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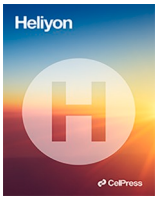

Research article

Comparative efficacy of antioxidant therapies for sepsis and septic shock in the intensive care unit: A frequentist network meta-analysis

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A R T I C L E I N F O

Keywords:
Antioxidant
Sepsis
Septic shock
Melatonin
High-dose vitamin C
Intensive care unit

A B S T R A C T

Background: Antioxidant therapy is gaining traction in managing sepsis and septic shock, owing to its perceived positive impact on patient outcomes. This study sought to compare the efficacy of five antioxidant therapies (melatonin, vitamin C, vitamin E, selenium, and *N*-acetylcysteine, both individually and in combination with other compounds such as vitamin B1, hydrocortisone, propolis, and glutamine) in treating sepsis or septic shock in the intensive care unit (ICU).
Methods: The study involved randomized and multi-arm trials with sepsis or septic shock patients using melatonin, vitamin C, vitamin E, selenium, or *N*-acetylcysteine. Studies were sourced from PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and WHO - Clinical Trials Registry Platform for the frequentist network meta-analysis on 28-day mortality and Sequential Organ Failure Assessment (SOFA) scores. The risk of bias was assessed using the Physiotherapy Evidence Database scale. Therapies were compared directly and indirectly using R software.
Results: The study of 56 trials involving 9,366 patients was included. Bias assessment revealed that 89.3 % of trials achieved excellent or good quality. Based on treatment ranking and pairwise comparisons, melatonin with propolis (SUCRA = 93.29 %) is effective in improving SOFA scores, statistically significant, with no publication bias (p= 0.73). High-dose vitamin C (SUCRA = 83.97 %), vitamin C with vitamin B1 (SUCRA = 78.72 %), and melatonin (SUCRA = 67.03 %) are potential therapies for organ dysfunction. Melatonin (SUCRA = 88.22 %) and high-dose vitamin C (SUCRA = 80.75 %) were the most effective in reducing 28-day mortality rates. However, analysis indicated that the results for 28-day mortality rates were not statistically significant. Also, these results contained publication bias (p= 0.02).

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Conclusion: The study offers fresh perspectives on antioxidant therapy treatments for sepsis or septic shock in ICU, emphasizing the combination of melatonin and propolis notably reduces SOFA scores for those patients.

1. Introduction

The global incidence of sepsis has been reported to range from 276 to 678 cases per 100,000 people annually, with a death rate between 22.5 % and 26.7 % [1]. This increase establishes sepsis (SS) and septic shock (ST) as a significant contributor to global mortality [2]. Oxidative stress (OS) and inflammation play central roles in the development of septicemia [3], causing multi-organ failure, compromised local blood flow, and acute respiratory distress syndrome [4]. Given the high death rates and severity of SS/ST, finding better ways to treat patients has become a crucial focus of current research.

Common treatments for SS/ST, such as giving fluids, antibiotics, and surgically removing infected or dead tissue, are crucial in clinical management [5]. However, there is growing interest in antioxidant therapy due to its potential positive impact on outcomes [6]. Studies indicate that vitamin C and vitamin E are potent antioxidants. Vitamin C neutralizes harmful reactive oxygen species (ROS) [7], whereas vitamin E controls ROS production in mitochondria, thus minimizing oxidative damage in septicemia [8]. Furthermore, melatonin, known for its versatile antioxidant and anti-inflammatory properties [9], significantly reduces oxidative injury in SS/ST states, particularly by decreasing lipopolysaccharide (LPS) levels [10,11]. Additionally, *N*-acetylcysteine (NAC), a precursor to glutathione, has anti-inflammatory and antioxidant effects, improving various heart and lung functions in SS/ST [12]. NAC also reduces the time on mechanical ventilation, days in the intensive care unit (ICU), and death rates [13]. Selenium has role in the mechanism of antioxidant defense of the body, especially in SS/ST, highlighted through selenoproteins and glutathione peroxidase [14–17]. Hence, using antioxidant agents is increasingly recognized as a crucial additional treatment in SS/ST management.

Through survey, results identify vitamin C, vitamin E, selenium, NAC, and melatonin as the five most commonly mentioned antioxidants in studies, especially in the context of SS/ST, particularly in the ICU settings [18,19]. Nevertheless, a comparative study is essential to evaluate the effectiveness of these therapies and determine which antioxidant has the most potential in supporting treatment, relieving symptoms, and reducing disease severity. Therefore, a network meta-analysis (NMA) was conducted to systematically compare the efficacy of these five antioxidant therapies (both individually and in combination with other compounds such as vitamin B1, hydrocortisone, propolis, and glutamine) in supporting the treatment of SS/ST in the ICU patients.

2. Methods

2.1. Protocol and registration

The NMA was conducted following the PRISMA-NMA checklist and explanations [20], and the guidance from "Doing Meta-Analysis with R" [21]. The NMA protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the ID: CRD42024505366.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

- Randomized Control Trials (RCTs) or Multi-arm Trials (MTs) employing interventions: vitamin C, vitamin E, selenium, NAC and melatonin as single agents or in combination other compounds such as vitamin B1, hydrocortisone, propolis, and glutamine, with reported outcomes of 28-day mortality rates and Sequential Organ Failure Assessment (SOFA) scores.
- Adult subjects diagnosed with SS/ST, as defined by the Third International Consensus Definitions for Sepsis and Septic Shock, were included in the study irrespective of their race or gender.

2.2.2. Exclusion criteria

- Studies simultaneously using antioxidant agents, as part of nutritional intervention in the setting of subarachnoid hemorrhage.
- Studies focusing on adverse outcomes in neonates with SS/ST/amniotic inflammation.
- Studies on treatment costs.
- Studies on SS/ST related to Covid-19.
- Unfinished studies.
- Without full-text articles.
- Studies with withdrawn registrations.

2.3. PICOS research questions

- P: SS/ST patients.

- I: Vitamin C, vitamin E, selenium, *N*-acetylcysteine, melatonin.
- C: Placebo, other drugs, or different doses of antioxidants.
- O: 28-day mortality rate, SOFA scores.
- S: RCTs, MTs.

2.4. Information sources

Searches was conducted across five databases: PubMed, Embase, Cochrane Library, ClinicalTrials.gov and WHO-Clinical Trials Registry Platform (ICTRP) encompassing studies published from January 1997 to December 2023.

2.5. Search strategy

Keywords used in this study included 'sepsis', 'septic shock', 'vitamin C', 'vitamin E', 'selenium', 'N-acetylcysteine' and 'melatonin'. These terms were searched using the Medical Subject Headings system to ensure comprehensive retrieval of all synonymous terms. A subsequent algorithmic search strategy was developed on PubMed, employing logical operators such as OR and AND to effectively combine these terms. The search was then expanded to include other major medical databases, such as Embase, Cochrane Library,

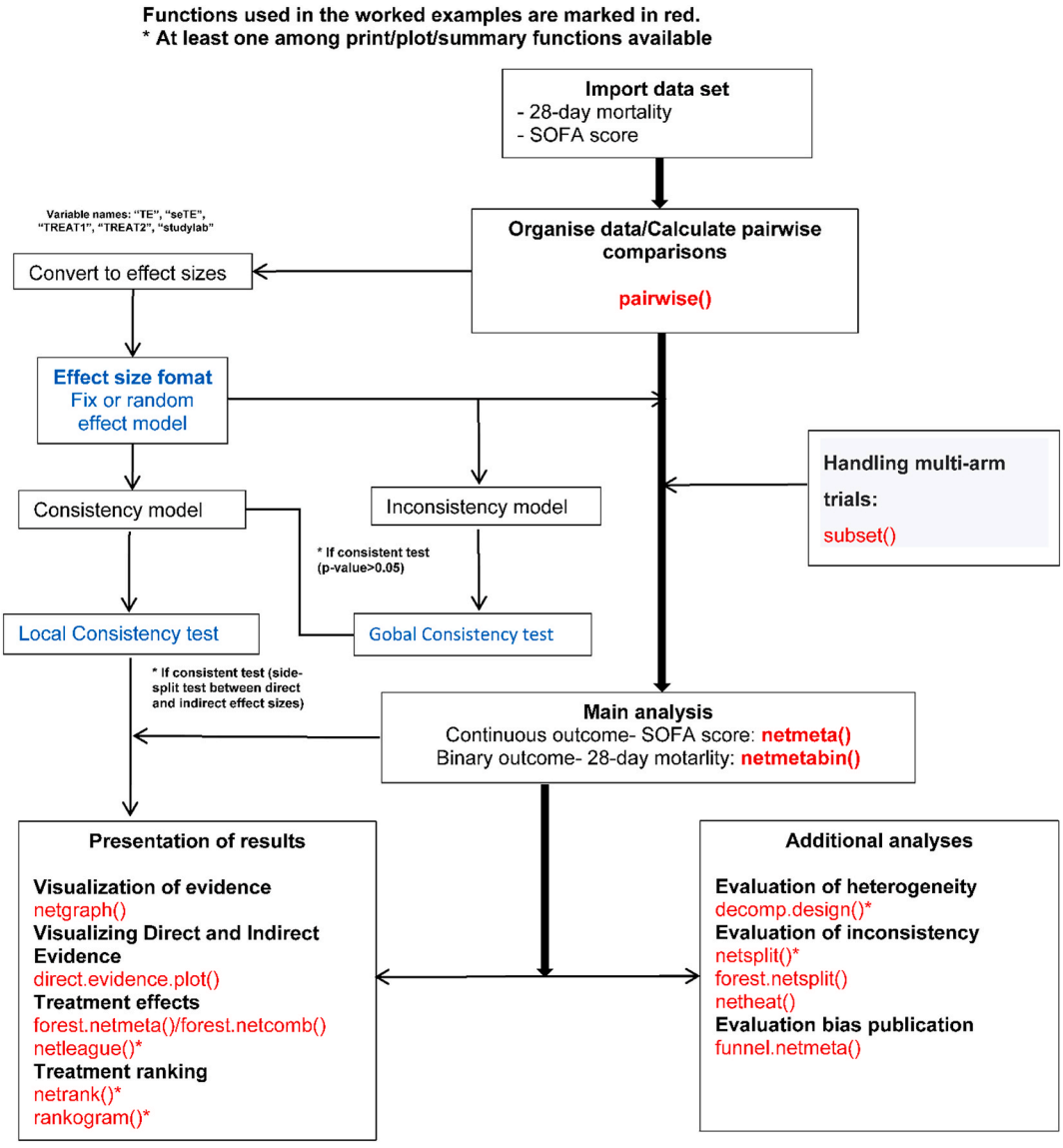

Fig. 1. Schematic representation of the network meta-analysis workflow using R software, detailing the steps from data extraction to analysis with 'netmeta' and 'netmetabin' packages.

ClinicalTrials.gov, and ICTRP, using the same methodology to ensure a thorough literature review. Entries searched from PubMed and these additional databases were systematically analyzed using the PICOS question framework to identify relevant studies. Details of the search terms and their application are described in Appendix A, table A.1.

2.6. Study selection (screening)

Semi-automated screening utilized the Covidence system, involving title screening, abstract screening, and full-text reading (details in Appendix A. table A.2.).

2.7. Data collection and data items

28-day mortality (binary outcome): The event, N, and treatment were recorded in both the intervention and control groups.

SOFA scores (continuous outcome): Mean, standard deviation, N, and treatment information were documented. Data collection included median, quartile, min-max, range, and 95 % confidence interval (95%-CI) values according to Cochrane training guidelines [22] and Mean Variance Estimation [23].

2.8. Risk of bias within individual studies

The methodological quality of the included studies was evaluated using the Physiotherapy Evidence Database (PEDro) scale [24], with scores categorizing studies as 'Fair' (scores of 4–5), 'Good' (scores of 6–8), or 'Excellent' (scores of 9–10).

Study selection, data collection, and study quality assessment were independently performed by five team members. Discrepancies were resolved through discussion and consensus.

2.9. Measures-planned methods of analysis

Data analysis was conducted using R within R Studio software (version 2023.12.0 + 369), the geometry of the treatment network base on utilizing netmeta and netmetabin packages (Appendix A. table A.3. and Fig. 1).

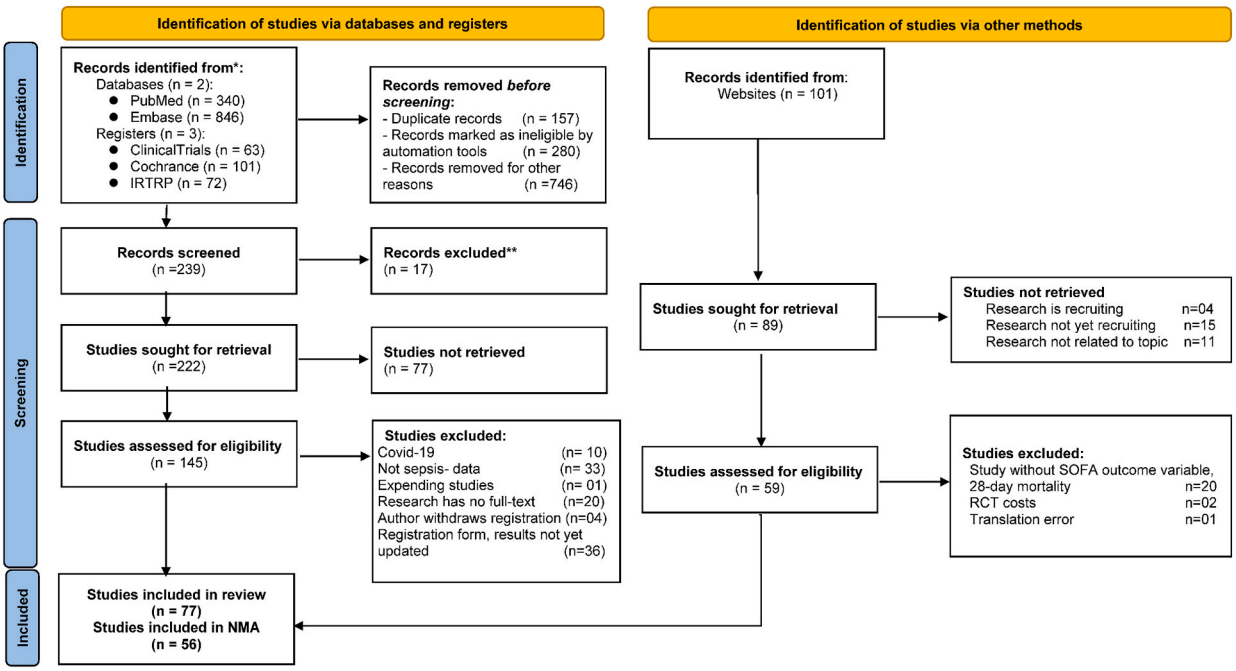

Fig. 2. PRISMA flow diagram illustrating the study selection process, from identification to inclusion in the meta-analysis, detailing numbers at each stage.

2.9.1. Key summary measures

- NMA frequentist approach, random effects and common effects models, Mean Difference (MD) for continuous data or Odds Ratio (OR) for binary data, 95%-CI.
- Additional statistical methods: Random effects model and common effects model were applied to handle data variations and generalize findings across studies. Heterogeneity assessment: Total heterogeneity (Q-total) and degrees of freedom (df) were calculated, along with I^2, tau^2, and tau values to assess the variability in effect estimates that could not be attributed solely to sampling error. Treatment ranking: League table, rankogram and SUCRA score. Publication bias assessment: Involved calculating the Z-score and *p*-value from the meta-analysis results, with further testing using the Egger's test (t) and Standard Error (SE) analysis to identify asymmetries.
- Specific statistical methods: Mantel and Haenszel method [25] for 28-day mortality analysis (binary data); Crippa and Orsini method [26] for SOFA scores analysis (continuous data).

3. Results

3.1. Study selection

Fig. 2 illustrates the PRISMA study selection process - including the number of studies from each search engine and all reasons for exclusion. Out of 1,422 articles, Covidence facilitated the removal of duplicates (n = 157), exclusion criteria (n = 280), and non-RCT (n = 746). This left 239 studies for screening, resulting in the exclusion of 17 studies based on titles and abstracts. Thorough full-text review led to the exclusion of 181 additional studies due to various reasons, including non-compliance with selection criteria (n = 77), lack of outcome data (n = 10), and other factors. Ultimately, 77 studies met the selection criteria for the systematic review, of which 56 studies were selected for NMA.

3.2. Study characteristics

Detailed study characteristics are presented in Appendix A, table A.4. A summary of basic study characteristics is provided in Fig. 3A–C. The selected publications were published from 1997 to 2023, conducted in 19 different countries, mainly in the United States (13 studies), Iran (8 studies), and India (6 studies). Among the 56 included studies, there were 9366 participants, irrespective of gender, race, with an age of 18 and older at the time of their inclusion in the trials. The studies included patients treated in the ICUs, accounting for 91 % (Appendix A. table A.4). Intervention therapies primarily involved single-agent antioxidants, including vitamin C, selenium, NAC, vitamin E and melatonin (Fig. 3C), with additional combinations of other compounds such as vitamin B1, hydrocortisone, propolis, and glutamine. The dosages of the therapies are specified as follows: vitamin C (high dose: 200 mg/kg/24 h, regular dose: 120 mg/kg/24 h, low dose: 50 mg/kg/24 h), selenium (high-dose therapy:158 μg–2000μg/24 h; standard therapy: 31

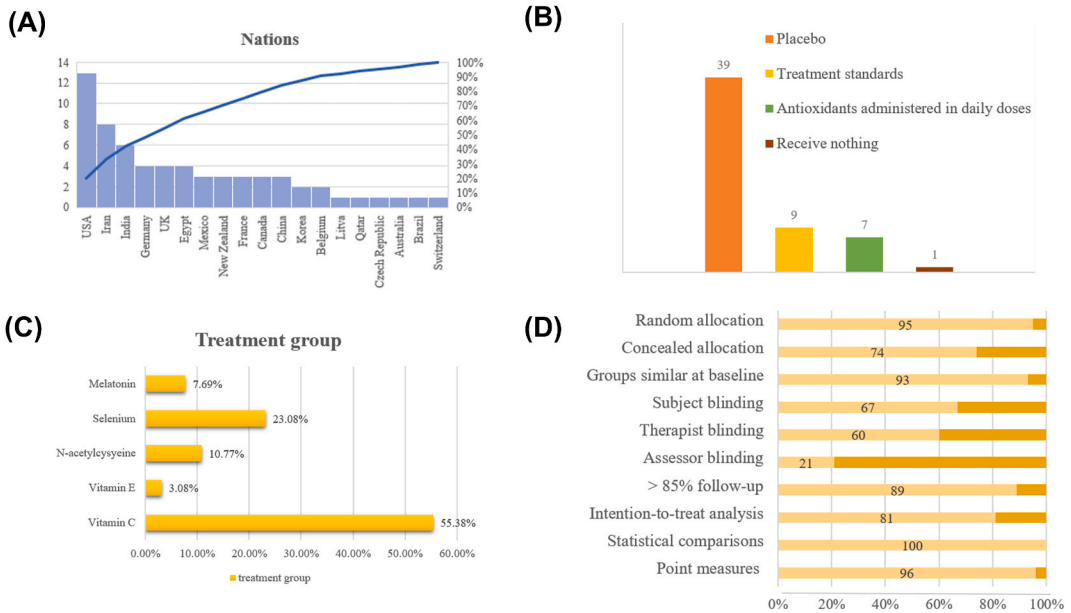

Fig. 3. Descriptive statistics of included studies categorized by (A) geographic location, (B) control group types (C) intervention types, and (D) Summarizing the risk of bias within included studies according to the PEDro scale, including individual criteria assessments.
PEDro: Physiotherapy Evidence Database.

μg–75μg/day), NAC (12.5–75 mg/kg/6 h), melatonin (50–60mg/24 h), and vitamin E (400 IU/8 h). The control group in most studies utilized a placebo (39 studies), with a minority employing standard therapy (9 studies) or low-dose daily antioxidant therapy for comparison (7 studies), as illustrated in Fig. 3B. The predominant administration route for interventions was intravenous injection (94.6 %), followed by oral administration (5.4 %).

3.3. Risk of bias within studies

Detailed information on the quality assessment of each RCT is provided in Appendix A. table A.5. The overall quality assessment yielded an average score of 7.7 out of 10. Specifically, 23 studies (41.07 %) were rated as excellent quality, 27 studies (48.21 %) as good quality, and 6 studies (10.71 %) as fair quality. Six studies achieved a perfect score of 10, meeting all evaluation criteria. The criterion "Reporting of statistical comparison results between groups" was well implemented across all 56 studies. Six studies were deemed low quality due to inadequate information on randomization procedures, allocation concealment, or blinding (patient, therapists/staff, outcome assessors). Fig. 3D presents the percentage adherence to the criteria on the PEDro scale for the RCTs included in our review. Notably, 95 % of studies used random allocation, 93 % ensured baseline group similarity, and 100 % performed statistical comparisons. However, adherence to assessor blinding was notably low at 21 %.

3.4. The network-graph

The NMA results are presented in Appendix A. table A.6. For the 28-day mortality common effect (Fig. 4A), 40 studies involving 13 intervention therapies were compared. The most frequent comparisons were vitamin C versus placebo, selenium high-dose therapy versus placebo, and hydrocortisone + vitamin C + vitamin B1 versus placebo, with 8 comparisons each. Comparisons involving glutamine + selenium high-dose therapy versus placebo, vitamin B1 versus placebo, and vitamin C versus low-dose vitamin C had only 1 comparison each. Heterogeneity between studies was at morderate level (I^2 = 43.6 % (15.2%-62.5 %), p = 0.073).

For the SOFA scores (Fig. 4B), 41 studies with 128 intervention comparisons were included. The most frequent comparisons were vitamin C versus placebo (18 comparisons), NAC versus placebo (16 comparisons), selenium high-dose therapy versus placebo or melatonin versus placebo (9 comparisons), and vitamin C + vitamin B1 + hydrocortisone versus placebo (13 comparisons). Comparisons involving selenium high-dose therapy versus glutamine + selenium high-dose therapy, glutamine + selenium high-dose therapy versus placebo, and high-dose vitamin C versus placebo had only 1 comparison each. The inconsistency between studies was high (I^2 = 96.7 % [96.2 %; 97.0 %]). The study group performed a design-based decomposition of Cochran's Q for assessing the homogeneity in the whole network (Appendix A. table A.7), but there is still inconsistency (formerly Q = 232.97 ($p < 0.0001$)), after separating individual designs, Q = 54.13 ($p < 0.0001$)). The single designs including placebo versus vitamin C (Q = 172.53), placebo versus NAC (Q = 206.53) placebo versus selenium high-dose therapy (Q = 231.89) have influenced strongly the inconsistency and heterogeneity in the NMA SOFA scores.

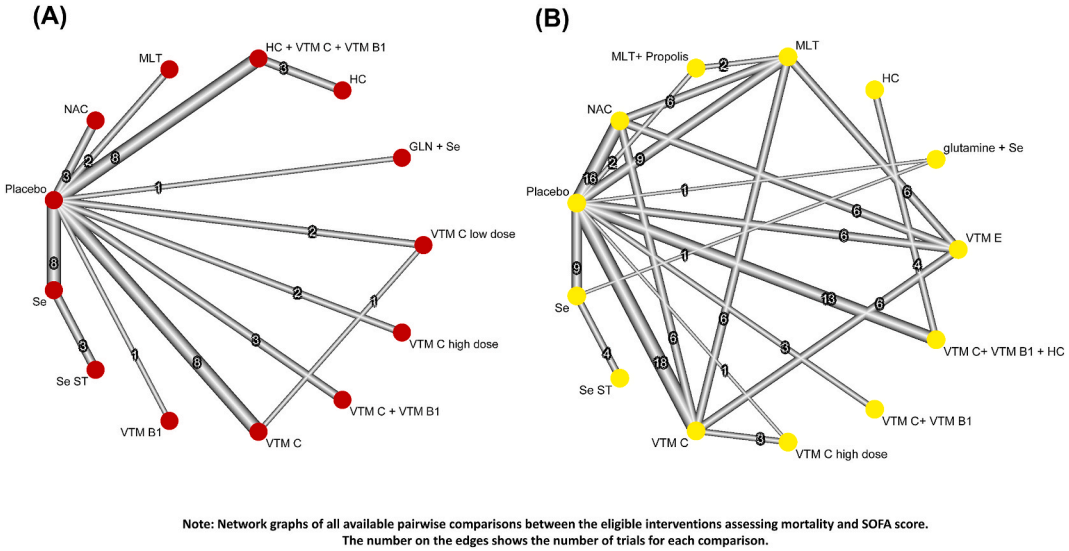

Fig. 4. Network graphs of pairwise comparisons for (A) 28-day mortality and (B) SOFA scores among antioxidant therapies, annotated with the number of contributing trials.
SOFA: Sequential Organ Failure Assessment; Se ST: selenium standard therapy; Se: selenium high-dose therapy; VTM C: vitamin C; VTM B1: vitamin B1; VTM E: vitamin E; MLT: melatonin; NAC: *N*-acetylcysteine; HC: hydrocortisone; GLN: glutamine.

3.5. Results of individual studies

Meta-analysis results for 28-day mortality and SOFA scores are presented in Fig. 5. Antioxidant therapies showed effectiveness in reducing the 28-day mortality rate compared to placebo (Fig. 5A–Appendix A. table A.6), including melatonin (OR = 0.48 (0.17–1.37; $z = -1.37 > -1.96$; $p = 0.17$), high-dose vitamin C (OR = 0.52; 95%-CI: 0.12–2.29; $z = -0.86$; $p = 0.39$), and vitamin C + vitamin B1 (OR = 0.88; 95%-CI: 0.39–2.02; $z = -0.30$; $p = 0.76$). Therapies with unclear treatment effects: hydrocortisone (OR = 0.9; 95%-CI: 0.55–1.48), hydrocortisone + vitamin C + vitamin B1 (OR = 1.03; 95%-CI: 0.82–1.29), selenium high-dose therapy (OR = 1.01; 95%-CI: 0.84–1.22), vitamin C (OR = 0.85; 95%-CI: 0.68–1.07). The remaining 4 therapies do not effectively reduce 28-day mortality. However, all these results lack of statistical significance, based on 95%-CI, Z-score and *p*-values.

For the SOFA scores (Fig. 5B), significant improvements compared to placebo were observed with melatonin + propolis (MD =

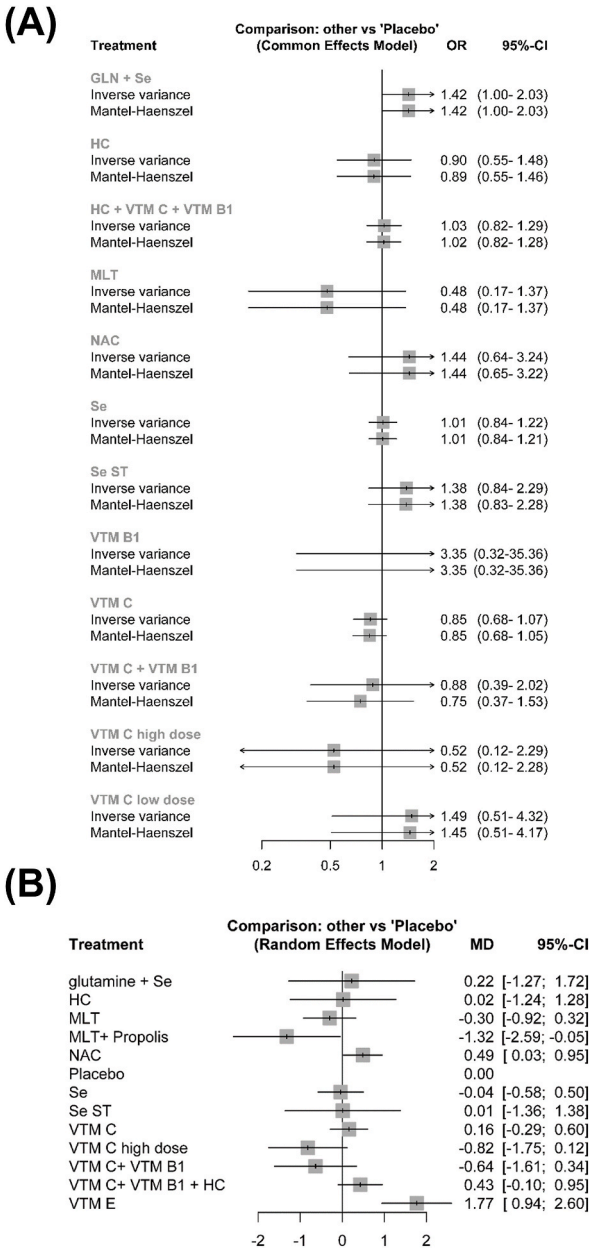

Fig. 5. Forest plots illustrating the comparative effects of antioxidant therapies on (A) 28-day mortality and (B) SOFA scores, with corresponding odds ratios or mean differences and confidence intervals.
SOFA: Sequential Organ Failure Assessment; Se ST: selenium standard therapy; Se: selenium high-dose therapy; VTM C: vitamin C; VTM B1: vitamin B1; VTM E: vitamin E; MLT: melatonin; NAC: *N*-acetylcysteine; HC: hydrocortisone; GLN: glutamine.

−1.32, 95%-CI = [−2.59; −0.05]) statistically significant when $z = -2.04 < -1.96$, $p = 0.04 < 0.05$ (Appendix A. table A.9). There was a treatment effect but not statistically significant: high-dose vitamin C (MD = −0.82, 95%-CI = [−1.75; 0.12]), vitamin C + vitamin B1 (MD = −0.64, 95%-CI = [−1.61; 0.34]), melatonin (MD = −0.3, 95%-CI = [−0.92; 0.32]). In contrast, vitamin E (MD = 1.77, 95%-CI = [0.94; 2.6]) and NAC (MD = 0.49, 95%-CI = [0.03; 0.95]) showed no treatment outcomes clearly, with $p < 0.05$ (Appendix A. table A.9).

3.6. Effect estimate table

For the 28-day mortality (Table 1), no statistically significant evidence was observed when comparing interventions.

Regarding the SOFA scores, the results bolded in Table 2 show that (melatonin + propolis) has high effectiveness, better than vitamin C, (vitamin C+ vitamin B1+hydrocortisone), and placebo. High-dose vitamin C is better than vitamin C and (vitamin C + vitamin B1 + hydrocortisone). Besides that, there are some direct comparisons namely (melatonin versus NAC), (melatonin + propolis versus placebo), (NAC versus vitamin C), (vitamin C versus vitamin E), (high-dose vitamin C versus vitamin C), (high-dose vitamin C versus placebo), (vitamin E versus placebo), and (vitamin E versus melatonin) had a large pooled effect size.

3.7. Treatment ranking

For the 28-day mortality (Fig. 6A), the top two probability ranked treatments were melatonin (42.8 %) and high-dose vitamin C (19.4 %). The SUCRA results (Table 3) indicated that melatonin with a SUCRA value of 88.22 % is the most preferred treatment for reducing 28-day mortality. Following melatonin, results suggested a preference for high-dose vitamin C (SUCRA = 80.75 %) over vitamin C (SUCRA = 72.62 %), and vitamin C+ vitamin B1 (SUCRA = 61.36 %) exhibited better treatment efficacy than vitamin C+ hydrocortisone + vitamin B1 (SUCRA = 50.50 %). The remaining interventions had SUCRA scores below 50 %, indicating no efficacy.

For the SOFA scores (Fig. 6B), the top two probability ranked interventions were melatonin + propolis (61.4 %) and high-dose vitamin C (32.4 %). The SUCRA results (Table 4) highlighted the highest efficacy for the combined therapy melatonin + propolis (SUCRA = 93.29 %). High-dose vitamin C (SUCRA = 83.97 %), vitamin C+ vitamin B1 (SUCRA = 78.72 %), and melatonin (SUCRA = 67.03 %) have high treatment effectiveness. The remaining interventions had SUCRA scoress below 50 %, indicating no efficacy.

3.8. Evaluating the validity of the results

To assess the consistency of the NMA for the 28-day mortality and SOFA scores, the Cochran's Q decomposition, netsplit analysis and netheat were performed. The corresponding results were presented in Appendix A table A.7, A.10 and Fig. 7.

For the 28-day mortality (Fig. 7A), three comparison pairs contributed to the inconsistency of the NMA. The gray-centered squares

Table 1
League table of 28-day mortality.

GLN + Se	.	.	.	.	1.42 (1.00- 2.03)	.	.	.	.	.	.	.
1.58 (0.86- 2.91)	HC	0.87 (0.56- 1.36)	.	.	.	.	.	.	.	.	.	.
1.39 (0.91- 2.11)	0.87 (0.56- 1.36)	HC + VTM C + VTM B1	.	.	1.03 (0.82- 1.29)	.	.	.	.	.	.	.
2.97 (0.98- 9.00)	1.87 (0.59- 5.99)	2.14 (0.73- 6.28)	MLT	.	0.48 (0.17- 1.37)	.	.	.	.	.	.	.
0.99 (0.41- 2.40)	0.62 (0.24- 1.62)	0.71 (0.31- 1.66)	0.33 (0.09- 1.26)	NAC	1.44 (0.64- 3.24)	.	.	.	.	.	.	.
1.42 (1.00- 2.03)	0.90 (0.55- 1.48)	1.03 (0.82- 1.29)	0.48 (0.17- 1.37)	1.44 (0.64- 3.24)	Placebo	0.99 (0.82- 1.19)	.	0.30 (0.03- 3.15)	1.15 (0.92- 1.43)	1.13 (0.50- 2.60)	1.91 (0.44- 8.34)	1.74 (0.39- 7.68)
1.41 (0.94- 2.10)	0.89 (0.52- 1.51)	1.02 (0.76- 1.36)	0.47 (0.16- 1.38)	1.42 (0.62- 3.27)	0.99 (0.82- 1.19)	Se	0.73 (0.46- 1.17)	.	.	.	.	.
1.03 (0.56- 1.90)	0.65 (0.32- 1.32)	0.74 (0.43- 1.29)	0.35 (0.11- 1.11)	1.04 (0.40- 2.70)	0.72 (0.44- 1.19)	0.73 (0.46- 1.17)	Se ST	.	.	.	.	.
0.42 (0.04- 4.60)	0.27 (0.02- 2.98)	0.31 (0.03- 3.27)	0.14 (0.01- 1.89)	0.43 (0.04- 5.19)	0.30 (0.03- 3.15)	0.30 (0.03- 3.21)	0.41 (0.04- 4.59)	VTM B1	.	.	.	.
1.67 (1.10- 2.53)	1.05 (0.61- 1.81)	1.20 (0.87- 1.66)	0.56 (0.19- 1.64)	1.68 (0.72- 3.91)	1.17 (0.94- 1.46)	1.18 (0.89- 1.58)	1.62 (0.93- 2.81)	3.92 (0.37- 41.82)	VTM C	.	.	0.22 (0.05- 0.98)
1.62 (0.66- 3.97)	1.02 (0.39- 2.68)	1.17 (0.49- 2.75)	0.54 (0.14- 2.07)	1.63 (0.51- 5.21)	1.13 (0.50- 2.60)	1.15 (0.49- 2.68)	1.57 (0.60- 4.14)	3.81 (0.31- 46.22)	0.97 (0.41- 2.29)	VTM C + VTM B1	.	.
2.72 (0.60- 12.38)	1.72 (0.36- 8.13)	1.96 (0.44- 8.72)	0.92 (0.15- 5.60)	2.75 (0.51- 14.79)	1.91 (0.44- 8.34)	1.93 (0.44- 8.54)	2.64 (0.56- 12.54)	6.40 (0.40-103.08)	1.63 (0.37- 7.24)	1.68 (0.31- 9.12)	VTM C high dose	.
0.96 (0.31- 2.94)	0.60 (0.19- 1.96)	0.69 (0.23- 2.05)	0.32 (0.07- 1.44)	0.97 (0.25- 3.69)	0.67 (0.23- 1.95)	0.68 (0.23- 2.01)	0.93 (0.29- 3.02)	2.25 (0.17- 29.91)	0.57 (0.20- 1.67)	0.59 (0.15- 2.28)	0.35 (0.06- 2.17)	VTM C low dose

Table 2
League table of SOFA score.

glutamine+Se	.	.	.	.	0.47 (-1.21; 2.16)	0.00 (-1.71; 1.71)	.	.	.	.	.	.
0.20 (-1.75; 2.16)	HC	.	.	.	.	.	.	.	.	.	-0.41 (-1.55; 0.73)	.
0.52 (-1.10; 2.14)	0.32 (-1.08; 1.72)	MLT	0.87 (-0.52; 2.25)	**-1.07 (-1.98; -0.15)**	-0.52 (-1.21; 0.17)	.	.	0.44 (-0.48; 1.36)	.	.	.	**-1.87 (-2.80; -0.94)**
1.54 (-0.42; 3.51)	1.34 (-0.45; 3.12)	1.02 (-0.24; 2.28)	MLT+Propolis	.	**-1.54 (-2.96; -0.12)**	.	.	.	.	.	.	.
-0.27 (-1.83; 1.30)	-0.47 (-1.81; 0.87)	**-0.79 (-1.49; -0.09)**	**-1.81 (-3.14; -0.48)**	NAC	0.42 (-0.06; 0.89)	.	.	**1.58 (0.56; 2.60)**	.	.	.	-0.77 (-1.79; 0.25)
0.22 (-1.27; 1.72)	0.02 (-1.24; 1.28)	-0.30 (-0.92; 0.32)	**-1.32 (-2.59; -0.05)**	**0.49 (0.03; 0.95)**	Placebo	0.04 (-0.50; 0.58)	.	0.12 (-0.35; 0.59)	**-2.90 (-4.34; -1.46)**	0.64 (-0.34; 1.61)	-0.43 (-0.95; 0.10)	**-1.79 (-2.72; -0.86)**
0.26 (-1.24; 1.76)	0.06 (-1.31; 1.43)	-0.26 (-1.08; 0.56)	-1.28 (-2.66; 0.10)	0.53 (-0.18; 1.24)	0.04 (-0.50; 0.58)	Se	-0.05 (-1.31; 1.21)	.	.	.	.	.
0.21 (-1.75; 2.17)	0.01 (-1.85; 1.87)	-0.31 (-1.81; 1.19)	-1.33 (-3.20; 0.54)	0.48 (-0.97; 1.92)	-0.01 (-1.38; 1.36)	-0.05 (-1.31; 1.21)	SeST	.	.	.	.	.
0.06 (-1.50; 1.63)	-0.14 (-1.47; 1.19)	-0.46 (-1.16; 0.24)	**-1.48 (-2.80; -0.15)**	0.33 (-0.28; 0.94)	-0.16 (-0.60; 0.29)	-0.20 (-0.90; 0.50)	-0.15 (-1.59; 1.29)	VTM C	**3.33 (2.18; 4.47)**	.	.	**-2.28 (-3.30; -1.27)**
1.04 (-0.72; 2.81)	0.84 (-0.73; 2.40)	0.52 (-0.58; 1.61)	-0.50 (-2.07; 1.07)	**1.31 (0.28; 2.34)**	0.82 (-0.12; 1.75)	0.78 (-0.30; 1.86)	0.83 (-0.83; 2.49)	**0.98 (0.07; 1.89)**	VTM C high dose	.	.	.
0.86 (-0.93; 2.65)	0.65 (-0.94; 2.25)	0.34 (-0.82; 1.49)	-0.68 (-2.28; 0.92)	**1.12 (0.05; 2.20)**	0.64 (-0.34; 1.61)	0.60 (-0.52; 1.71)	0.65 (-1.04; 2.33)	0.79 (-0.28; 1.87)	-0.18 (-1.53; 1.17)	VTM C+VTM B1	.	.
-0.20 (-1.79; 1.38)	-0.41 (-1.55; 0.73)	-0.73 (-1.54; 0.09)	**-1.74 (-3.12; -0.37)**	0.06 (-0.64; 0.76)	-0.43 (-0.95; 0.10)	-0.47 (-1.22; 0.29)	-0.42 (-1.88; 1.05)	-0.27 (-0.96; 0.42)	**-1.24 (-2.32; -0.17)**	-1.06 (-2.17; 0.05)	VTM C+VTM B1+HC	.
-1.55 (-3.26; 0.17)	**-1.75 (-3.25; -0.24)**	**-2.07 (-2.96; -1.17)**	**-3.09 (-4.56; -1.62)**	**-1.28 (-2.16; -0.40)**	**-1.77 (-2.60; -0.94)**	**-1.81 (-2.80; -0.82)**	**-1.76 (-3.36; -0.16)**	**-1.61 (-2.48; -0.73)**	**-2.59 (-3.81; -1.37)**	**-2.40 (-3.68; -1.12)**	**-1.34 (-2.32; -0.36)**	VTM E

in the heatmap indicate the contribution of each direct estimate to the NMA, with no prominent red or blue regions. The yellow region suggests potential inconsistency affecting the estimates for comparisons placebo versus low-dose vitamin C, vitamin C versus low-dose vitamin C, and placebo versus vitamin C. However, the netsplit analysis and indirect evidence analysis results (Appendix A figure A.1 and figure A.3) indicated consistency for these comparisons ($p = 0.07 > 0.05$). Thus, the Cochran's Q separation was identified as the primary cause of observed inconsistency in some comparison pairs, but this did not significantly affect the overall NMA.

For the SOFA scores (Fig. 7B), six comparison pairs contributed to the inconsistency of the NMA. It is easy to can see that the gray boxes signify the importance of a treatment comparison is for the estimation of another treatment comparison, and these boxes are large in the diagonal of the heat map. This means that direct evidence was used. The evidence contributed by vitamin C versus high-dose vitamin C and placebo versus vitamin C for the estimation of vitamin C versus high-dose vitamin C, placebo versus high-dose vitamin C, placebo versus vitamin C, and placebo versus NAC are inconsistent strongly. On the other hand, a blue-colored element indicates that the evidence of the design in placebo versus NAC supports the evidence in placebo versus vitamin C.

3.9. Publication bias

Publication bias was assessed using funnel plots and Egger test. For 28-day mortality (Fig. 8), Egger test was conducted with $p = 0.0161$ (<0.05) shows asymmetry in the histogram. This analysis indicates that the results may be biased by small studies (with larger SEs) generating high effect size estimates. This test yielded a t-value of 2.5, lying outside the critical range of -1.96 to 1.96, which indicates a significant deviation from the expected distribution. The calculated bias was 0.7186 with a standard error of 0.2869, further affirming the presence of publication bias among the studies analyzed.

For SOFA scores (Fig. 9), Egger test was conducted with $p = 0.7273$ (>0.05), indicated no significant publication bias, with a t-value of 0.35. This outcome suggests that the results are symmetrically distributed around the mean effect size, providing a higher degree of reliability in these findings. The bias estimate of 0.1535 with a standard deviation of 0.4393 supports the robustness of the meta-analysis results concerning SOFA scores, indicating a balanced and unbiased sample of published studies.

4. Discussion

This study provides a comprehensive summary of direct and indirect comparisons of five antioxidant therapies in the treatment of SS/ST in the ICU. The study focused on two outcome measures: 28-day mortality rate and SOFA scores. The analysis included a total of 56 studies involving 9366 eligible patients. Bias assessment revealed that 89.3 % of trials achieved high or excellent quality.

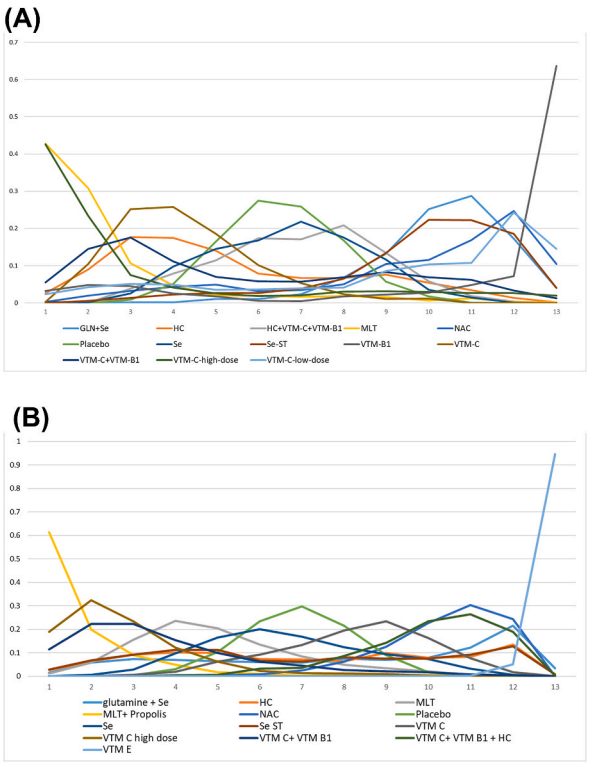

Fig. 6. Rankograms visualizing the probability rankings of antioxidant therapies based on their effectiveness for (A) 28-day mortality and (B) SOFA scores from the network meta-analysis.
SOFA: Sequential Organ Failure Assessment. Se ST: selenium standard therapy; Se: selenium high-dose therapy; VTM C: vitamin C; VTM B1: vitamin B1; VTM E: vitamin E; MLT: melatonin; NAC: *N*-acetylcysteine; HC: hydrocortisone; GLN: glutamine.

Table 3
Treatment ranking on 28-day mortality by SUCRA percentage.

.Treatment	SUCRA (%)
MLT	88.22
VTM C high dose	80.75
VTM C	72.62
Se	63.37
VTM C + VTM B1	61.36
HC	55.77
Placebo	52.52
HC + VTM C + VTM B1	50.50
SeST	31.42
VTM C low dose	28.01
GLN + Se	26.42
NAC	22.57
VTM B1	18.48

HC: hydrocortisone; MLT: melatonin; NAC: *N*-acetylcysteine; SeST: selenium standard therapy; Se: selenium high-dose therapy; VTM C: vitamin C; VTM B1: vitamin B1; VTM E: vitamin E.

4.1. NMA results 28-day mortality

The 28-day mortality NMA, comprising 40 studies and 13 intervention therapies, demonstrated positive effects of melatonin, vitamin C + vitamin B1, and high-dose vitamin C compared to placebo. Melatonin emerged as the most effective intervention with the highest SUCRA value of 88.22 %. Melatonin, known for its anti-inflammatory, anti-apoptotic, and antioxidative properties, has the potential to regulate immune response and metabolic recovery [27]. Melatonin is also highly beneficial in preventing cell damage and multiple organ failure [28]. Therefore, melatonin may be the first candidate for adjuvant antioxidant therapies to reduce ICU mortality, from the perspective of immunomodulation and metabolic resuscitation. Despite these promising findings, the forest plots and

Table 4
Treatment ranking by SOFA score by SUCRA percentage.

Treatment	SUCRA (%)
MLT + Propolis	93.29
VTM C high dose	83.97
VTM C + VTM B1	78.72
MLT	67.03
Se	52.38
Placebo	51.49
SeST	48.51
HC	48.38
VTM C	39.23
glutamine + Se	39.10
VTM C + VTM B1 + HC	24.84
NAC	22.46
VTM E	00.59

SOFA: Sequential Organ Failure Assessment; HC: hydrocortisone; MLT: melatonin; NAC: *N*-acetylcysteine; SeST: selenium standard therapy; Se: selenium high-dose therapy; VTM C: vitamin C; VTM B1: vitamin B1; VTM E: vitamin E.

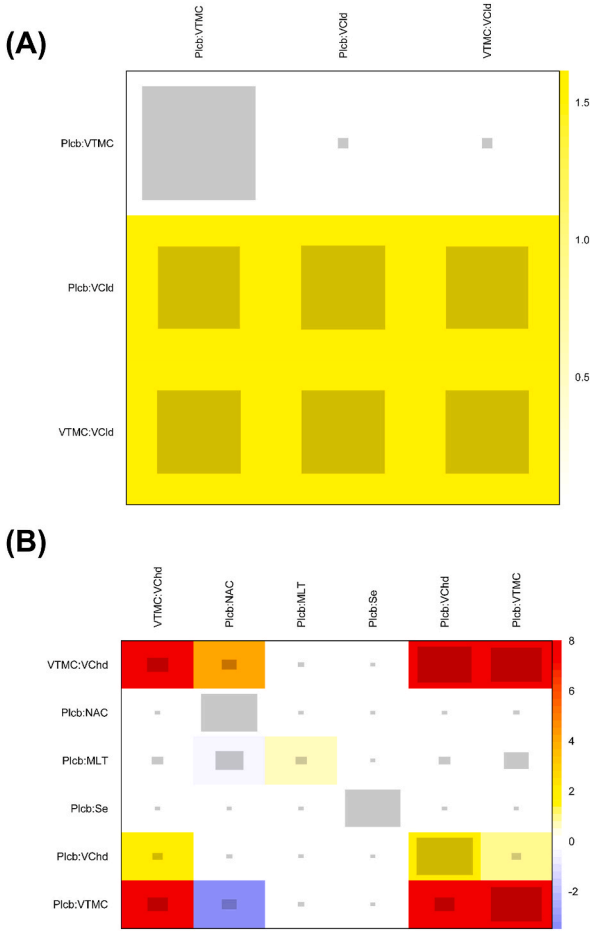

Fig. 7. Heatmap of net heat plots assessing the consistency across direct and indirect comparisons for treatments influencing (A) 28-day mortality and (B) SOFA scores.
Plcb: placebo; Se: selenium high-dose therapy; MLT: melatonin; NAC: *N*-acetylcysteine; VTMC: vitamin C; VChd: high-dose vitamin C; VCld: low-dose vitamin C.

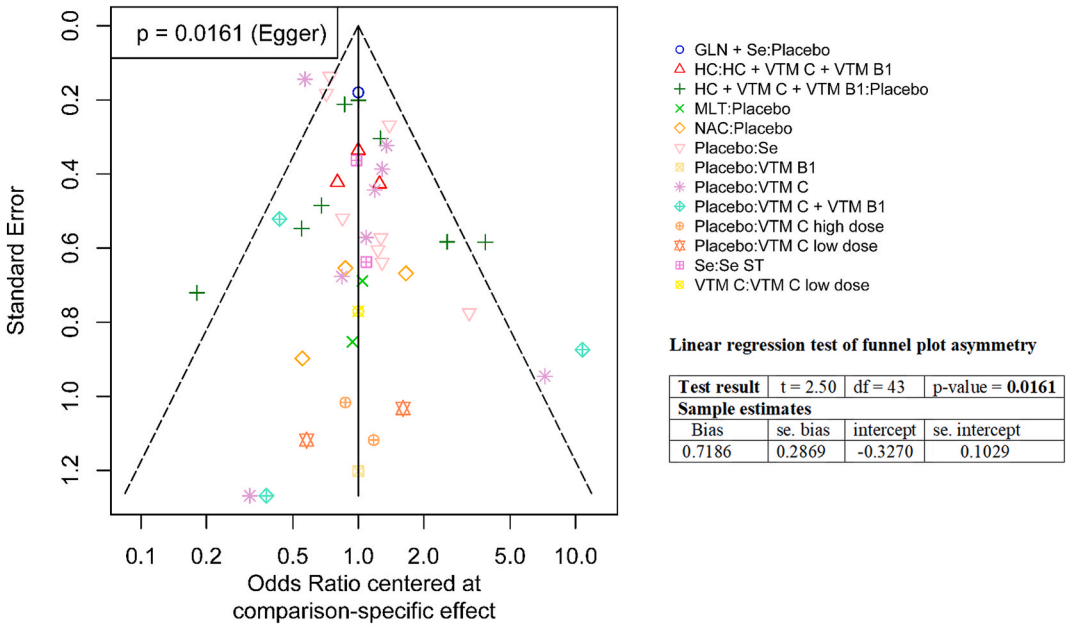

Fig. 8. Funnel plot for the assessment of publication bias in studies reporting 28-day mortality, with asymmetry indicative of potential bias.
Se ST: selenium standard therapy; Se: selenium high-dose therapy; VTM C: vitamin C; VTM B1: vitamin B1; VTM E: vitamin E; MLT: melatonin; NAC: *N*-acetylcysteine; HC: hydrocortisone; GLN: glutamine.

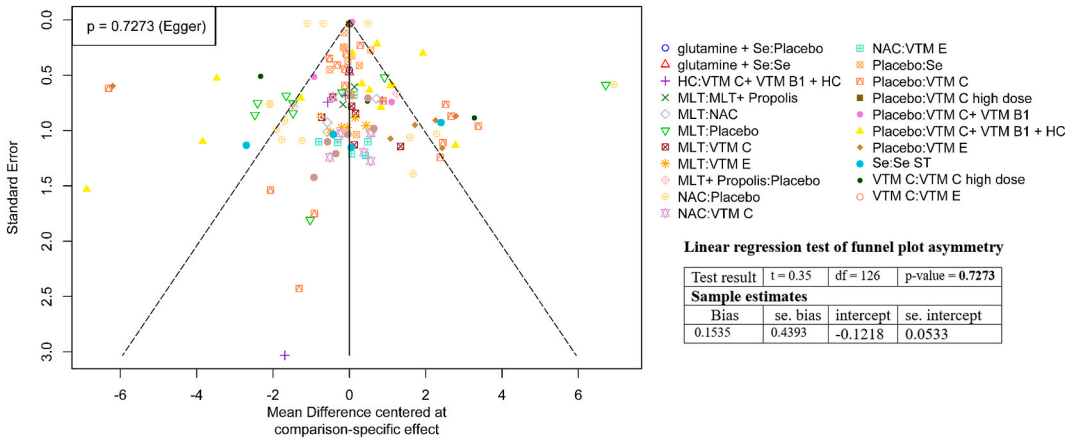

Fig. 9. Funnel plot for the assessment of publication bias in studies reporting SOFA scores, demonstrating the distribution of studies around the mean effect size.
SOFA: Sequential Organ Failure Assessment. Se ST: selenium standard therapy; Se: selenium high-dose therapy; VTM C: vitamin C; VTM B1: vitamin B1; VTM E: vitamin E; MLT: melatonin; NAC: *N*-acetylcysteine; HC: hydrocortisone; GLN: glutamine.

treatment ranking tables suggest that robust evidence supporting optimal therapeutic efficacy in reducing 28-day mortality is still lacking. Notably, treatments with high efficacy, such as melatonin and high-dose vitamin C, were based on small trials, potentially influencing NMA publication bias (Egger's test, $p = 0.0161$).

Following melatonin, vitamin C emerged as the second most effective antioxidant in reducing 28-day mortality, as both vitamin C and high-dose vitamin C ranked high in the treatment rankings (Table 3). This aligns with recent meta-analyses highlighting the potential benefits of intravenous vitamin C in improving short-term mortality due to septic shock, albeit with moderate-quality evidence [29]. Previous NMA [30,31] reported similar results where high-dose vitamin C was significantly associated with a reduction in short-term mortality, but the evidence was certainly low. This NMA results, the netheat analysis (Fig. 6) and netsplit results (Appendix A table A.8) further reinforce the consistency and robustness of comparisons of vitamin C. The results of evaluating the proportion of direct and indirect evidence (Appendix A figure A.1) also show that the comparison between placebo versus low-dose vitamin C and vitamin C versus low-dose vitamin C supports the certainty of the network aggregate estimate higher than the

remaining interfering substances. Furthermore, this study supported by a considerable number of studies (24 studies), indicate a higher level of confidence in the effectiveness of vitamin C. Thus, recommending the use of vitamin C, particularly at a high dose (200 mg/kg/24 h), appears justified for patients with SS/ST.

4.2. NMA results SOFA scores

SOFA scores is a crucial clinical indicator in predicting mortality in patients with infection or suspected infection [32]. Given that early mortality in the ICU often results from multi-organ dysfunction, the SOFA scores is valuable in assessing organ dysfunction in septic patients [33,34], used to evaluate multi- organ functional damage in SS/ST patients [35]. It represents respiratory conditions, liver function, kidney function, blood clotting function, circulatory condition and nervous system scoress.

This NMA for SOFA scores reveals high heterogeneity (Q = 232.97). Decomposition Cochran's Q significantly reduced this heterogeneity (Q = 54.13), but the between-design inconsistency is still high ($p < 0.0001$). The reason for that is the evidence contributed by vitamin C versus high-dose vitamin C and placebo versus vitamin C for the estimation of vitamin C versus high-dose vitamin C, placebo versus high-dose vitamin C, placebo versus vitamin C, and placebo versus NAC has inconsistent strongly (Fig. 7B). Nevertheless, forest plots, treatment ranking tables, and SUCRA scoress collectively identified that only intervention melatonin + propolis was effective in reducing SOFA scores ($p = 0.04$). In addition, the study recommends high-dose vitamin C is better than regular-dose vitamin C and (vitamin C + vitamin B1 + hydrocortisone). While treatment of high-dose vitamin C (SUCRA = 83.97 %), vitamin C+ vitamin B1 (SUCRA = 78.72 %), and melatonin (SUCRA = 67.03 %) as potential therapies targeting non-oxygen-dependent organ dysfunction in critically ill patients treated in the ICU, that of (vitamin C+ vitamin B1 + hydrocortisone) (SUCRA = 24.84 %) does not bring treatment effectiveness. Similar findings were reported in two latest 2023 meta-analysis (MA) [36,37], vitamin C+ vitamin B1 + hydrocortisone therapy did not improve SOFA scores within 72 h.

Moreover, severe septic patients often experience rapid depletion of vitamin C levels [38]. A New Zealand RCT on septic patients reported a 40 % decrease in vitamin C concentrations (≤11 μmol/L) in serum, despite following recommended supplementation [39]. Additionally, thiamine deficiency was observed in 20 % of SS/ST patients [40], and thiamine supplementation has shown benefits in improving lactate clearance [41,42]. Therefore, the combination of vitamin C + vitamin B1 could synergistically improve the systemic prevention of progressive organ dysfunction. The result in MA of Ge et al. also exhibited vitamin C + vitamin B1 improving SOFA scores during the first 72 h [43].

4.3. Significance of the study

In the current landscape, exploring new therapeutic approaches for treating SS/ST poses significant challenges [44]. Despite substantial advancements in understanding the pathophysiology of SS/ST [45], the supplementation of antioxidant agents is not incorporated into the standard guidelines for septic shock treatment, even though oxidative stress remains elevated in these patients. This study, through a NMA results, evaluates the clinical benefits of melatonin and high-dose vitamin C in reducing the 28-day mortality rate and the combination of melatonin + propolis, high-dose vitamin C, and vitamin C + vitamin B1 in improving SOFA scores for patients with SS/ST in the ICU. The findings contribute new insights into potentially decreasing short-term mortality and mitigating organ dysfunction in critically ill patients with SS/ST. However, while advocating for the increased use of high-dose vitamin C, clinicians should exercise caution, particularly in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In high doses, vitamin C can deplete glutathione reserves in red blood cells, leading to oxidative stress and subsequent hemolysis in G6PD-deficient individuals [46]. Additionally, the results challenge the existing perceptions about antioxidant therapies, emphasizing the need for further research and consideration in the treatment guidelines for SS/ST.

4.4. Strengths and limitations

This study represents new attempt at an NMA comparing five antioxidant therapies (vitamin C, vitamin E, selenium, NAC and melatonin) with or without combination. Rigorous literature searches and inclusion criteria resulted in a substantial number of studies included in the NMA. However, the scarcity of direct comparisons among the five antioxidant therapies (Appendix A Figure A.3&4) (12.8 % direct evidence for 28-day mortality and 26.9 % for SOFA scores) contributes to potential uncertainties in the outcomes. The reliance on indirect evidence might lead to false-negative or false-positive results. With only two studies directly comparing the five therapies [18,19,33], further research with a specific focus on these comparisons is crucial for a more comprehensive understanding of their relative effectiveness.

This meta-analysis is limited by insufficient data granularity in the included RCTs, particularly concerning patient demographics, comorbidity profiles, treatment initiation timing, and vasopressor use. These gaps hindered our ability to conduct detailed subgroup analyses and may affect the generalizability of our findings. Future research should focus on detailed reporting of these variables to enable more robust subgroup-specific conclusions.

5. Conclusion

To summarize, this comprehensive NMA assesses the effectiveness of five antioxidant therapies in treating SS/ST in the ICU. Melatonin combination with propolis demonstrates effectiveness in enhancing SOFA scores with significant and conclusive results, without any publication bias. Melatonin, high-dose vitamin C, and the combination of vitamin C with vitamin B1 emerge as promising

interventions, exhibiting the potential to reduce 28-day mortality and SOFA scores. Vitamin E, selenium, and *N*-acetylcysteine are deemed ineffective.

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Ethical statement

No ethical approval was required as this study did not involve human participants or laboratory animals.
All results are included in the article.

Data availability statement

All data that supports the results were included in the article.

CRediT authorship contribution statement

Thi-Phuong-Thao Pham: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Formal analysis, Data curation, Conceptualization. **Thi-Hoai-Thu Le:** Writing – original draft, Visualization, Investigation, Data curation. **Huynh-Thien-Xuan Pham:** Writing – original draft, Visualization, Methodology, Data curation. **Thanh-Thien Tran:** Writing – original draft, Visualization, Investigation, Data curation. **Van-Truong Pham:** Visualization, Validation, Data curation. **Okti Ratna Mafruhah:** Writing – review & editing, Visualization, Validation. **Hai-Anh Ha:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31447.

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