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Efficacy of intravenous vitamin C intervention for septic patients: A systematic review and meta-analysis based on randomized controlled trials

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ABSTRACT

Background: The role of vitamin C in sepsis is still controversial, we aimed to systematically review the efficacy of intravenous vitamin C supplementation in the treatment of sepsis.
Methods: MEDLINE, EmBase, Web of Science, WanFang Data and CNKI were comprehensively searched to collect randomized controlled trails (RCTs) of vitamin C supplementation for patients with sepsis or sepsis shock from January 2000 to March 2021. Two researchers independently screened the literature, extracted the data and accessed the risk of bias in the included studies; meta-analysis was then performed by using Revman 5.4 software.
Results: A total of 10 RCTs involving 1400 participants were included. The results of meta-analysis showed that intravenous vitamin C supplementation can improve SOFA (ΔSOFA) within 72 h [RR = 1.32,95% CI(0.80,1.85), $P < 0.0001$] of septic patients. There were no difference on short term mortality (28–30d)[RR = 0.83,95% CI (0.65,1.05), $P = 0.11$], long term mortality (90d) [RR = 1.16,95% CI(0.82,1.66), $P = 0.40$], hospital LOS[RR = 0.15,95% CI(−0.73,1.03), $P = 0.55$], ventilator-free days[RR = 0.09,95% CI(−0.24,0.42), $P = 0.60$], ICU-LOS[RR = 0.22,95% CI(−0.13,0.57), $P = 0.22$], between two groups. The results of Subgroup analysis showed that intravenous vitamin C alone can reduce the risk of short term mortality (28–30d) [RR = 0.61,95% CI(0.47,0.79), $P = 0.0002$]of sepsis patients.
Conclusion: Based on current RCTs, our work indicated that mono-intravenous vitamin C therapy may reduce short-term mortality of sepsis patients, and it may protect organ functions. Due to the limitation of the quantity and quality of included studies, the above conclusions need to be verified by more large scale and high quality randomized control trials.

1. Background

Sepsis is a devastating clinical syndrome that often leads to organ failures and death among patients admitted to intensive care units [1]. According to data from the World Health Organization (WHO), approximately 49 million people suffer from sepsis per year, resulting in 11 million deaths [2]. Although many new drugs have been introduced to sepsis therapy during the past decade, the mortality rate has not been reduced de facto [3-6]. Considering the high mortality of sepsis and limited therapy options, more effective treatments are urgently needed.

Recently, emerging evidence indicated that the application of vitamin C is a potentially effective therapy for sepsis. Vitamin C, also

Abbreviations: RCT, randomized controlled trail; WHO, World Health Organization; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; ICU, intensive care unit; LOS, length of stay; MeSH, medical subheading; RR, relative risk; SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology, and Chronic Health Evaluation.

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known as ascorbic acid, plays an important physiological and metabolic role in the sepsis process. It can regulate the pro-inflammatory and coagulation gene expression, orchestrate the immune system and circulate cytokine homeostasis [7-10]. An increasing number of studies have shown that the plasma vitamin C concentration in critically ill patients is usually below normal level, especially in patients with sepsis [11-13]. Depletion of vitamin C is associated with a higher incidence of organ failures and poorer prognosis in sepsis patients [14].

Numerous clinical studies have been conducted to exam the efficacy of intravenous vitamin C for treating sepsis. In 2014, Fowler et al. conducted a phase I clinical trial and found that exogenous vitamin C administration may improve inflammatory biomarker levels and prevent multi-organ failures [13]. In addition, a cohort study published in 2020 also found that intravenously administrated high doses of vitamin C was associated with mortality reduction in patients with septic shock [15]. However, subsequent studies on the effect of vitamin C for sepsis patients have reached different conclusions [16-18]. We performed a systematic review and meta-analysis based on RCTs to identify the efficacy of vitamin C supplementation in patients with sepsis as an attempt to resolve the controversies.

2. Materials and methods

2.1. Inclusion and exclusion criteria

We follow the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines to conduct this review [19,20]. The inclusion criteria were as follows:

- Study population: Patients diagnosed with sepsis or septic shock according to the diagnostic criteria of sepsis-3 [1,21]
- Intervention: Vitamin C alone or in combination with other drugs, vs placebo or standard regimen
- Study design: RCTs
- Outcomes measure:
  - o Primary outcomes were short term mortality (28-30d) and long-term mortality (90d).
  - o Secondary outcomes: change in SOFA (ΔSOFA) within 72 h after experimental intervention (ΔSOFA within 72 h = SOFA score after initial enrolment - SOFA score after 72 h), ventilator-free days, hospital and intensive care unit (ICU) length of stay(LOS).

Cohort studies, case reports, reviews, abstracts from conferences, animal experiments and studies published prior to 2000 were excluded. In addition, RCTs with fewer than 10 participants, were also excluded.

2.2. Literature retrieval and selection

We conducted a comprehensive systematic search of online databases for literature from January 2000 to March 2021 including MEDLINE (through PubMed), EmBase, Web of Science, WanFang Data and CNKI, for RCTs investigating the role of vitamin C in adult patients with sepsis or septic shock. Terms were searched in medical subheading (MeSH) and free terms searched in PubMed. The published language was limited in English and Chinese. English MeSH terms include "sepsis", "septic shock", "ascorbic acid" and "Vitamin C". Chinese terms include "nong du zheng", "nong du zheng xiu ke", "wei sheng su C", "kang huai xue suan". We also reviewed the references of included articles and related systematic reviews to identify additional studies. Two authors independently screened the titles, abstracts, and full texts of the included articles. Any discrepancy between the findings was settled by a third reviewer. The search strategy employed in the PubMed database is shown in Table 1.

Table 1
Strategy for search in PubMed.

#1	sepsis: ti, ab, kw OR septicemia: ab, ti OR septicemias: ab, ti OR 'poisoning, blood': ab, ti OR 'blood poisoning': ab, ti OR 'blood poisonings': ab, ti OR 'severe sepsis': ab, ti OR 'sepsis, severe': ab, ti OR bacteremia: ab, ti OR 'hemorrhagic septicemia': ab, ti OR septic*:ab, ti OR 'inflammatory response syndrome*': ab, ti
#2	'shock, septic': ti, ab, kw OR 'septic shock': ab, ti OR 'shock, toxic': ab, ti OR 'toxic shock syndrome': ab, ti OR 'shock syndrome, toxic': ab, ti OR 'toxic shock syndromes': ab, ti OR 'toxic shock': ab, ti OR 'shock, endotoxic': ab, ti OR 'endotoxin shock': ab, ti OR 'endotoxin shocks': ab, ti OR 'shock, endotoxin': ab, ti OR 'shocks, endotoxin': ab, ti
#3	'Ascorbic acid': ti, ab, kw OR 'acid, ascorbic': ab, ti OR 'L-ascorbic acid': ab, ti OR 'acid, l-ascorbic': ab, ti OR 'l ascorbic acid': ab, ti OR 'vitamin c': ab, ti
#4	#1 OR #2
#5	#3 AND #4

2.3. Data extraction and quality assessment

Data extraction and the evaluation of literature quality were conducted independently by two investigators (L.T. and Y. GY.). We recorded all available information, including baseline details, the primary outcomes (short term mortality (28-30d), long term mortality (90d)), and the secondary outcomes (ΔSOFA within 72 h, Hospital LOS, ICU-LOS, and ventilator-free days). The quality of RCTs was evaluated by two reviewers according to the modified Jadad scoring scale for RCTs [22]. The scale included four items: randomization, randomization concealment, blinding, withdrawals and dropouts. The full score of this scale was 7 points, and when the score was ≥4 points, it was considered to be of high quality. Otherwise, it was considered to be of low quality. Any disagreement was resolved by a senior investigator (H.J.)

2.4. Statistical analysis

When the mean and variance data for the outcome variables were not available, we estimated the mean and standard deviation from reported median and interquartile ranges using a standard approach [23,24]. The analytical statistics of relative risk (RR) and standardized mean difference (SMD) at 95% confidence intervals (95% CIs) were used to determine the clinical outcomes of Vitamin C supplementation with septic patients for dichotomous and continuous outcomes, respectively. Statistical heterogeneity among the included research was analyzed using the Chi^2 test (the test level was $\alpha = 0.05$) and I square (I^2) statistic [25], in which $I^2 > 50\%$ suggested significant heterogeneity across studies. And when heterogeneous results appeared, a random-effects model was chosen to pool the results. Otherwise, a fixed-effects model was used. In addition, subgroup analysis was performed according to the confounding factors of patient type and therapeutic regimen. We also performed sensitivity analysis by the sequential removal of trials for each outcome. In addition, funnel plots are performed to evaluate whether the intervention measures have small study effect or publication bias [26]. RevMan version 5.4 software was used for data analysis.

3. Results

3.1. The search process and study selection

An initial search identified a total of 932 articles from databases. After reviewing for inclusion and exclusion and the removal of duplication, 35 studies were eligible for full text screening, ten studies were finally included final analysis with 1400 patients (Fig. 1).

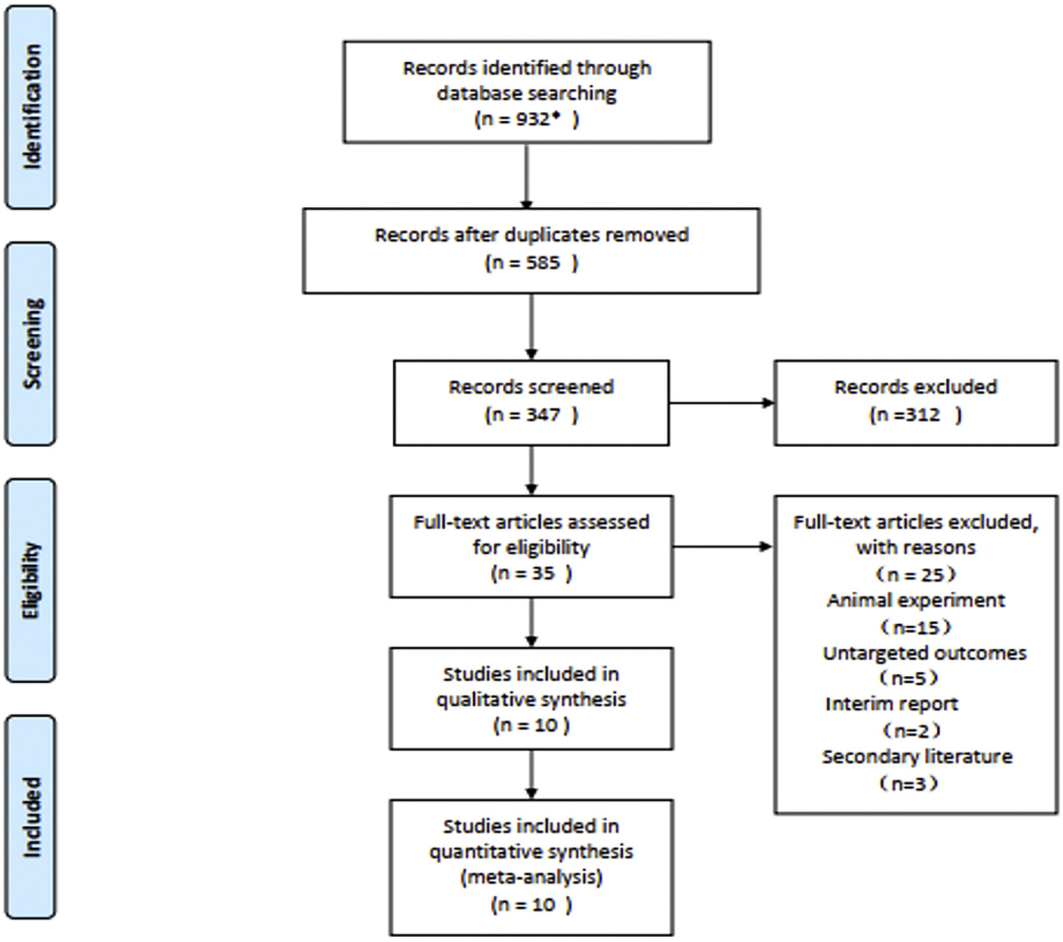

Fig. 1. Research result.
*Name of database and number of literatures searched: PubMed ($n = 425$); EMbase ($n = 346$); Web of Science (109); CNKI ($n = 27$); WanFang Data ($n = 25$).

3.2. Summary of included studies and the results of study quality assessment

Ten eligible studies were published between 2019 and 2020. They were from United States (2), India (2), Korea (1), Australia (1), and China (4). The range of age of the study participants was varied (30.0 to 71.9), with roughly equal ratios of men to women. The range of Sequential Organ Failure Assessment (SOFA score) and Acute Physiology, and Chronic Health Evaluation (APACHE II score) at enrolment in these participants were varied (6.97 to 12.38, 18.5 to 24.9, respectively). Outcomes reported in studies included short term mortality (28–30d), long term mortality (90d), ΔSOFA within 72 h, Hospital LOS, ICU-LOS and ventilator-free days. Detailed baseline characteristics of the evaluated studies are summarized in Table 2.

All included studies were described as randomized controlled trials. All studies reported the number of patients who dropped out, and the results are shown in Table 3. According to the criteria of modified Jadad scoring scale, eight of the studies (8/10) were considered to be high quality while two (2/10) were considered to be low quality.

3.3. Clinical outcomes

3.3.1. Mortality

3.3.1.1. Short term mortality (28–30d). Fig. 2 shows the effect of vitamin C supplementation on short term mortality. A total of 8 RCTs were included, including 613 patients in the experimental group and 602 patients in the control group. There was heterogeneity ($I^2 = 40\%$) among the studies, so the random effect model was used. The pooled result showed vitamin C intervention has a tendency to reduce short term mortality (28–30d), but it was not statistically significant[RR = 0.83,95% CI(0.65,1.05), $P = 0.11$].

3.3.1.2. Long term mortality (90d). Fig. 3 shows the effect of vitamin C supplementation on long term mortality. A total of 2 RCTs were included, including 158 patients in the experimental group and 160 patients in the control group. There was no statistical heterogeneity between the studies, so the fixed effect model was used. The combined result showed that long term mortality (90*d*) of Vitamin C group was not statistically significant compared to the control group [RR = 1.16,95% CI(0.82,1.66), $P = 0.40$].

3.3.2. ΔSOFA within 72 h

Fig. 4 shows the effect of vitamin C supplementation on theΔSOFA within 72 h, including 471 patients in the experimental group and 453 patients in the control group. There was significant heterogeneity ($I^2 = 88\%$) among the studies, so the random effect model was used. The ΔSOFA within 72 h was 1.32 (95% CI (0.80, 1.85), $p < 0.01$), indicating that vitamin C supplementation did significantly improve the change in SOFA within 72 h.

3.3.3. Ventilator-free days

Fig. 5 shows the effect of vitamin C supplementation on ventilator-free days, including 222 cases in the experimental group and 226

Table 2
Characteristics of participants in trials.

Study ID	Country	Sepsis diagnostic Criteria	Research period	Sample size(T /C)	Patient Type	Male% (T/C)	Age (T/C)	SOFA score at enrolment (T/C)	APACHE II score at enrolment (T/C)	Intervention (T/C)	
Hwang 2020 [27]	Korea	Sepsis3.0	2018.12–2020.1	53/58	septic shock	37.7/37.9	70 (62–76)/69 (62–74)	8 (6–10)/8 (6–10)	22(14–32)/22(17–32)	vitamin C + thiamine	placebo
Chang 2020 [28]	China	Sepsis3.0	2017.12–2019.1	40/40	sepsis and septic shock	57.5/52.5	59.5 ± 15.0/63.7 ± 12.8	9.6 ± 4.5/10.1 ± 4.0	22.1 ± 8.4/23.8 ± 7.6	hydrocortisone +vitamin C + thiamine	placebo
Moskowitz2020 [29]	USA	Sepsis3.0	2018.2–2019.11	101/99	septic shock	56.4/ 54.6	68.9 ± 15.0/67.7 ± 13.9	9.1 ± 3.5/9.2 ± 3.2	–	vitamin C + thiamine	placebo
Iglesias 2020 [30]	USA	Sepsis3.0	2018.2–2019.8	68/69	sepsis or septic shock	47/39	70 ± 12/67 ± 14	8.3 ± 3/7.9 ± 3.5	24 ± 7.6/24.9 ± 8.7	hydrocortisone + vitamin C + thiamine	placebo
Wani 2020 [31]	India	Sepsis3.0	2018.08–2019.06	50/50	sepsis and septic shock	56/62	59(25–72)/56 (25–72)	9.22 ± 3.54/9.36 ± 3.66	18.5 (15–24.75)/20 (15–24)	vitamin C + hydrocortisone + thiamine	conventional therapy
Lv 2020 [32]	China	Sepsis3.0	2017.06–2019.05	61/56	sepsis	49.2/51.8	58.7 ± 14.3/60.2 ± 14.1	8.6 ± 2.9/8.9 ± 3.1	21.0 (19.0, 28.0)/23.0 (20.0, 29.0)	vitamin C	placebo
Fujii 2020 [33]	Australia	Sepsis3.0	2018.05–2019.06	107/104	septic shock	63.6/62.5	61.9 ± 15.9/61.6 ± 13.9	8.6 ± 2.7/8.4 ± 2.7	–	vitamin C + thiamine	hydrocortisone
Mohamed2020 [34]	India	Sepsis3.0	2018.6–2019.8	43/45	sepsis	69/74	58.69 ± 14.89 59.37 ± 15.01	11.22 ± 2.99 10.89 ± 3.82	–	vitamin C + thiamine + hydrocortisone	standard treatment
Niu2019 [35]	China	Sepsis3.0	2017.6–2018.5	122/112	sepsis	48.4/50.9	58.2 ± 14.1/60.1 ± 14.2	8.3 ± 2.7/8.7 ± 2.9	22.0(18.0, 29.0)/24 (19.0,29.0)	vitamin C	placebo
Chen2020 [36]	China	Sepsis3.0	2016.6–2019.1	39/41/42	sepsis	71.79/80.49/64.29	67.38 ± 17.34/69.00 ± 13.49/ 71.95 ± 16.59	6.97 ± 2.65/6.32 ± 2.52/6.31 ± 2.83	19.56 ± 6.00/18.46 ± 5.06/18.14 ± 5.66	vitamin C	placebo

Abbreviations: T, treatment group; C, control group; SOFA, Sepsis-Related Organ Failure Assessment, APACHE II, Acute Physiology, and Chronic Health Evaluation, IQR, interquartile range.
The data are the mean ± SD or median (IQR), (−) mean ± SD or median (IQR) is not provided.

Table 3
Modified Jadad scores of the included studies.

Study ID	Randomization	Randomization concealment	Blinding	Withdrawals and dropouts	Total points
Sung2020	2	2	2	1	7
Chang2020	1	0	2	1	4
Moskowitz2020	2	2	2	1	7
Iglesias2020	2	2	2	1	7
Wani2020	1	0	0	1	2
Lv2020	2	1	0	1	4
Fujii2020	2	2	0	1	5
Mohamed2020	2	1	0	1	4
Niu2020	1	1	0	1	3
Chen2020	2	1	0	1	4

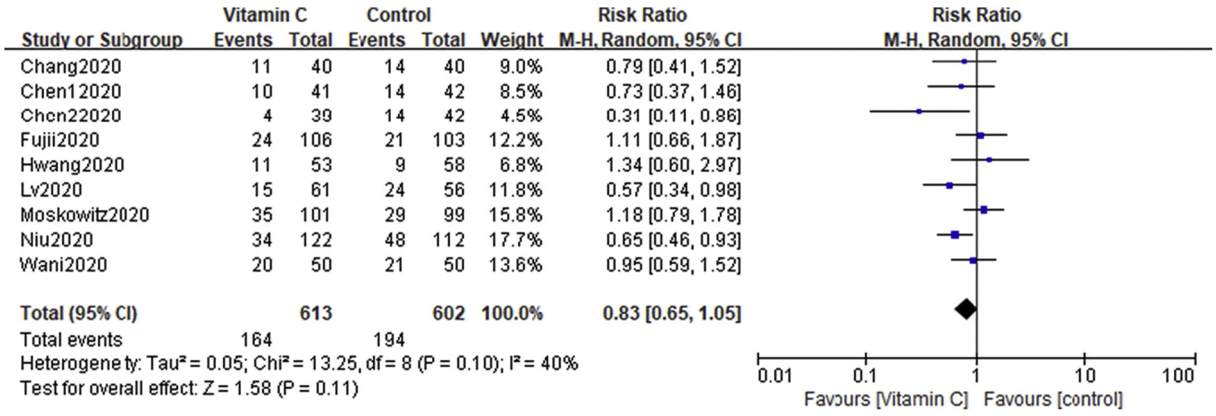

Fig. 2. Forest plot of short term mortality (random effects model).

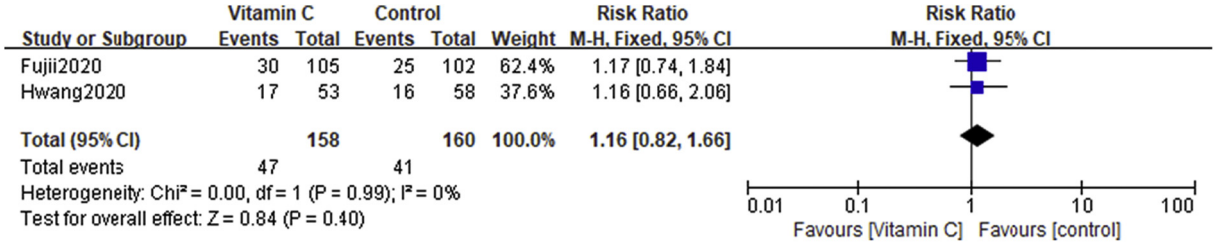

Fig. 3. Forest plot of long term mortality (fixed effects model).

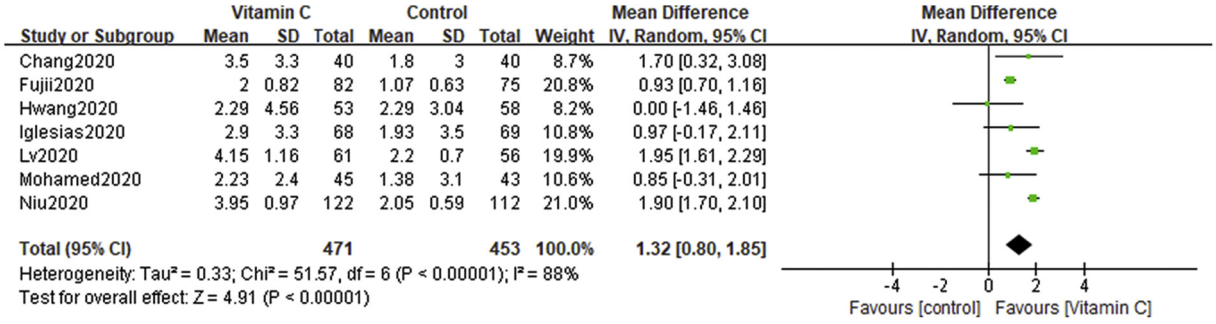

Fig. 4. Forest plot ofΔSOFA within 72 h (random effects model).

cases in the control group. There was no statistical heterogeneity between the studies, so the fixed effect model was used. Meta-analysis results showed that the ventilator-free days of vitamin C group was not statistically significant compared with the control group [RR = 0.09,95% CI(−0.24,0.42), $P = 0.60$].

3.3.4. ICU LOS

Fig. 6 shows the effect of vitamin C supplementation on ICU LOS, including 260 cases in the experimental group and 260 cases in the control group. There was no statistical heterogeneity between the studies, so the fixed effect model was used. Meta-analysis results

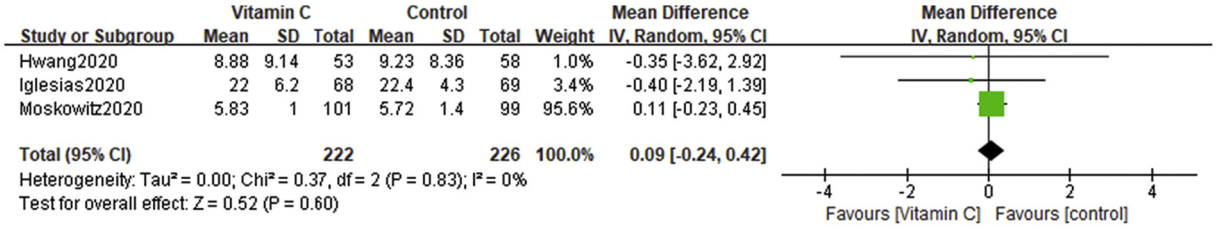

Fig. 5. Forest plot of ventilator-free days (fixed effects model).

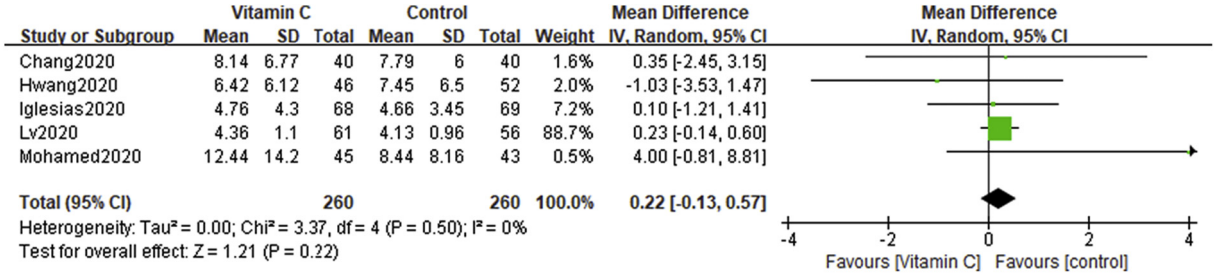

Fig. 6. Forest plot of ICU LOS (fixed effects model).

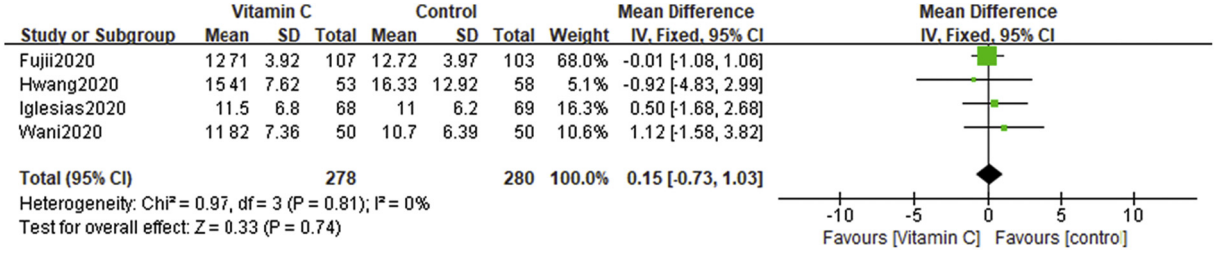

Fig. 7. Forest plot of Hospital LOS (fixed effects model).

showed that the ICU LOS of Vitamin C group was not statistically significant compared to the control group [RR = 0.22,95% CI (−0.13,0.57), $P = 0.22$].

3.3.5. Hospital LOS

Fig. 7 shows the effect of Vitamin C supplementation on the Hospital LOS, including 278 cases in the experimental group and 280 cases in the control group. There was no Statistical heterogeneity between the studies, so the fixed effect model was used. Meta-analysis results showed that the Hospital LOS of Vitamin C group was not statistically significant compared to the control group [RR = 0.15,95% CI(−0.73,1.03), $P = 0.55$].

3.4. Subgroup analysis

Subgroup analyses were performed for short term mortality, according on the patient type and vitamin C administration strategy. The short term mortality for the "vitamin C alone" subgroup was found to be lower than that of the "vitamin C plus Thiamine" and "vitamin C plus thiamine plus hydrocortisone" subgroup (Fig. 8). In addition, the subgroup analysis for short term mortality according to patient type showed that the short term mortality for the "sepsis" subgroup was significantly lower than that of the "sepsis and septic shock" and "septic shock" subgroup (Fig. 9).

3.5. Sensitivity analysis

Sensitivity analysis was conducted for results with heterogeneity by removing each study from the analysis. The results indicated that the remove of Moskowitz et al. [29] study from the analysis of short term mortality decreased the pooled effect estimate by 6% from 0.83[0.65, 1.05] ($P = 0.1$, $I^2 = 40\%$) to 0.77 [0.61, 0.98] ($P = 0.03$, $I^2 = 28\%$). This suggested that vitamin C supplementation may reduce the risk of short-term mortality. We analyzed the data from the Moskowitz et al. study in-depths and found two differences between this study and the others: 1) It was a multi-center RCT that contain heterogeneity of population races; 2) The enrollment of participants had not considered the previous Vitamin C deficiency level. These factors may contribute to clinical heterogeneity; thus, the exclusion of this trial significantly decreases the I^2. Sensitivity analysis for ΔSOFA within 72 h showed that the overall estimate was not influenced by the elimination of any included studies, and that the result of ΔSOFA within 72 h was robust. In addition, sensitivity analysis was performed based on the quality of the included studies for short term mortality. Two low quality studies [31,35] were excluded and the remaining trials were pooled. Seven trials were included, and heterogeneity was found ($I^2 = 44\%$). Random model was used to pooled data. Results indicated that intravenous vitamin C has a tendency to reduce short term mortality (28-30d), but it was not statistically significant [RR = 0.85,95% CI (0.62,1.16), $P = 0.29$]. This result is consistent with the overall analysis results. For sensitivity analysis results see Supplemental file 1.

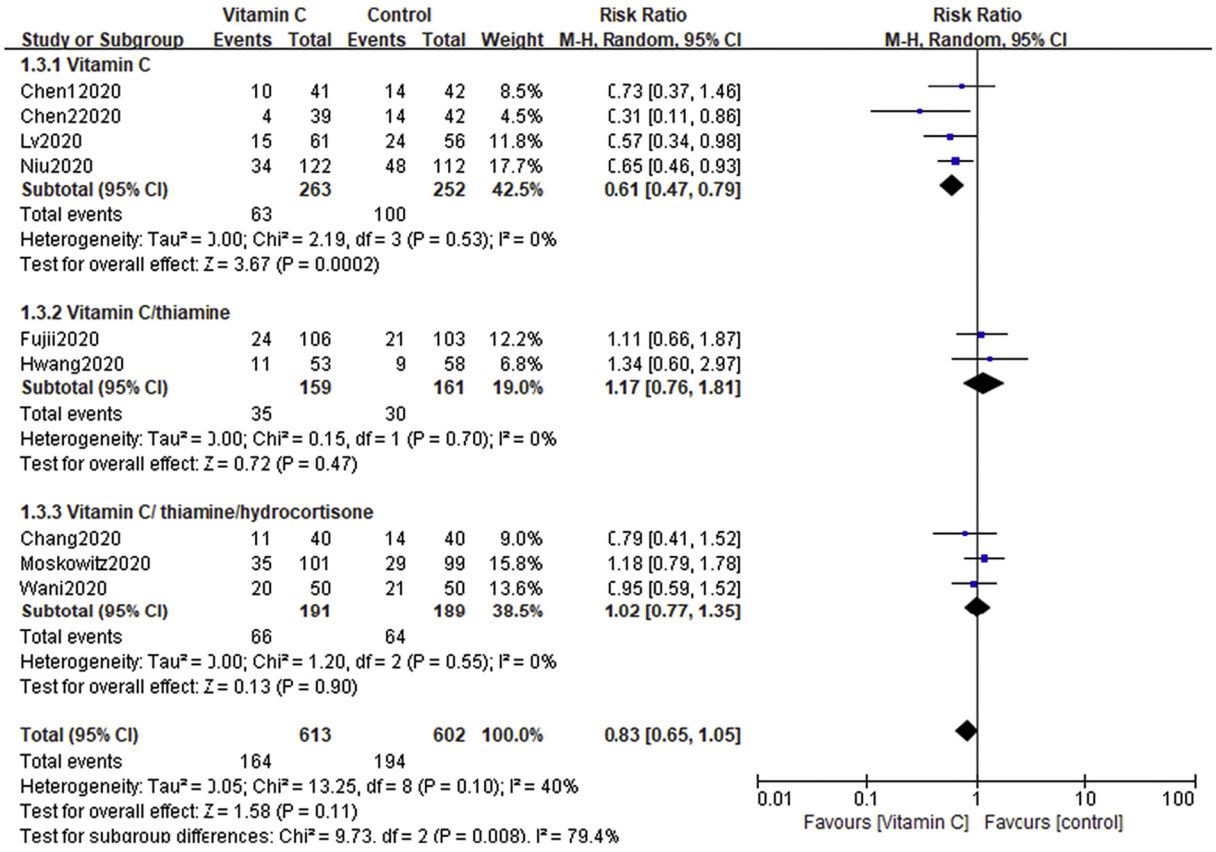

Fig. 8. Vitamin C administration subgroup analysis of short term mortality forest plot.

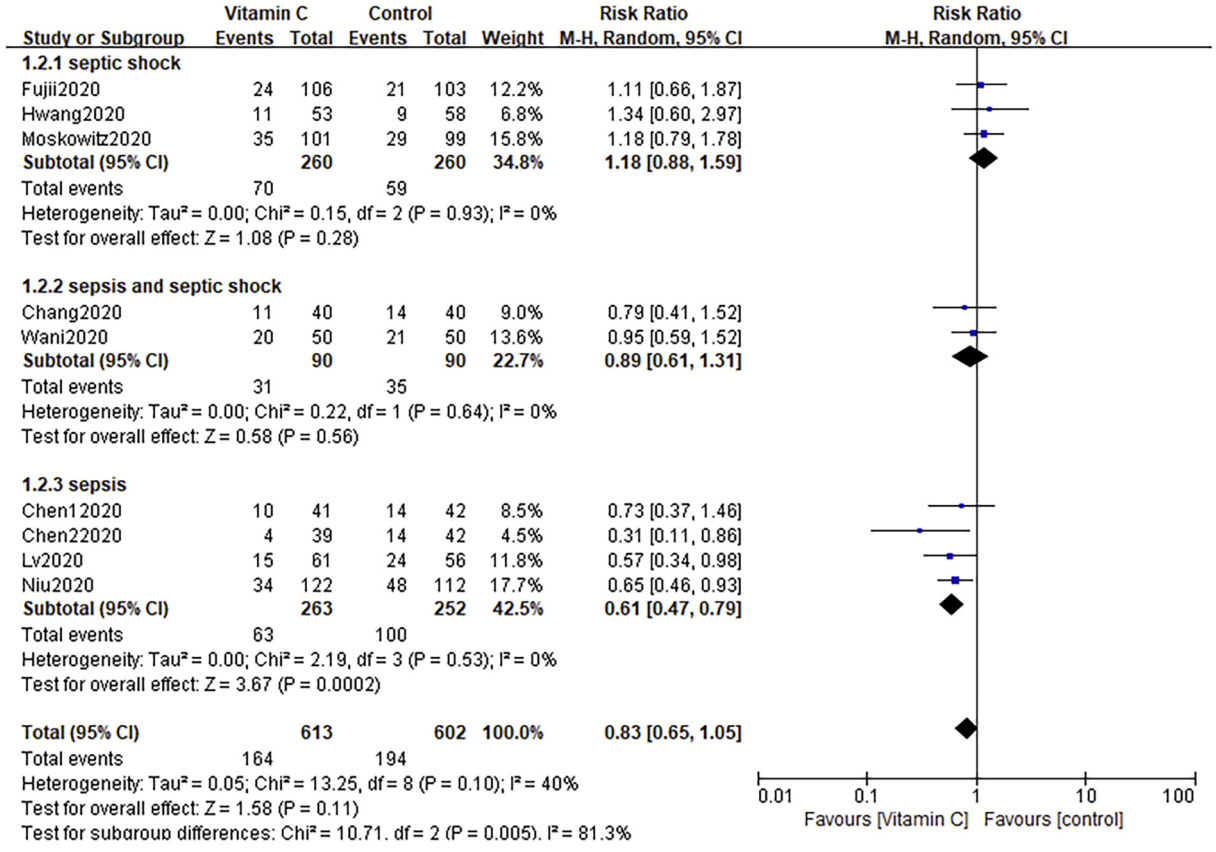

Fig. 9. Patient type subgroup analysis of short term mortality forest plot.

3.6. Publication bias

Funnel plots used to evaluate publication bias were symmetrical indicating that there were no publication biases discovered. For funnel plots of all outcomes see Supplemental file 1.

4. Discussion

In our systematic review and meta-analysis, we evaluated the effect of intravenous vitamin C on mortality (28–30d, 90d) and secondary outcomes in 10 studies, including 1400 patients with sepsis or septic shock. The overall meta-analysis results indicated that intravenous vitamin C can improve ΔSOFA within 72 h, but have no effect on hospital LOS, ventilator-free days, ICU-LOS, and mortality (28–30d, 90d). These results are consistent with earlier systematic reviews [37,38]. However, subgroup results suggest that intravenous vitamin C alone (not combined with steroids or other antioxidant) is associated with reducing short term mortality [25]. This effect was first explored by our study. Previous meta-analyses pooled cohort studies and randomized controlled trials with low quality together, thus the effect of confounding is inevitable. In addition, these meta-analyses ignored factors that may influence the outcomes, e.g., combination of corticosteroids and the severity of patients (pooled septic shock patients and sepsis patients together). It is well known that the use of glucocorticoids not only inhibited the inflammatory response, but also disturbed the body's immune response [39]. In addition, sepsis is caused by a range of factors and is a highly heterogeneous clinical syndrome. When sepsis progresses to septic shock, the patients' condition becomes more severe. In this circumstance, no matter what treatments were employed, it is difficult to reverse the condition. Thus, our study identified these confounders and excluded them from sub-analysis and reached to a result that is likely approaching the true effect of vitamin C administration.

Compared with earlier published systematic reviews and meta-analyses, our study has the following advantages: 1) we enrolled only randomized control trials that excluded the effects which minimized the selection bias from non-randomized study; 2) we carefully identified the confounders/heterogeneity sources among enrolled RCTs and found that only vitamin C monotherapy for sepsis patients provided clinical benefits; 3) we included studies based on sepis-3.0 as the diagnostic criteria, which reduced the clinical heterogeneity caused by different diagnostic criteria.

Our study has several limitations. First, heterogeneity is still a challenge. It turned out that patients in various stages of the disease were the sources of heterogeneity. Therefore, we have done subgroup analysis by pooling patients with similar clinical characteristics. However, heterogeneity still existed. We believe that this result may be related to the complexity of sepsis patients, with different disease courses leading to greater heterogeneity in our study. Second, several articles did not report the standard deviation of the outcomes. We applied data reduction method to restore it, but there was a certain deviation from the real value, causing the combined results to be potentially unstable. Finally, the intervention groups and the control groups were enrolled at various stages of sepsis progression and may affect the combined results. We also considered that different doses of vitamin C administration may be associated with different effects. In most studies, doses as high as 1 to 2 g q8h of vitamin C were administered intravenously. Unfortunately, the absence of dosing data from some of studies limited our dose-effect relation analysis.

5. Conclusion

Based on current RCTs, we can conclude that mono-intravenous vitamin C therapy may reduce short term mortality of sepsis patients, and it may protect organ functions. Due to the limitation of the quantity and quality of included studies, the above conclusions need to be verified by more large scale and high-quality randomized control trials.

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Author contributions

TL and HJ conducted the study design and drafting of the systematic review. GYY, DHL and HFD performed literature search and data retrieval. KW supplied statistical analysis. JZ contributed to the subsequent revisions of the manuscripts. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

This study does not contain individual data.

Competing interests

The authors declared that they do not have conflicting interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2021.08.012.

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