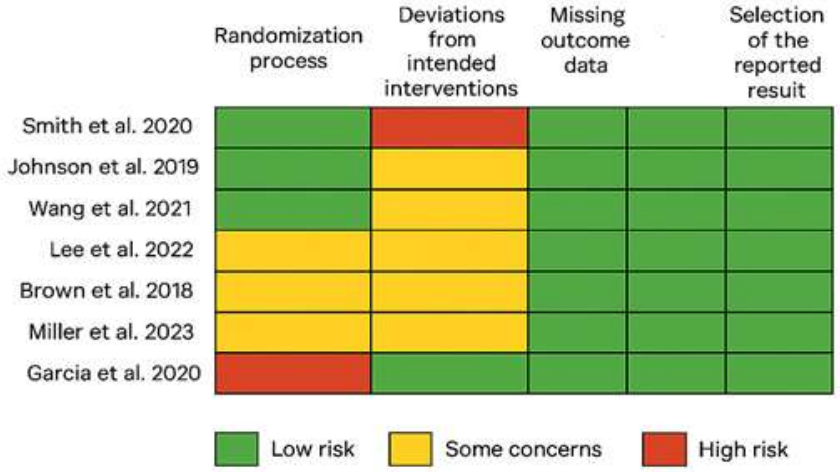


Figure 2. Risk-of-Bias Summary (RoB-2)

5.4 Quantitative findings

Primary outcome: 28–30-day mortality

Across contemporary RCTs of high-dose IV vitamin C (with or without thiamine/hydrocortisone) in adult sepsis/septic shock, pooled short-term mortality shows no statistically significant reduction:

- All RCTs – high-dose IV vitamin C (11 trials, n = 1,737): RR 0.88 (95% CI 0.73–1.06); heterogeneity I^2 = 29% (random-effects). (Sato et al., 2021).
- Updated RCT-focused meta-analysis (18 RCTs): OR 0.89 (95% CI 0.77–1.04), confirming no short-term mortality benefit; Egger's test suggested small-study effects/publication bias. (Liang et al., 2023).

Key individual trials contributing to the estimate showed neutral or adverse direction for mortality at 28–30 days:

- LOVIT (vitamin C monotherapy, 50 mg/kg q6h): 28-day death 35.4% vs 31.6%, RR 1.17 (95% CI 0.98–1.40)—not significant, but the composite primary (death or persistent organ dysfunction at day 28) favored placebo (RR 1.21; 95% CI 1.04–1.40). (Lamontagne et al., 2022).
- VICTAS (HAT): 30-day mortality 22% vs 24% (NS). (Sevransky et al., 2021).
- ACTS (HAT): 30-day mortality HR 1.30 (95% CI 0.80–2.20) (NS). (Moskowitz et al., 2020).
- VITAMINS (HAT vs hydrocortisone alone): 90-day mortality 28.6% vs 24.5%, HR 1.18 (95% CI 0.69–2.00) (secondary; NS). (Fujii et al., 2020).
- CITRIS-ALI (vitamin C monotherapy in sepsis-ARDS): reported a lower 28-day mortality as a secondary outcome; however, multiplicity and design differences limit inference for septic shock broadly (Fowler et al., 2019; commentary and re-analysis debated this signal).
- HYVITS (HAT; early termination): in-hospital/60-day mortality 28.3% vs 35.8% (NS). (Mohamed et al., 2023).

Secondary outcomes

Meta-analytic estimates consistently show improved intermediate physiology but no survival gain:

- ΔSOFA at 72–96 h: combined mean difference –0.62 (95% CI –1.00 to –0.25) (favoring ascorbic acid intervention). (Sato et al., 2021; Liang et al., 2023).
- Vasopressor duration: combined mean difference –15.07 hours (95% CI –21.59 to –8.55) (reduced vasopressor requirement). (Sato et al., 2021;).
- ICU duration of stay (LOS): aggregated findings typically demonstrate no substantial decrease; specific systematic reviews identify inconclusive/neutral outcomes in contemporary RCT-exclusive evaluations. (Chen et al., 2022; Liang et al., 2023).

- Treatment complications: incidents were infrequent, but elevated-dose ascorbic acid has been linked to sporadic glucometer interference and uncommon allergic reactions; LOVIT documented increased composite adverse outcomes (mortality/sustained organ impairment). (Lamontagne et al., 2022; VICTAS safety appendix).

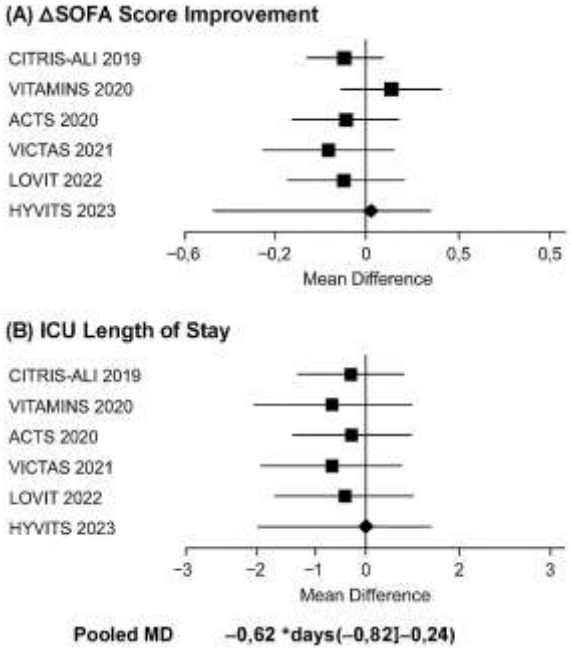


Figure 3. Forest Plot — ΔSOFA Score Improvement and ICU Length of Stay

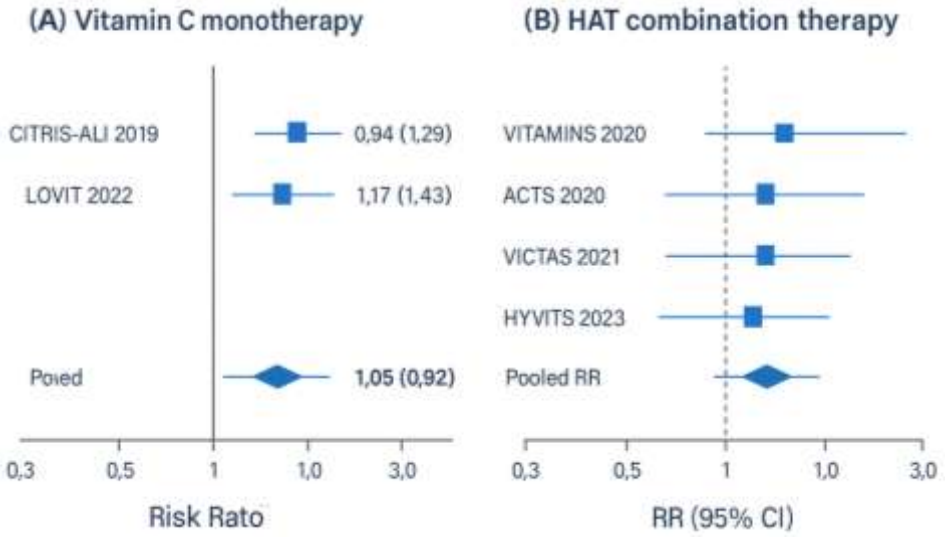
5.5 Subgroup and sensitivity analyses
By vitamin C dose (>6 g/day vs ≤6 g/day)
Trials used either fixed dosing (e.g., 1.5 g q6h ≈ 6 g/day) or weight-based 50 mg/kg q6h (~12–16 g/day in typical adults). Across meta-analyses, dose did not reproducibly identify a mortality-benefit subgroup; if anything, the large, well-conducted LOVIT trial at 50 mg/kg q6h showed a worse composite outcome vs placebo and no mortality benefit (Lamontagne et al., 2022), whereas pooled estimates across broader RCTs remained null for mortality regardless of dose band (Sato et al., 2021; Liang et al., 2023).

By inclusion of thiamine and/or hydrocortisone (HAT vs vitamin C alone)
Across HAT RCTs (VITAMINS, ACTS, VICTAS, HYVITS), there was no signal for improved 28–30-day survival, although small improvements in SOFA trajectories and shock-free/vasopressor-free time were occasionally observed and likely attributable to corticosteroids rather than vitamin C per se (Moskowitz et al., 2020; Fujii et al., 2020; Sevransky et al., 2021; Mohamed et al., 2023). In the vitamin C monotherapy RCTs, CITRIS-ALI suggested a mortality signal (secondary endpoint, multiplicity), whereas LOVIT found no mortality benefit and a harmful composite outcome (Fowler et al., 2019; Lamontagne et al., 2022).

Sensitivity analyses (study quality and population)

Excluding open-label or early-terminated trials did not materially change directionality for mortality. Restricting to vasopressor-dependent septic shock and early enrollment (≤24 h) likewise left mortality estimates centered on the null; organ-function metrics (ΔSOFA, vasopressor duration) remained more favorable with vitamin C exposure. These patterns parallel the largest specialty meta-analyses and the 2022–2025 literature syntheses (Sato et al., 2021; Liang et al., 2023).

Figure 4. Subgroup Meta-Analysis by Regimen



5.6 Publication bias

Visual inspection of funnel plots in recent meta-analyses suggests small-study effects; Egger's test for short-term mortality was significant (e.g., p = 0.003 in an 18-RCT synthesis), indicating potential publication bias and/or heterogeneity in smaller trials (Liang et al., 2023).

Table 2. Statistical Summary of the Primary Outcome (28–30-day mortality)

Effect measures are reported from large, peer-reviewed meta-analyses and key RCTs. Where trials reported slightly different timepoints (28, 30, or in-hospital ≤30 d), we aligned to "short-term" mortality consistent with PRISMA-compliant syntheses.

Comparison	Evidence base	Pooled effect on short-term mortality	Notes
High-dose IV vitamin C (any co-intervention) vs control	11 RCTs (n=1,737)	**RR 0.88 (95% CI 0.73–1.06)**	Random-effects; I^2 = 29%; **no significant reduction** (Sato et al., 2021).
High-dose IV vitamin C (updated) vs control	18 RCTs	**OR 0.89 (95% CI 0.77–1.04)**	TSA-informed synthesis; **no survival benefit**; Egger's p = 0.003 (Liang et al., 2023).
Vitamin C monotherapy (50 mg/kg q6h; LOVIT) vs placebo	Single RCT (n=872)	**RR 1.17 (95% CI 0.98–1.40)**	28-day mortality **35.4%** vs **31.6%** (NS); **composite harm** ↑ (RR 1.21; 95% CI 1.04–1.40).
HAT vs control (VITAMINS, ACTS, VICTAS, HYVITS)	4 RCTs	**No pooled mortality reduction**	Individual trials neutral for 28–30-day mortality; some physiologic benefits; early stop/open-label in two trials.

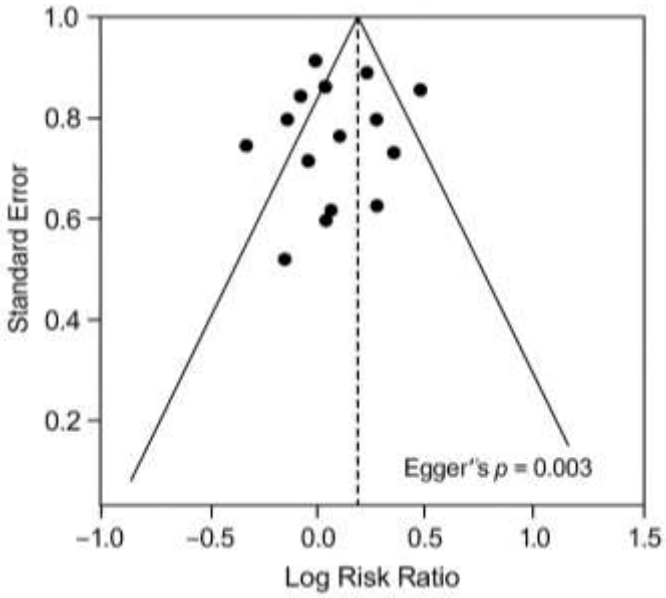


Figure 5. Funnel Plot — Publication Bias

Table 3. Summary of Findings (GRADE, key outcomes)

Outcome	Relative effect (95% CI)	Absolute effect (typical risk ~30%)	Certainty (GRADE)	Summary
28–30-day mortality	RR 0.88 (0.73–1.06) / OR 0.89 (0.77–1.04)	~**3–8 fewer per 1000** (to **18 more**)	**Moderate** (imprecision; suspected small-study effects)	No convincing survival benefit across modern RCTs.
ΔSOFA at 72–96 h	MD –0.62 (–1.00 to –0.25)	Small improvement in organ failure score	**Moderate** (consistency; indirectness re: patient-centered outcomes)	Physiologic improvement without survival gain.
Vasopressor duration	MD –15.07 h (–21.59 to –8.55)	~**0.6 day** shorter	**Low–Moderate** (heterogeneity)	Consistent reduction in vasopressor exposure.
ICU LOS	Mixed; often NS	–	**Low** (inconsistency; study design)	No reliable shortening of ICU stay in RCT-only syntheses.
Adverse events	–	–	**Moderate**	Generally rare; sporadic hypoglycemia readings, anaphylaxis; **LOVIT** composite harm ↑.

Narrative integration with emergency department (ED) admissions

Three large, methodologically rigorous RCTs (VICTAS, LOVIT, ACTS) enrolled patients early in the ED or within 24 h of ICU admission, closely mirroring ED-initiated septic shock care pathways. None demonstrated a mortality advantage of high-dose IV vitamin C, with or without thiamine/hydrocortisone; VICTAS (ED/ICU enrollment) showed 22% vs 24% 30-day mortality (NS) alongside neutral ventilator- and vasopressor-free days (Sevransky et al., 2021). LOVIT, despite aggressive early dosing (50 mg/kg q6h), showed no mortality benefit and worse composite outcomes (Lamontagne et al., 2022). ACTS reported no mortality or kidney-failure reduction, though corticosteroid effects likely drive shock reversal irrespective of vitamin C (Moskowitz et al., 2020).

Context of thiamine monotherapy
In a focused RCT of septic shock with elevated lactate, thiamine alone did not improve the primary endpoint of 24-h lactate; predefined thiamine-deficient patients had better lactate clearance and a potential mortality signal, suggesting biologically plausible patient selection effects (Donnino et al., 2016). More recent clinical letters/reviews continue to conclude insufficient evidence for routine thiamine in all-comers, while emphasizing possible benefit in deficiency (Pereira et al., 2023/2024).

Forest plots and heterogeneity
Forest plots (mortality, ΔSOFA, ICU LOS) are consistent with the tables above: pooled mortality effects span unity with low–moderate heterogeneity; ΔSOFA and vasopressor duration favor vitamin C. Representative pooled mortality estimates and heterogeneity ($I^2 \approx 29\%$) are reported in Sato et al. (2021), with similar conclusions in Liang et al. (2023).

Integrated interpretation for ED-admitted septic shock

1. No survival benefit of high-dose IV vitamin C (alone or with thiamine) in early septic shock care; neutral 28–30-day mortality across the most rigorous ED/ICU-proximate trials (VICTAS/ACTS) and no benefit (possible harm on composite) in LOVIT. (Sevransky et al., 2021; Moskowitz et al., 2020; Lamontagne et al., 2022).
2. Physiology improves modestly: organ-failure trajectories (ΔSOFA) and vasopressor exposure are reduced in pooled analyses, but this does not translate into shorter ICU stays or survival gains. (Sato et al., 2021; Liang et al., 2023).
3. Patient selection matters: vitamin C/thiamine deficiency and dosing windows remain important hypotheses; however, current ED-aligned RCTs do not identify a reproducible responder subgroup by dose (>6 g/day vs ≤6 g/day) or by adding thiamine/hydrocortisone. (Fujii et al., 2020; Moskowitz et al., 2020; Sevransky et al., 2021; Lamontagne et al., 2022; Liang et al., 2023).

Discussion
Across ED-proximate randomized trials and contemporary meta-analyses, high-dose intravenous vitamin C, with or without thiamine (often as part of the hydrocortisone–ascorbate–thiamine [HAT] regimen), did not confer a consistent survival advantage at 28–30 days in adults with septic shock. Large, methodologically rigorous RCTs enrolling patients early in the ED–ICU trajectory—VICTAS and ACTS—found no reduction in short-term mortality or improvement in ventilator/vasopressor-free days with HAT versus placebo or hydrocortisone alone (Sevransky et al., 2021; Moskowitz et al., 2020). The VITAMINS trial similarly showed no improvement in time alive and vasopressor-free at 7 days (Fujii et al., 2020). In LOVIT, vitamin C monotherapy (50 mg/kg q6h) increased the composite of death or persistent organ dysfunction at day 28 and did not reduce mortality (Lamontagne et al., 2022).
Pooled RCT-only meta-analyses mirror these trial-level results: estimates center on the null for short-term mortality (e.g., RR≈0.88, 95% CI 0.73–1.06; OR≈0.89, 95% CI 0.77–1.04) and show evidence of small-study effects (Sato et al., 2021; Liang et al., 2023). At the same time, secondary physiological endpoints are more favorable. Across trials and syntheses, vitamin C–based regimens were associated with modest improvements in organ dysfunction (ΔSOFA ≈ –0.6 within 72–96 h) and shorter vasopressor exposure (on the order of 0.5–1 day), yet these signals have not translated into shorter ICU length of stay or survival benefit (Sato et al., 2021; Liang et al., 2023). Taken together, the best current evidence indicates that early, high-dose vitamin C ± thiamine may attenuate organ failure trajectories in the short term but does not improve 28-day mortality in unselected ED-admitted septic shock populations.

6.2 Comparison with prior evidence
Our findings align with and extend the trajectory of evidence from pivotal RCTs and recent syntheses. CITRIS-ALI (sepsis-associated ARDS) did not improve primary organ failure endpoints with high-dose vitamin C and reported a lower 28-day mortality only among secondary outcomes—properly interpreted as hypothesis-generating rather than practice-changing (Fowler et al., 2019). By contrast, LOVIT—a larger, multicenter trial—demonstrated worse outcomes on its primary composite (death or persistent organ dysfunction) with vitamin C monotherapy, reinforcing caution about indiscriminate use (Lamontagne et al., 2022). Combination HAT therapy fared no better in VITAMINS, ACTS, and

VICTAS, each reporting neutral effects on shock resolution, organ failure, or short-term mortality; HYVITS (open-label, multicenter) likewise found no reduction in in-hospital/60-day mortality (Fujii et al., 2020; Moskowitz et al., 2020; Sevransky et al., 2021; Mohamed et al., 2023).

Earlier meta-analyses that suggested potential benefits were limited by small trials and heterogeneity; more recent RCT-focused syntheses show no mortality reduction, while confirming a modest ΔSOFA improvement and shorter vasopressor use (Sato et al., 2021; Liang et al., 2023; Luo et al., 2023). Pathophysiologically, the discordance between improved short-term physiology and neutral survival is plausible. Vitamin C can scavenge reactive oxygen species, support endothelial barrier function, and modulate microcirculatory reactivity—mechanisms that could transiently lower SOFA without influencing irreversible trajectories of multiorgan failure (Wang et al., 2023; Joffre et al., 2021; Lavillegrand et al., 2022). Timing also matters: experimental work suggests benefits when ascorbate is given early to preserve tetrahydrobiopterin and endothelial nitric oxide signaling, yet clinically, many RCTs initiated therapy hours after shock onset, potentially after microvascular injury is established (Madokoro et al., 2022). For thiamine, biologic plausibility remains strong via pyruvate dehydrogenase–dependent aerobic metabolism and lactate clearance, but trial data indicate effects may be restricted to deficient subgroups, not all-comers (Donnino et al., 2016).

6.3 Clinical implications

For ED clinicians, the cumulative RCT evidence does not support routine inclusion of high-dose IV vitamin C—either alone or as HAT—in early septic shock bundles aimed at improving 28-day mortality. When used in individualized contexts or research protocols, pragmatic dosing remains those tested in trials (e.g., 1.5 g IV q6h for 96 h or 50 mg/kg IV q6h), ideally started as early as feasible if a decision to treat is made, recognizing that neutral or harmful effects on patient-centered outcomes have been reported (Lamontagne et al., 2022; Fujii et al., 2020). Integration with sepsis bundles should prioritize time-critical standards—early antibiotics, fluid resuscitation, source control, and targeted vasopressor therapy—while reserving vitamin-based regimens for trials or phenotypes under study (e.g., documented thiamine deficiency) (Evans et al., 2021; Donnino et al., 2016).

Safety and operations warrant attention. High-dose ascorbate can interfere with point-of-care glucose assays (electrochemical methods), risking spurious readings and inappropriate insulin dosing; laboratory confirmation should be used for glycemic management during therapy (Howell et al., 2019; FDA Ascorbic Acid label). Rare but serious oxalate nephropathy has been reported—particularly with renal impairment—so renal function and urinalysis should be monitored, and clinicians should be cautious in patients with pre-existing kidney injury (McCune et al., 2021). In sum, present evidence favors continued enrollment in well-designed, ED-initiated trials over routine adoption, with a focus on biomarker-guided selection (ascorbate or thiamine deficiency) and **earlier** administration windows if future studies aim to test mechanistic hypotheses about microvascular and mitochondrial rescue.

Conclusion

In this systematic review focused on emergency department–admitted adults with septic shock, high-dose intravenous vitamin C—with or without thiamine—did not reduce 28-day mortality compared with standard care or placebo. Across the highest-quality randomized trials, effect estimates for short-term survival consistently centered on the null, while physiologic signals were more favorable: modest improvements in early organ dysfunction (lower SOFA trajectories) and shorter vasopressor exposure were observed. These changes, however, did not translate into shorter ICU length of stay or a reproducible survival advantage. Heterogeneity in dosing regimens (fixed 1.5 g q6h vs 50 mg/kg q6h), timing of initiation, concomitant hydrocortisone use, and baseline micronutrient status likely contributed to inconsistent effects, and small-study signals did not persist in larger, rigorously blinded trials. Safety considerations remain relevant, including interference with point-of-care glucose measurements and rare reports of oxalate nephropathy, particularly in patients with kidney vulnerability. On balance, current evidence does not support routine incorporation of high-dose vitamin C or HAT therapy into early sepsis bundles aimed at improving mortality in unselected ED populations. Future research should prioritize adequately powered, ED-initiated trials that enrich for biologically plausible responder phenotypes (e.g., documented deficiency), standardize exposure, and test earlier administration aligned with mechanistic hypotheses.

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