Heliyon 10 (2024) e29156

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

The effects of antioxidant supplementation on short-term mortality in sepsis patients

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ARTICLE INFO

Keywords:
Antioxidant
Sepsis
Ascorbic acid
Thiamine
N-acetylcysteine
Selenium
Short-term mortality

ABSTRACT

Background: The occurrence and development of sepsis are related to the excessive production of oxygen free radicals and the weakened natural clearance mechanism. Further dependable evidence is required to clarify the effectiveness of antioxidant therapy, especially its impact on short-term mortality.

Objectives: The purpose of this systematic review and meta-analysis was to evaluate the effect of common antioxidant therapy on short-term mortality in patients with sepsis.

Methods: According to PRISMA guidelines, a systematic literature search on antioxidants in adults sepsis patients was performed on PubMed/Medline, Embase, and the Cochrane Library from the establishment of the database to November 2023. Antioxidant supplements can be a single-drug or multi-drug combination: HAT (hydrocortisone, ascorbic acid, and thiamine), ascorbic acid, thiamine, N-acetylcysteine and selenium. The primary outcome was the effect of antioxidant treatment on short-term mortality, which included 28-day mortality, in-hospital mortality, intensive care unit mortality, and 30-day mortality. Subgroup analyses of short-term mortality were used to reduce statistical heterogeneity and publication bias.

Results: Sixty studies of 130,986 sepsis patients fulfilled the predefined criteria and were quantified and meta-analyzed. Antioxidant therapy reduces the risk of short-term death in sepsis patients by multivariate meta-analysis of current data, including a reduction of in-hospital mortality ($OR = 0.81$, *95% CI* 0.67 to 0.99; $P = 0.040$) and 28-day mortality ($OR = 0.81$, *95% CI* 0.69 to 0.95]; $P = 0.008$). Particularly in subgroup analyses, ascorbic acid treatment can reduce in-hospital mortality ($OR = 0.66$, *95% CI* 0.90 to 0.98; $P = 0.006$) and 28-day mortality ($OR = 0.43$, *95% CI* 0.24 to 0.75; $P = 0.003$). However, the meta-analysis of RCTs found that antioxidant therapy drugs, especially ascorbic acid, did substantially reduce short-term mortality($OR = 0.78$, *95% CI* 0.62 to 0.98; $P = 0.030$; $OR = 0.57$, *95% CI* 0.36 to 0.91; $P = 0.020$).

Conclusions: According to current data of RCTs, antioxidant therapy, especially ascorbic acid, has a trend of improving short-term mortality in patients with sepsis, but the evidence remains to be further demonstrated.

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https://doi.org/10.1016/j.heliyon.2024.e29156
Received 14 July 2023; Received in revised form 28 March 2024; Accepted 2 April 2024
Available online 4 April 2024

1. Introduction

Sepsis seriously endangers the life and health of patients, which is currently the leading cause of death in intensive care units (ICU) [1]. There are more than 30 million sepsis patients worldwide, of which 19.4 million are severe sepsis patients, and about 5 million sepsis-related deaths occur every year [2]. Approximately one-third of sepsis patients admitted to the intensive care unit survived for fewer than 30 days, and the mortality of patients deteriorated with advanced age and multiple organs states, according to preliminary statistics [3].Short-term mortality induced by organ dysfunction consume a substantial amount of financial and medical resources, negatively impacting patient prognosis [4].

Numerous clinical research discovered a connection between sepsis short-term mortality and abnormal oxidative stress activation. In the past five years, international medical organizations have carried out a lot of clinical studies on antioxidants in the treatment of sepsis. Commonly used antioxidants such as ascorbic acid [5,6], thiamine [7], melatonin [8], N-acetylcysteine [9,10], and selenium compounds [11,12]have been used in animal models of sepsis and clinical trials.But limited by the lack of large randomized clinical trials and even more lack of head-to-head studies on different antioxidants in patients, the clinical evidence for the effectiveness of antioxidant therapy was still very insufficient. Antioxidant therapy remains an area of controversy in the management of sepsis. Even the highly anticipated HAT (hydrocortisone, ascorbic acid, and thiamine) treatment strategy is believed to have a synergistic effect that can lower the mortality of sepsis and septic shock patients, the duration of vasopressor usage, and the frequency of renal replacement therapy. According to the ACTS trial [13], VITAMINS trial [14], and VICTAS trial [5], the HAT therapy does not improve SOFA score, duration of vasopressor and mortality. Even one of the HAT trial [15] was prematurely stopped because of worries about the intervention group's exposure to hypernatremia.

Although antioxidant administration may be one of the useful supplement in the treatment of septic shock. Previous meta-analyse [19] had showed that 3–10 g/d of ascorbic acid reduces patient mortality, although high and low of ascorbic acid did not significant. However, the latest meta-analysis [20–22] found that ascorbic acid and HAT treatment did not reduce the mortality rate of sepsis patients The current academic debate on antioxidant therapy has not yielded clear results. Compared with the 2016 international sepsis guidelines, the latest 2021 sepsis management guidelines [23] from the European Society of Critical Care Medicine (ESICM) and American Society of Critical Care Medicine (SCCM) only give a weak recommendation for ascorbic acid in sepsis or septic shock. However, the latest Japanese clinical practice guidelines for the management of sepsis and septic shock [24] suggest providing ascorbic acid as the sole antioxidant for sepsis patients.

It is undeniable that antioxidants have also achieved some positive therapeutic results in terms of efficacy and safety in sepsis, but more trustworthy data are still needed to support it. Therefore, it is necessary to review the existing literature on antioxidant therapy to provide possible clinical guidance and conduct a meta-analysis to assess the impact of antioxidant therapy on short-term mortality in septic patients.

2. Methods

This systematic review and meta-analysis of clinical studies were conducted and reported in adherence with the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25]. The research was not registered as well as the review protocol. Data extraction and risk assessment were independently done by multiple observers and cross-checked to avoid errors. The quality of included studies was critically examined following the Cochrane guidelines [26].

2.1. Search strategy

The study searched PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials to identify potential studies from the inception of all databases to November 2023. The search strategies of each database were shown in Supplemental. Thorough manual search was conducted for existing reviews and conference abstracts, and relevant articles were retrieved from references. Finally, we performed a recursive search, using the bibliographies of all obtained articles. All differences of opinion were resolved through consultation, and a third party was involved in the evaluation if disagreements cannot be negotiated. In addition, we searched published meta-analyses and screened included studies and references for manual retrieval.

2.2. Study selection

All published clinical trials of antioxidant therapy were included to assess the effect of antioxidants on short-term mortality in sepsis. There were no language restrictions on study selection; both English and non-English articles were reviewed. Antioxidants include HAT(hydrocortisone, ascorbic acid, and thiamine), ascorbic acid, thiamine, N-acetylcysteine, and selenium. Short-term mortality assessments for all studies included in-hospital mortality, 28-day mortality, ICU mortality, and 30-day mortality. Subgroup analyses of short-term mortality were further performed according to different antioxidant therapy or study type.

2.3. Data extraction

All included literature review and data extraction were carried out by two independent working groups (Hui Pei and Jie Qu, Jianming Chen and Yaolu Zhang) and cross-checked to avoid the error. We also extracted the following data for all studies, including the type of study, type of analysis, specific intervention, number of participants screened, primary and secondary outcomes, and

duration of follow-up after the intervention.

2.4. Statistical analysis

The Cochrane Collaboration meta-analysis software Review Manager 5.3 was used for the meta-analysis. Dichotomous data were reported using odds ratio (*OR*) with 95% confidence intervals (*95%CI*) following the Cochrane guidelines. When the coefficient of

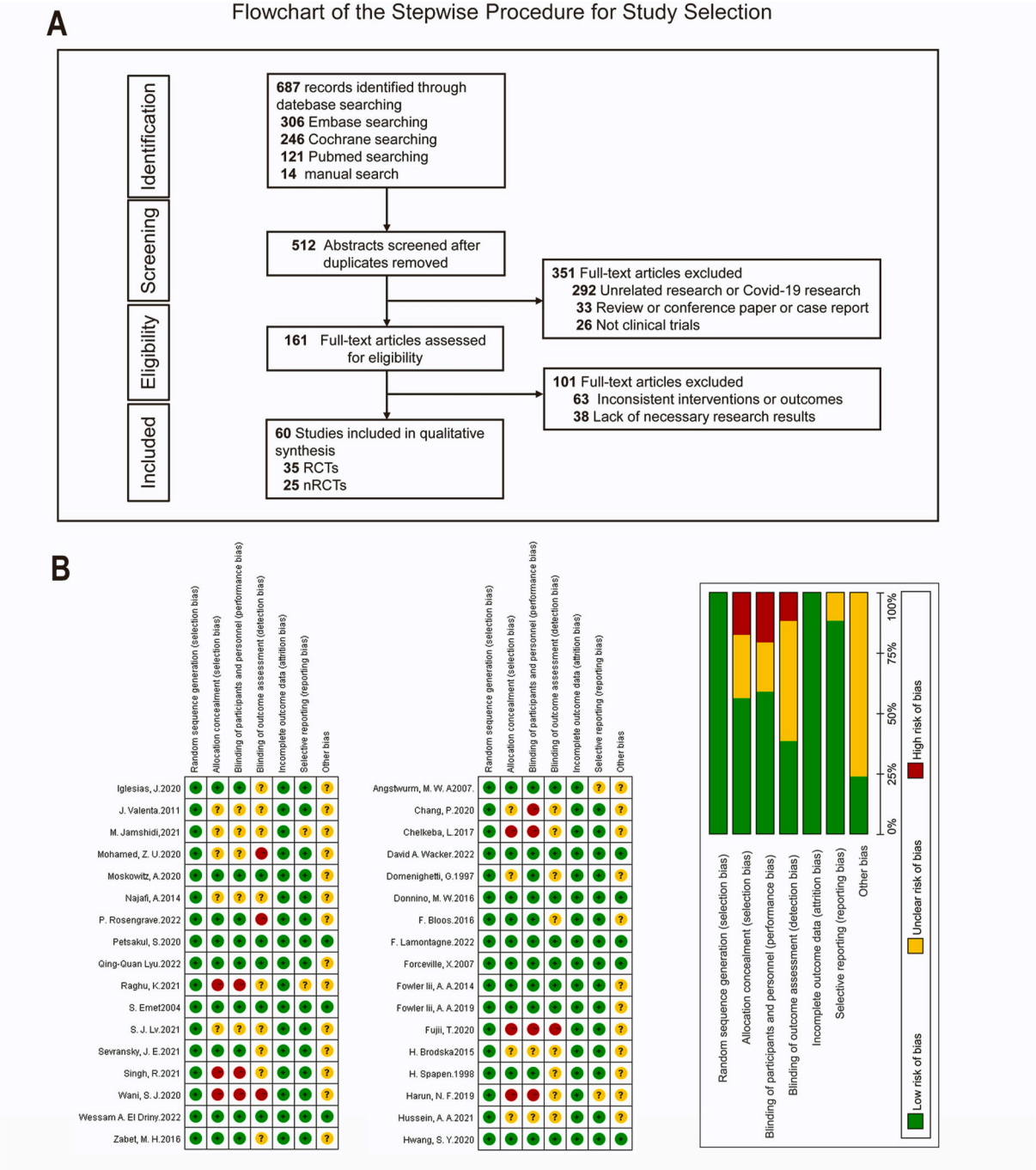

Fig. 1. The PRISMA flowchart and the risk assessment of the included studies. A. The PRISMA flowchart of this Systematic Review from Database search results as November 2023.; B. Results of risk assessment of all randomized controlled studies. Low risk, unclear risk, and high risk of bias were indicated by the green, yellow, and red colours, respectively. Abbreviations: RCTs: randomized controlled trial; nRCTs: non randomized controlled trial. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

heterogeneity $I^2 > 50\%$, the random-effects model (Mantel-Haenszel method) were performed using, otherwise the variables were calculated using the fixed-effects model. A two-sided p-value ≤ 0.05 was considered statistically significant. The trial sequence analysis (TSA) and sensitivity analysis were conducted using TSA software and STATA17, and visualization by Sangbox network platform [27, 28].

2.5. Risk of bias

The quality of the selected studies and the risk of bias was critically examined following the Cochrane guidelines [29]. The quality assessment system includes analysis type or not, random sequence generation or not, allocation concealment or not, blinding of participants and personnel, and blinding of outcome assessment.

2.6. Heterogeneity and subgroup analysis

For the effect of antioxidant therapy on short-term mortality, we conducted four subgroup analyses by different outcome measures. Secondly, an in-depth subgroup analysis was carried out for different antioxidant drugs and study type. In addition, trial sequential

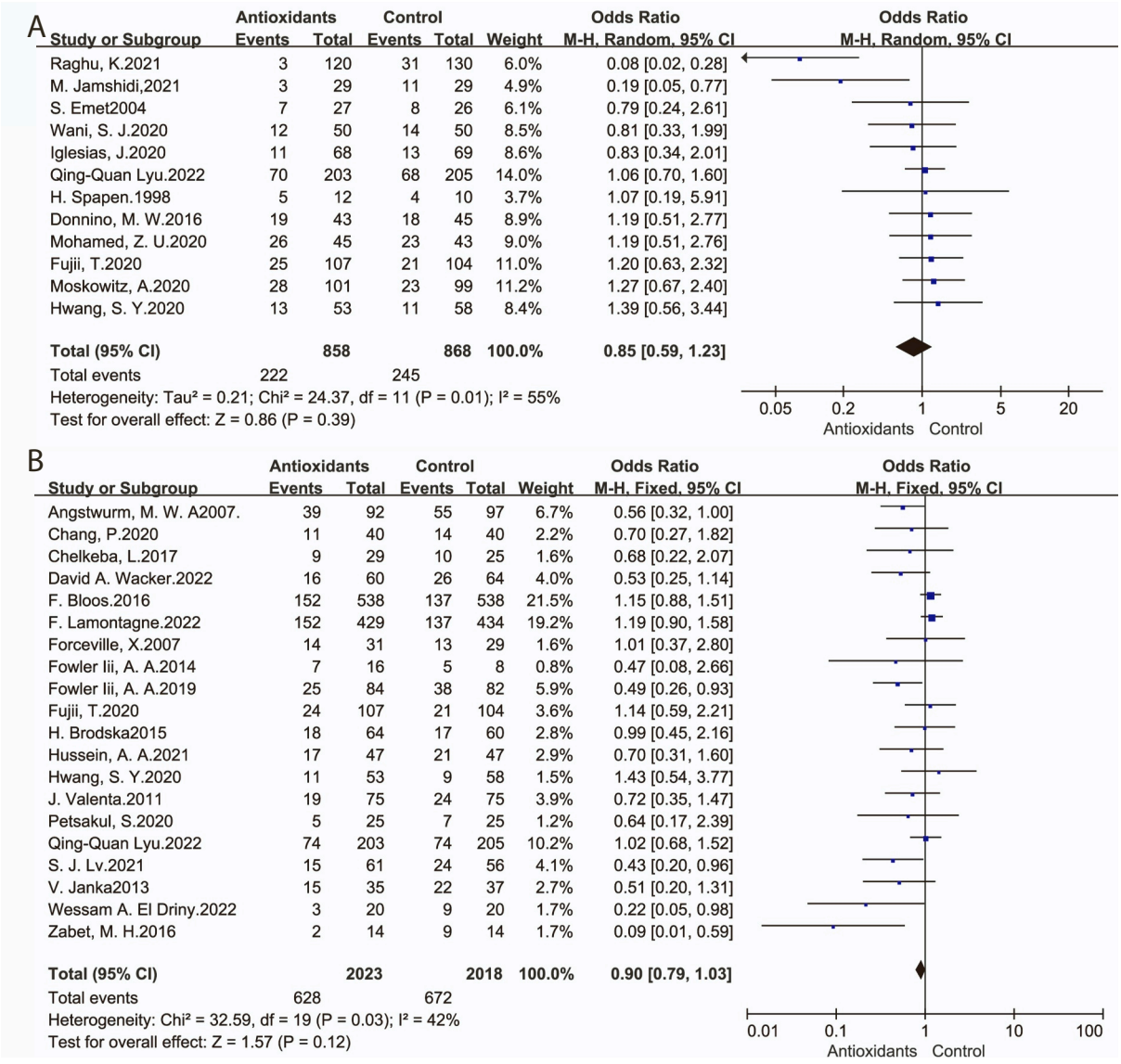

Fig. 2. The effect of antioxidant therapy on in-hospital mortality and 28-day mortality in sepsis patients. A. The subgroup analysis of RCTs on in-hospital mortality. of sepsis patients by antioxidant therapy compared with the reference; B. Results of antioxidant therapy on 28-day mortality by 20RCTs.

analysis was used to evaluate the quantity and consistent trend. The sensitivity analysis and funnel plot were constructed to visual assessment of heterogeneity and publication bias.

3. Result

3.1. Study characteristics

The initial literature search identified 687 studies from various databases, and an additional 14 studies were retrieved through the manual reference search. 512 research were included in the primary screening by duplicate publications were eliminated. After reviewing the abstracts, we again excluded 351 articles due to the following reasons: irrelevant research, COVID-19, animal experiments, reviews, conference papers, and case reports, and 161 articles were included in the full-text reading and screening process. Finally, 60 articles were included in this meta-analysis, including 35 randomized controlled studies [5–7,11,13–15,30–58] and 25 non-randomized controlled studies [42,56,59–81]. The PRISMA flowchart and the risk assessment results of the randomized controlled studies were shown in Fig. 1A/B. The study characteristics of included studies were summarized in Supplementary Table S1.

4. Antioxidant therapy's outcome in in-hospital mortality

A total of 29 studies were included in the meta-analysis on in-hospital mortality. Pooled analysis indicated a significantly lower in-hospital mortality in patients receiving antioxidant therapy compared with the standard treatment group, (*OR* = 0.81, *95%CI* 0.67 to 0.99; *P* = 0.040). Non-randomized controlled studies (17/29) and three-drug combination therapy (14/29) accounted for a large proportion of this subgroup. More importantly, the meta-analysis of RCTs showed that antioxidant therapy did not improve in-hospital mortality in sepsis patients, (*OR* = 0.85, *95%CI* 0.59 to 1.23; *P* = 0.390). Although, the nRCT study and HAT therapy reduced the in-hospital mortality of patients (*OR* = 0.79, *95%CI* 0.62 to 1.00; *P* = 0.050; *OR* = 0.72, *95%CI* 0.51 to 1.01; *P* = 0.060). Either ascorbic acid or thiamine monotherapy showed significant advantages in reducing hospital mortality (*OR* = 0.66, *P* < 0.001; *OR* = 0.64, *P* = 0.020), the combination of the two drugs did not show an ideal effect (*OR* = 0.88, *P* = 0.340). The result of comprehensive analysis and subgroup analysis of antioxidant treatment on in-hospital mortality were shown in Figs. 2A and 5A.

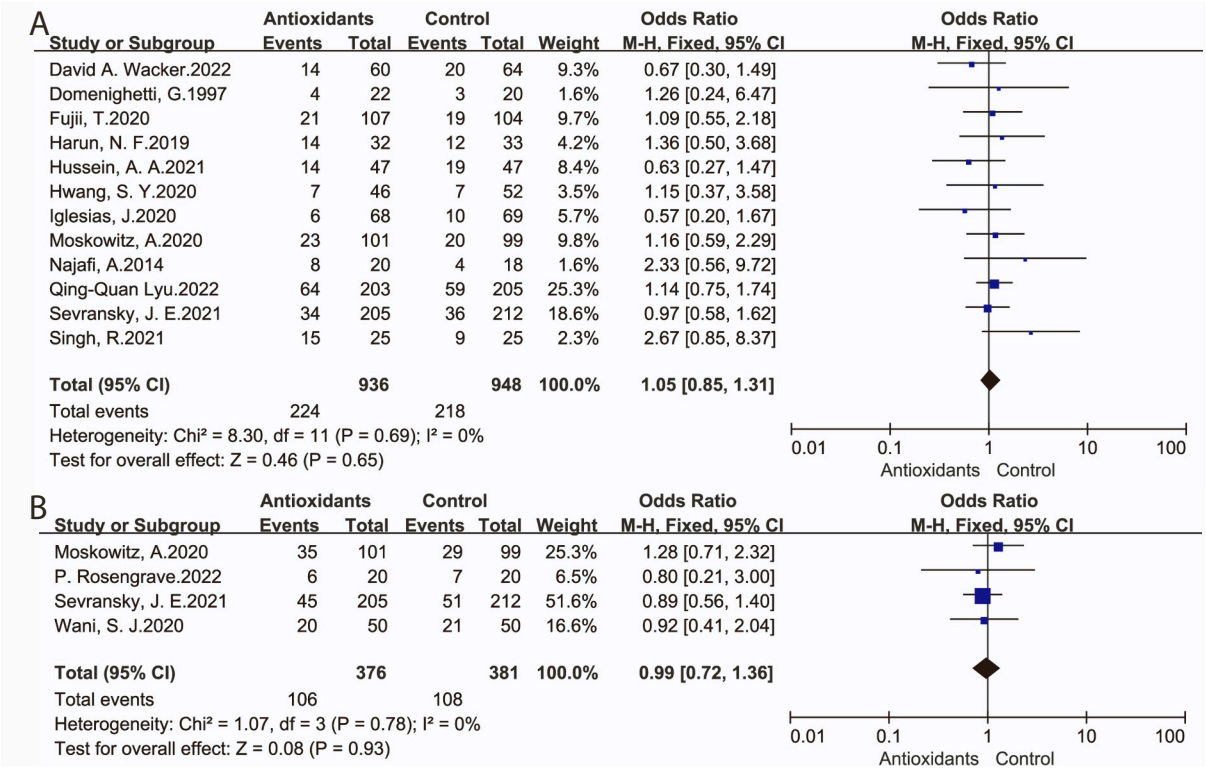

Fig. 3. The subgroup analysis of antioxidant therapy on ICU mortality and 30-day in sepsis patients. A. The subgroup analysis of RCTs on 28-day mortality of sepsis patients by antioxidant therapy compared with the reference; B. Result of antioxidant therapy on 30-day mortality by 4 RCTs.

4.1. Antioxidant therapy's outcome in 28-day mortality

A total of 29 studies were included in the meta-analysis on 28-day mortality. The pooled analysis showed that receiving antioxidant therapy significantly reduced 28-day mortality in sepsis patients, (*OR* = 0.81, *95%CI* 0.69 to 0.95; *P* = 0.008). Randomized controlled studies accounted for a large proportion (20/29). Howere, the meta-analysis of RCTs showed that antioxidant therapy did not improve 28-day mortality in sepsis patients, (*OR* = 0.90, *95%CI* 0.79 to 1.03; *P* = 0.120). Although, ascorbic acid therapy significantly reduced 28-day mortality in sepsis patients compared to standard treatment, (*OR* = 0.43, *95%CI* 0.24 to 0.75; *P* = 0.003),as shown in Figs. 2B and 5B.

5. Antioxidant therapy's outcome in ICU mortality

The meta-analysis of the effect of antioxidant therapy on ICU mortality includes 22 studies. The pooled analysis showed that receiving antioxidant therapy had no significant effect on ICU mortality in sepsis patients (*OR* = 0.98, *95%CI* 0.88 to 1.10; *P* = 0.770).

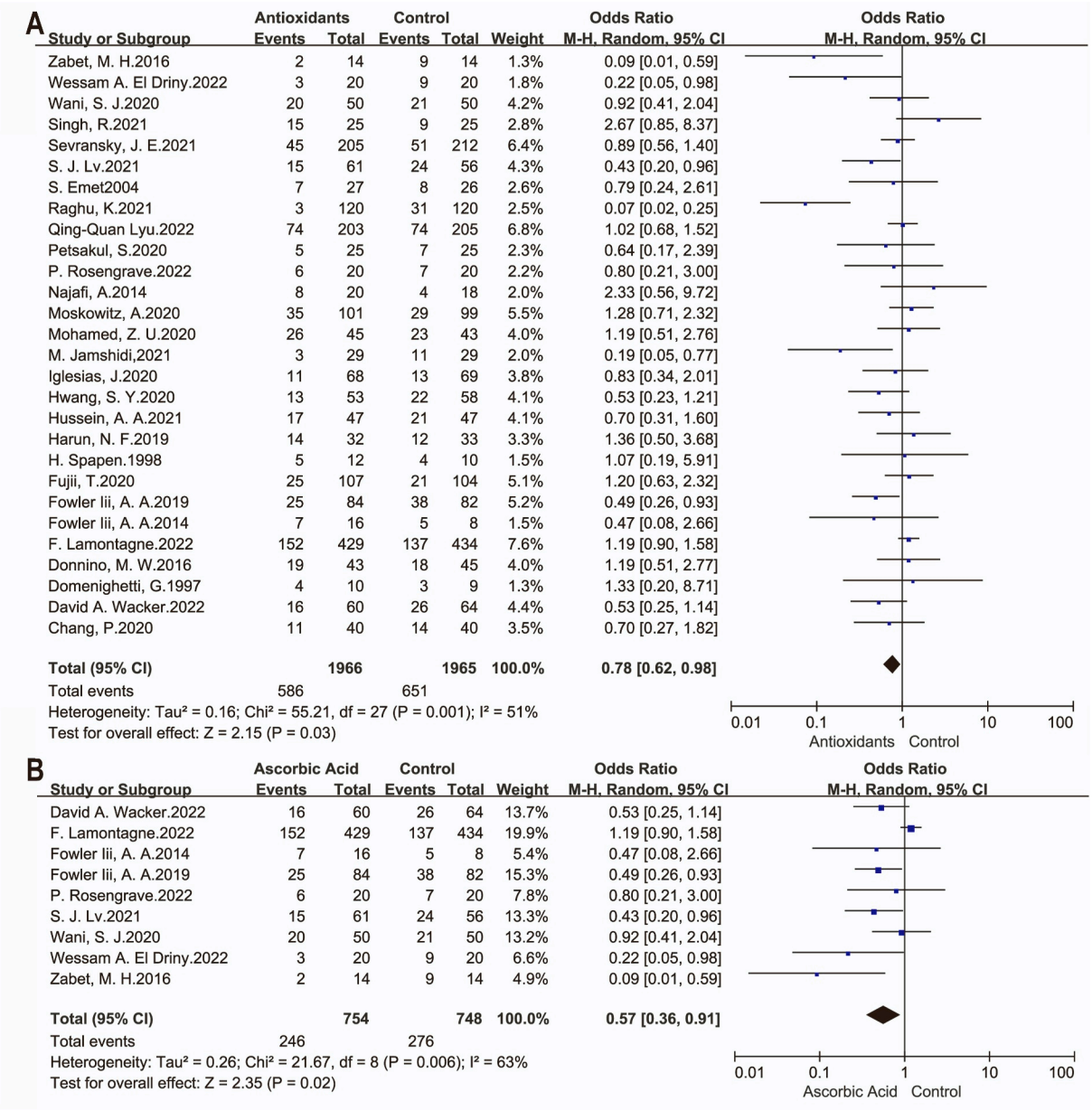

Fig. 4. The effect of antioxidant therapy on mixed short-term mortality in sepsis patients. A. The subgroup analysis of RCTs on mixed short-term mortality of sepsis patients by antioxidant therapy compared with the reference; B. Result of ascorbic acid onmixed short-term mortality by 9 RCTs.

The proportion of randomized controlled studies and non-randomized controlled studies was roughly equal (12/10). Howere, the meta-analysis of RCTs showed that antioxidant therapy did not improve ICU mortality in sepsis patients, (*OR* = 1.05, *95%CI* 0.85 to 1.31; *P* = 0.650). Unfortunately, even subgroup analyses did not find a significant difference in ICU mortality of antioxidant therapy,as shown in Figs. 3A and 5C.

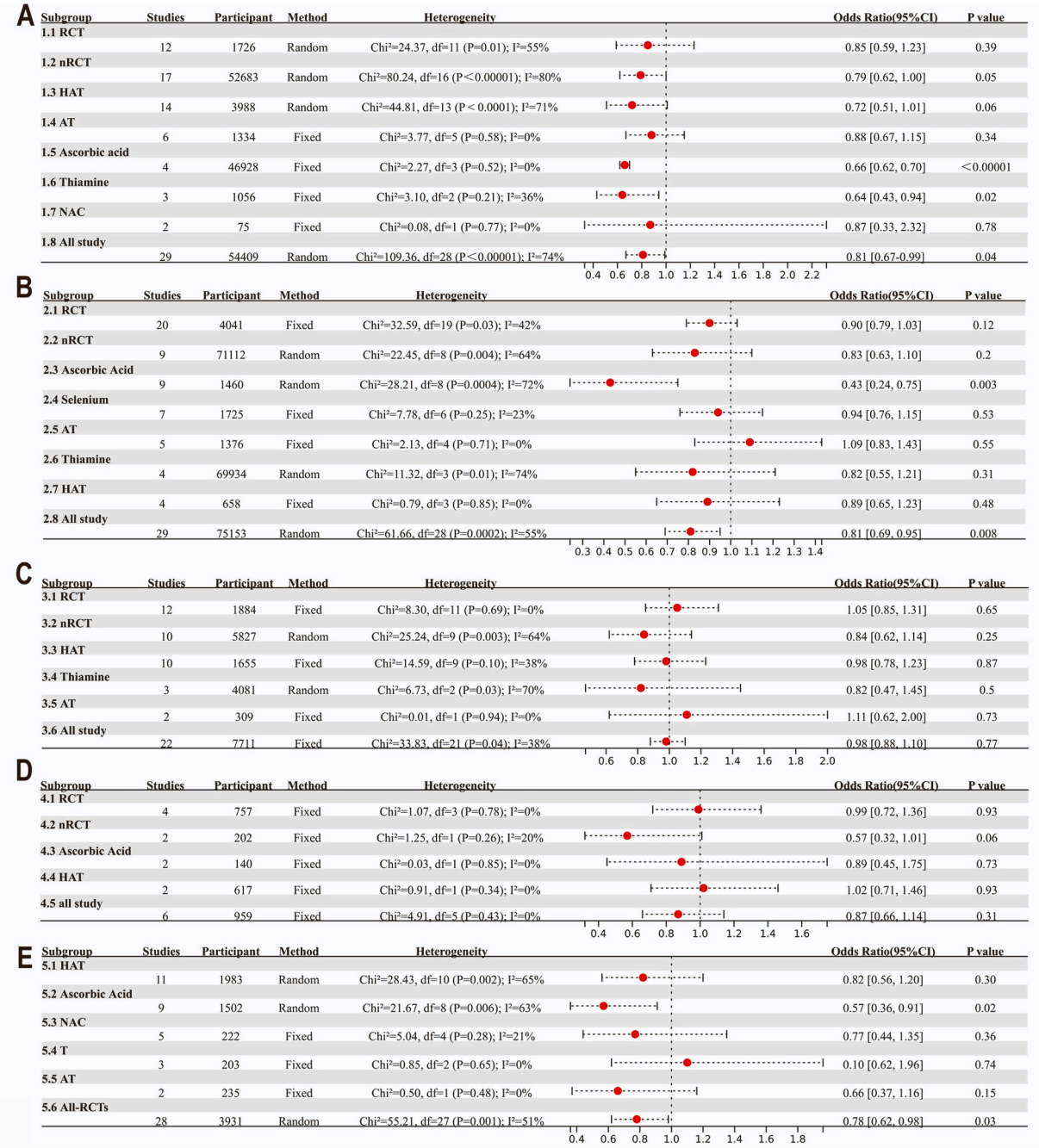

Fig. 5. Assessment of the risk of short-term mortality in sepsis patients by antioxidant therapy. A. Pooled and subgroup analysis of antioxidant therapy on in-hospital mortality; B. Pooled and subgroup analysis of antioxidant therapy on 28d mortality; C. Pooled and subgroup analysis of antioxidant therapy on ICU mortality; D. Pooled and subgroup analysis of antioxidant therapy on 30d mortality; E. Pooled and subgroup analysis of antioxidant therapy on mixed short-term mortality. Abbreviations: OR: odds ratio, CI: confidence interval, Random: random effects model, Fixed: fixed effects model, nRCT: non randomized controlled trial; RCT: randomized controlled trial; HAT: hydrocortisone, ascorbic acid, and thiamine; AT: ascorbic acid and thiamine; NAC: N-acetylcysteine.

6. Antioxidant therapy's outcome in 30-day mortality

Only 6 studies were included in the meta-analysis on 30-day mortality. The pooled analysis showed that antioxidant therapy had a trend of reducing 30-day mortality in sepsis patients (*OR* = 0.87, *95%CI* 0.66 to 1.14; *P* = 0.310). The meta-analysis of RCTs showed that antioxidant therapy did not improve 30-day mortality in sepsis patients, (*OR* = 0.99, *95%CI* 0.72 to 1.36; *P* = 0.930).Although, the subgroup analysis of nRCT found that antioxidative effects relatively reduced 30-day mortality (*OR* = 0.57, *95%CI* 0.32–1.01; *P* = 0.060), as shown in Figs. 3B and 5D.

7. Antioxidant therapy's outcome in short-term mortality

After summarizing the maximum mortality in RCTs into short-term mortality, a meta-analysis was conducted on different antioxidant therapy. Antioxidant therapy substantially reduce mixed short-term mortality(*OR* = 0.78, *95% CI* 0.62 to 0.98; *P* = 0.030). Particularly, the subgroup analysis of ascorbic acid significantly reduced the short-term mortality in sepsis patients, (*OR* = 0.57, *95%CI* 0.36 to 0.91; *P* = 0.020), as shown in Fig. 4A/B and Fig. 5E.

7.1. Sensitivity analysis and trial sequence analysis

The sensitivity analysis was used to further examine the impact of individual RCTs on the overall outcomes and found that the outcomes remained stable and reliable, as shown in Supplementary Fig. 1. Trial sequential analysis in Supplementary Fig. 2 confirmed that cumulative Z-curves of subgroup analysis surpassed both conventional test boundary and TSA bounds, and attained the acceptable sample size. The conclusions of the above subgroup meta-analysis were reliable and sufficient. Especially, the multimodal antioxidant therapy or single-drug ascorbic acid therapy in RCTs considerably decreased the mixed short-term mortality of patients.

8. Discussion

In severe patients with sepsis or septic shock, oxidative stress is an important risk factor for multiple organ dysfunction and disease progression [82]. Antioxidant therapy prevent the oxidative stress response of sepsis patients, block their damage to cellular proteins, lipids, and DNA, alleviate the resulting multiple organ dysfunction, and ultimately reduce patients short-term mortality [85–87]. Antioxidant therapy has therefore always been a crucial adjunctive treatment for sepsis. However, it is not difficult to find that antioxidant therapy have not achieved the desired expected results. Moskowitz's study found that HAT therapy did not reduce 72-h SOFA scores and 30-day mortality [13,72]. Similar studies [5,14,38] also found that HAT treatment did not significantly reduce short-term mortality in severe sepsis patients. Therefore, we conducted this meta-analysis to evaluate the effect of commonly used antioxidants on short-term mortality in sepsis patients, with the aim of discovering new combination strategies. Antioxidant therapy in randomized controlled studies tended to improve short-term mortality in sepsis patients compared with standard care. This study innovatively analyzed the outcomes of different antioxidant drugs used alone or combinations and found that ascorbic acid was superior to other antioxidants and combinations strategies.

The meta-analysis of different antioxidant drugs and short-term mortality indicators must be based on the principles of high consistency and stability. This meta-analysis decreased the heterogeneity of the study through subgroup analysis. HAT therapy efficiently manages the in-hospital mortality of sepsis patients with trending downward. Ascorbic acid or thiamine by subgroup analysis also exhibit a specific therapeutic effect, which can significantly reduce in-hospital mortality or 28-day mortality.

We deeply consideration to the negative outcomes of this meta-analysis, which included inconsistent results between the evaluations of four short-term mortality indicators. On the one hand, the amount of data obtained for the four indicators was different, with a meta-analysis of in-hospital mortality and 28-day mortality each incorporating results from a maximum of 29 studies. It was also precisely because the included sample size was large enough that the results of the above two subgroup analysis were positive treatment effects. Second, the short-term mortality distribution from sepsis occurred in a biphasic pattern, with an initial peak due to inadequate resuscitation resulting in cardiac and pulmonary failure and a second peak several weeks later due to persistent organ dysfunction [88]. The statistical results on patients' in-hospital mortality and 28-day mortality might be more consistent with the natural course of sepsis patients, except for the ICU mortality data of sepsis patients with chronic complicated conditions, which made the data included statistics present better consistent.

In light of the positive benefits of ascorbic acid and thiamine that are revealed by our analysis, why is the benefit of the combined efficacy of the two medications not show significant superiority? Even the highly expected HAT therapy failed to show ideal outcomes. We found that the effect of the combination of the three drugs was not significantly better than that of the simple application of ascorbic acid or thiamine. The network meta-analysis [22] from 43 RCTs also partially confirms our study that vitamin C, glucocorticoids, thiamine, or their combination was not proven to decrease long-term mortality. The conclusions of the meta-analysis of the data have been impacted by the existing dearth of research and the inconsistent quality of that research. On the one hand, we believe that the confounding variables brought on by additional medications reduce the effectiveness of the treatment. On the contrary, steroid supplementation increases the incidence of secondary infections and new septic shock. Sprung CL et colleagues [89] discovered that hydrocortisone did not increase septic shock patient survival or shock reversal. The ACTS trial [13], VITAMINS trial [14], and VICTAS trial [5] respectively confirmed that HAT combined therapy does not reduce SOFA scores or mortality, nor does it increase survival days without vasopressors. On the other hand, although adrenal cortical dysfunction can affect the prognosis of septic shock [90,91], blindly supplementing corticosteroids is not harmless. The appropriate corticosteroid dosage and duration of treatment are still

uncertain [92]. Even though short-term low-dose corticosteroid therapy may be beneficial [93,94], standardised adrenal function testing was still required to assist reverse septic shock and reduce mortality [95–97].

It must be seen that there are still many clinical problems that need to be resolved, and antioxidant therapy's ideal timing, method of administration, and dosage are all still up for debate. Ascorbic acid was the most commonly used antioxidant drug at present. Studies have found that the efficacy of ascorbic acid is dose-dependent. Previous meta-analyse [19] had showed that 3–10 g/d of ascorbic acid reduces patient mortality, although high and low of ascorbic acid did not significant. The CITRIS-ALI trial [40], which used a higher dose of ascorbic acid (200 mg/kg/day), demonstrated that high-dose ascorbic acid significantly reduced short-term mortality in patients. Interestingly, another study [46] by the same author also found that neither low-dose (50 mg/kg/d) nor high-dose (200 mg/kg/d) ascorbic acid improved 28-day mortality. At the same time, the effectiveness of anti-oxidative drugs in sepsis patients is also time-dependent. It has to be admitted that S. Y. Jung's research [59] on the 5-day ascorbic acid treatment of sepsis has great clinical significance. Intravenous ascorbic acid for $\geq$5 days were significantly associated with reduced hospitalization and 90-day mortality in patients with sepsis. Treatment with ascorbic acid for >5 days significantly improved survival compared with patients treated for 1–2 days or 3–4 days. (15.8% vs 18.8% vs 18.3%; $p < 0.001$).

It is not difficult to find that international guidelines are increasingly focusing on the use of antioxidants in patients with sepsis, and the two most recent international guidelines have supplemented the recommendations for the use of antioxidants in sepsis or septic shock. In the future, with the study of HAT therapy and the application of more antioxidants (such as melatonin, zinc-selenium mixture, glutathione, lipoic acid, etc.) to patients with sepsis, with the gradual advancement of clinical research, guidelines for the management of sepsis will give clear recommendations for antioxidant therapy.

9. Conclusions

According to current data of RCTs, antioxidant therapy, especially ascorbic acid, has a trend of improving short-term mortality in patients with sepsis, but the evidence remains to be further demonstrated.

Ethical approval

Review and/or approval by an ethics committee was not needed for this study because it is a systematic review and meta-analyse.

Funding

This research was supported by the Key R&D Program Projects of Zhejiang Province (2021C03072), the National Natural Science Foundation of China (82272201, 82272202), the General scientific research project of the Zhejiang Provincial Department of Education (Y202250204) and the key specialty of traditional Chinese Medicine of Zhejiang Provincial in the 13th Five-Year Plan period (Emergency Department), and Zhejiang Provincial interdisciplinary Traditional Chinese Medicine Innovation Team for the diagnosis and treatment of sepsis.

Data availability statement

All relevant data are within the manuscript and its supplementary files.

CRediT authorship contribution statement

Hui Pei: Writing – original draft, Supervision, Software, Formal analysis, Data curation. **Jie Qu:** Data curation. **Jian-Ming Chen:** Data curation. **Yao-Lu Zhang:** Data curation. **Min Zhang:** Data curation. **Guang-Ju Zhao:** Writing – review & editing. **Zhong-Qiu Lu:** Writing – review & editing, Supervision, Funding acquisition.

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.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29156.

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