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ORIGINAL ARTICLE

Parenteral Vitamin C in Patients with Severe Infection: A Systematic Review

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Abstract

BACKGROUND Inflammation and oxidative damage caused by severe infections may be attenuated by vitamin C.

METHODS We conducted a systematic review of randomized controlled trials (RCTs) of parenteral vitamin C as combined therapy or monotherapy versus no parenteral vitamin C administered to adults hospitalized with severe infection. The primary outcome was mortality. We performed random-effects meta-analyses and assessed certainty in effect estimates.

RESULTS Of 1547 citations, 41 RCTs (n = 4915 patients) were eligible for inclusion. Low-certainty evidence suggested that vitamin C may reduce in-hospital mortality (21 RCTs, 2762 patients; risk ratio, 0.88 [95% confidence interval (CI), 0.73 to 1.06]), 30-day mortality (24 RCTs, 3436 patients; risk ratio, 0.83 [95% CI, 0.71 to 0.98]), and early mortality (before hospital discharge or 30 days; 34 RCTs, 4366 patients; risk ratio, 0.80 [95% CI, 0.68 to 0.93]). Effects were attenuated in sensitivity analyses limited to published blinded trials at low risk-of-bias (in-hospital mortality: risk ratio, 1.07 [95% CI, 0.92 to 1.24], moderate certainty; 30-day mortality: risk ratio, 0.88 [95% CI, 0.71 to 1.10], low certainty; and early mortality: risk ratio, 0.88 [95% CI, 0.73 to 1.06], low certainty). For 90-day mortality, all trials had low risk-of-bias; moderate-certainty evidence suggested harm (five RCTs, 1722 patients; risk ratio, 1.07 [95% CI, 0.94 to 1.21]). Moderate-certainty evidence suggested an increased risk of hypoglycemia (risk ratio, 1.20 [95% CI, 0.69 to 2.08]). Effects on other secondary outcomes were mixed and informed by low-certainty evidence. No credible subgroup effects were observed for mortality related to cointerventions (monotherapy vs. combined therapy), dose, or type of infection (Covid-19 vs. other).

CONCLUSIONS Overall, evidence from RCTs does not establish a survival benefit for vitamin C in patients with severe infection. (PROSPERO number, CRD42020209187.)

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Introduction

Severe infections manifest with inflammation and oxidative damage.[1] Vitamin C (ascorbic acid) deficiency has been reported in patients with severe infection.[2-4] Preclinical evidence suggests that vitamin C supplementation may reduce endothelial injury in the pulmonary and systemic vasculature, oxidative damage, and harmful inflammation.[5] Critically ill patients and those with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have low plasma vitamin C levels,[6,7] and the World Health Organization (WHO) has included vitamin C among candidate therapies for coronavirus disease 2019 (Covid-19).[8]

Randomized controlled trials (RCTs) evaluating the effectiveness of vitamin C supplementation for severe infections, either alone or in combination with other therapies such as glucocorticoids and thiamine, have yielded varied results[9-12]; systematic reviews have also shown variable effects.[13-17] The recent publication of results from LOVIT (Lessening Organ Dysfunction with Vitamin C), the largest trial to date addressing this question, justifies a comprehensive re-examination of the evidence.[18]

Our objective was to systematically review the literature and assess the efficacy and safety of parenteral vitamin C administration, as monotherapy or in combination with other therapies, in adult patients with severe infections, including Covid-19.

Methods

Our systematic review and meta-analysis adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines (Table S1 in the Supplementary Appendix).[19] The review protocol is publicly available.[20]

SEARCH

We searched the following databases from inception to March 25, 2022: Ovid MEDLINE Daily and MEDLINE (from 1946), EMBASE (from 1974), CINAHL (from 1984), Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. We also searched the WHO COVID-19 database (formerly the U.S. Centers for Disease Control COVID-19 database) from inception to March 25, 2022. For the latter, we exported all Covid-19–related articles into a reference database, used keyword searching with "vitamin C" and "ascorb" to filter studies evaluating vitamin C and used a second filter to identify RCTs (additional material in the Supplementary Appendix). No language restrictions were applied.

We did not explicitly search for gray literature[21]; however, we included conference abstracts and unpublished data retrieved in our searches. We also identified additional trials from clinical experts within and beyond the review team and from other recent systematic reviews.[13-17,22-40]

ELIGIBILITY CRITERIA

We included parallel-group RCTs evaluating adults 18 years of age or older with severe infection that compared at least one arm treated with parenteral vitamin C to at least one arm without. Severe infection was defined as the presence of suspected or microbiologically confirmed infection, including Covid-19, requiring hospitalization. We specified this population, rather than sepsis as defined by consensus criteria,[41] to encompass trials enrolling severely ill patients hospitalized due to infection in settings where consensus sepsis criteria may not be routinely applied. We included studies with 80% of patients or more meeting this population definition, in addition to trials including patients with acute respiratory distress syndrome in which severe infection was the primary underlying etiology. We considered administration of parenteral vitamin C in any regimen, alone or in combination with other therapies, at any dose greater than 100 mg per day to be eligible.

Our prespecified primary outcome was mortality, measured at three time points: before hospital discharge, at 30 days, and at 90 days. We used outcome data reported within a 5-day window of our time points of interest where necessary. Because hospital discharge and 30 days were both considered to represent similar time points for mortality measurement after an intervention for an acute condition, we conducted a post hoc analysis of "early" mortality by adding 30-day mortality data to the meta-analysis of hospital mortality for studies not reporting the latter. Secondary outcomes included use of and duration of intensive care unit (ICU) admission and invasive mechanical ventilation, duration of hospitalization, time to clinical improvement using change in WHO 7-point ordinal scale scores for clinical status[42] or other severity measures, 72-hour change in Sequential Organ Failure

Assessment (SOFA) score from baseline,[43] stage 3 acute kidney injury based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria,[44] use of renal replacement therapy, serious adverse events leading to discontinuation of vitamin C, and specific prespecified adverse events (hemolysis, nephrolithiasis, and hypoglycemia). These adverse events were selected based on prior reports[45]; hypoglycemia may occur following insulin administration for factitious hyperglycemia detected on many hospital glucometers.[46,47] The time point of interest for all secondary outcomes was 30 days (except 72 hours or 3 days for SOFA scores), or the closest available.

STUDY SELECTION

Paired reviewers conducted title and abstract screening and full-text screening independently and in duplicate, with discrepancies resolved by discussion or adjudication by a third reviewer. Screening was completed using standardized forms and predefined eligibility criteria.

DATA EXTRACTION AND RISK-OF-BIAS ASSESSMENT

Data were extracted on publication characteristics, baseline demographic and clinical characteristics, intervention and control arms, outcomes, and reported subgroup analyses. We classified vitamin C dosing as high (>12 g per day), moderate (6-12 g per day), and low (<6 g per day).[48] In studies using a weight-based regimen of vitamin C, we used the mean patient weight to calculate a total daily dose; if not provided, we assumed 70 kg as the mean body weight. For trials with multiple vitamin C arms, we combined data across arms for the main analysis.[49,50] For one trial with two control groups without vitamin C, we combined data from both control groups.[51] In subgroup analyses by vitamin C dose, we combined vitamin C regimens in trials randomly assigning patients to one or more dosing regimens where both regimens fell into the same dose band. When vitamin C arms fell into different dose bands,[49] we split patients in the control group to avoid counting patients twice.[52]

Paired reviewers conducted data extraction and risk-of-bias assessments independently and in duplicate using standardized and piloted forms, with consensus reached by discussion. We used a modified version of the Risk of Bias 2.0 tool (adapted from the tool used in a recent living network meta-analysis[53]) for outcome-level assessments of every eligible study (Table S2). Risk-of-bias was classified as low, probably low, probably high, or high for every outcome based on randomization, deviations from the intended intervention, missing outcome data, measurement of the outcome, selection of the reported result, and other considerations. We rated the overall risk-of-bias as the highest risk attributed to any domain. A third reviewer (A.A. or N.K.J.A.) independently verified extracted data and risk-of-bias assessments.

CERTAINTY OF EVIDENCE

We rated overall certainty in evidence for each outcome of interest using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework, based on risk-of-bias, imprecision, inconsistency, indirectness, and publication bias. For the outcome of mortality, we did not rate down for risk-of-bias when the sole concern was lack of patient or health care provider blinding.[54] When point estimates suggested an appreciable intervention effect, we rated down for imprecision when the 95% confidence interval (CI) crossed the threshold of no effect. When point estimates were close to the null, we rated down for imprecision if the 95% CI crossed, for binary outcomes, thresholds of an increase or reduction in mortality of 0.5% and, for duration outcomes, 1 day.[55] For other outcomes, we rated down for imprecision when the 95% CI crossed the threshold of no effect. Overall certainty of evidence was rated as very low, low, moderate, or high.[56] We described treatment effects using GRADE-recommended language.[57] We rated the credibility of effect modification analyses using a validated instrument.[58]

STATISTICAL ANALYSES

Inverse variance random-effects meta-analyses were performed in RevMan 5.3 (Cochrane Collaboration); selected analyses were verified using R 4.0.3 (R Foundation for Statistical Computing). Dichotomous outcomes are presented as risk ratios and absolute differences (using a pooled control group event rate) and continuous outcomes as mean differences (MDs), with 95% CIs. For rare outcomes of serious adverse events leading to discontinuation and hemolysis, effects are summarized using risk differences (RDs).[59] We interpreted two-sided $P<0.05$ as statistically significant.

We assumed a normal distribution for continuous outcomes and converted medians to means and interquartile ranges to SDs.[60] We estimated the change in SOFA score between baseline and 72 hours using available scores at both times and assuming a correlation of 0.4 (or higher if required) between the scores to calculate the SD of the change score[61]; day 1 data were taken as baseline data

when other data labeled as baseline were not explicitly provided. We assessed heterogeneity between studies using I^2 and visual inspection of forest plots,[62,63] and publication bias by visual inspection of funnel plots with 10 trials or more.

SUBGROUP AND SENSITIVITY ANALYSES

We conducted three prespecified subgroup analyses: high-dose versus moderate-dose versus low-dose vitamin C (as defined above; hypothesis: greater effect in the high-dose group); vitamin C as monotherapy versus combination therapy with other interventions (hypothesis: no difference in effect); and treatment of patients with Covid-19 versus other severe infection (hypothesis: no difference in effect). We conducted several post hoc analyses. First, we merged data from studies evaluating moderate- and low-dose regimens as lower dose regimens compared with high-dose regimens (hypothesis: greater effect in high-dose group). Second, we assessed the treatment effect on mortality, and conducted a separate GRADE assessment, in low risk-of-bias trials published in full text, with blinding of patients, health care providers, and study personnel. The rationale was twofold: first, study methods are more difficult to ascertain when only abstracts are available; and second, recent meta-epidemiologic research suggests greater treatment effects for mortality in unblinded trials.[64] This approach replaced our prespecified sensitivity analyses limited to trials published in full text and at low risk-of-bias, which for the outcome of mortality could include unblinded trials. Third, where 72-hour data for SOFA were missing, we also incorporated change in SOFA from baseline to 96 hours[11,51] in the meta-analysis of change in SOFA from baseline to 72 hours. Fourth, we excluded trials where day 1 SOFA data were plausibly recorded after randomization rather than representing a true baseline.[51,65-69] Finally, in the subset of trials reporting 90-day mortality, we also assessed the effect on early mortality.

DEVIATIONS FROM THE PROTOCOL

We did not consider the outcomes of vasopressor-free days, renal replacement therapy-free days, invasive ventilation-free days, or new infectious complications due to sparse data or variable definitions of these outcomes among included trials.

ROLES AND RESPONSIBILITIES

F.L. and N.K.J.A. designed the study. R.C. designed the search strategy and retrieved citations. A.A., J.B., S.M.F., F.Z.G., Y.X., H.F., K.H., M.H., V.L., K.L., and N.K.J.A. identified eligible studies and abstracted data. A.A. analyzed the data, and N.K.J.A. verified extracted data and analyses. A.A., F.L., and N.K.J.A. drafted the manuscript, vouch for the data and analyses, and decided to publish the manuscript. All authors approved the final version.

Results

Of 1547 unique citations identified by our search, 41 trials[9-12,18,49-51,65-97] with 4915 patients met the eligibility criteria (Fig. 1). Among the eligible studies, four trials did not report data for primary or secondary outcomes.[93-96] We obtained clarifications or additional data from three studies[51,85,92] but were unable to establish contact with authors of several others.[25,65,67,80,84,93,96] Ten trials[66,70,76,78-80,84,86,88,91] reported in-hospital mortality only, 13 trials[11,12,49,50,65,68,71,72,75,83,87,89,97] reported 30-day mortality only, and 11 trials[9,10,18,51,69,73,74,77,81,90,92] reported data for both time points.

STUDY CHARACTERISTICS

Table S3 summarizes the study characteristics. The median number of patients was 80 (range, 18 to 872). Two studies were multinational and conducted in high-income[18] or high- and upper-middle income countries.[9] Of the others, 13 were conducted in high-income countries,[10-12,49,51,70,74,78,89-91,93,97] 7 in upper-middle income countries,[50,65,68,69,71,85,94] 18 in lower-middle income countries,[66,67,72,73,76,77,79-84,86-88,92,95,96] and 1 did not explicitly report the country of recruitment.[75] Among studies with data, the median patient age was 60 years (range, 37 to 71) and the median proportion of female patients was 54%. Twenty-six studies reported baseline use of vasopressors, invasive ventilation, or other organ support.[9-12,18,49,51,65,67,70-72,74,75,78,80,81,83,84,86,88-92,97] Six studies included patients exclusively with Covid-19[69,76,79,82,85,94]; one multinational study also included a small proportion of patients with a positive SARS-CoV-2 result.[18]

Nine trials evaluated low-dose therapy,[49,68,76,78,85,88,91,95,96] 25 evaluated moderate-dose therapy,[9,10,12,65-67,70-75,77,79-84,86,87,89,90,92,97] 6 evaluated high-dose therapy,[11,18,49,51,69,93] and 2 did not report doses evaluated.[50,94] One trial evaluated both low and high doses.[49] Eleven trials[11,18,49,51,72,75,76,85,88,90,93] used a weight-based regimen. The most common daily dose was 6 g (21 studies).[9,10,

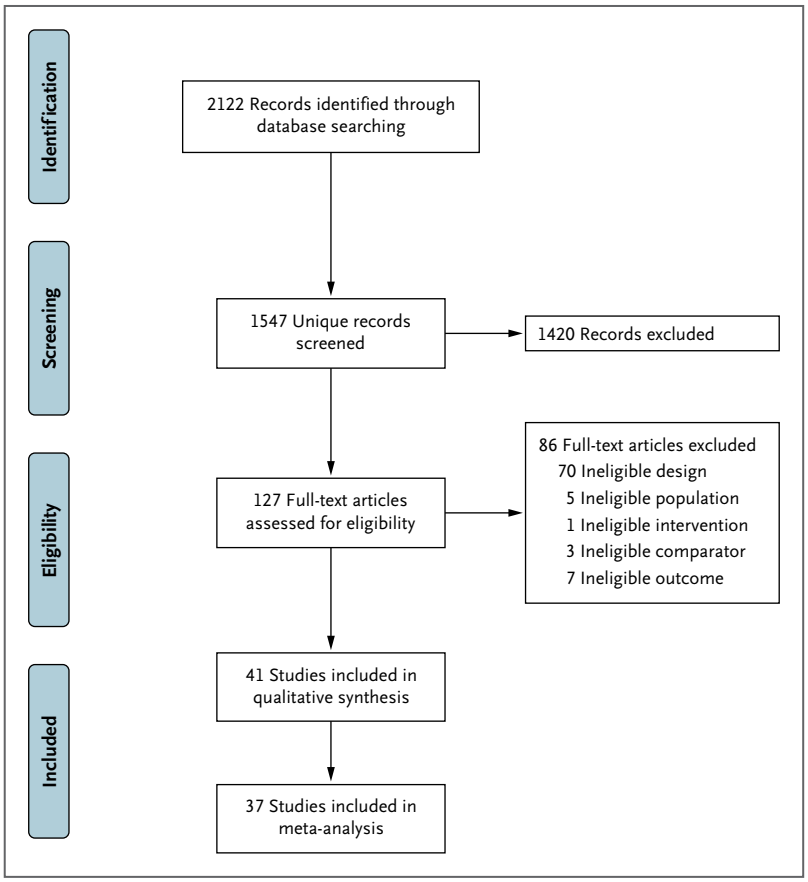

Figure 1. Flow of Trials through the Systematic Review.

[12,65-67,70,71,73,74,77,79-81,83,84,86,87,89,92,97] Of 22 trials evaluating combination therapy,[9,10,12,51,66,67,70,71,73,74,77,78,81-87,92,94,97] 16 evaluated vitamin C therapy combined with hydrocortisone and thiamine.[9,10,12,66,67,70,71,73,77,81,83,84,86,87,92,97] The control arm was placebo or usual care without vitamin C in 36 trials.[10-12,18,49-51,65-80,82-84,86,88-91,93-97] In three trials, both vitamin C and control groups received an additional treatment as part of the regimen.[51,85,94] In three trials, patients in the control group received hydrocortisone[9,81,92]; and in one trial each, they received ulinastatin[87] and oral vitamin C.[95]

RISK-OF-BIAS

Table S4 presents assessments of risk-of-bias for all included trials. Fourteen of 21 trials for in-hospital mortality,[9,10,18,70,73,74,76-78,81,84,86,90,91] 16 of 24 trials for 30-day mortality,[9-12,18,49,72-74,77,81,83,87,89,90,97] 20 of 34 trials for early mortality,[9-12,18,49,70,72-74,76-78,81,83,86,87,89-91] and all five trials for 90-day mortality[9,12,18,74,90] were rated as low risk-of-bias. Inadequate concealment and lack of blinding were primary issues across trials rated as having some concerns or as high risk-of-bias.

EFFECTS OF VITAMIN C

Primary Outcomes

Tables 1, 2, and S5 present the GRADE summary of findings for all outcomes. Low-certainty evidence suggested that vitamin C may reduce in-hospital mortality (21 RCTs, 2762 patients; risk ratio, 0.88 [95% CI, 0.73 to 1.06]; Fig. S1), 30-day mortality (24 RCTs, 3436 patients; risk ratio, 0.83 [95% CI, 0.71 to 0.98]; Fig. S2), and early mortality (34 RCTs, 4366 patients; risk ratio, 0.80 [95% CI, 0.68 to 0.93]; Fig. 2). The certainty of evidence for these meta-analyses was reduced because of risk-of-bias of included trials, imprecision of the summary risk ratios, and inconsistent results among trials. In sensitivity analyses limited to published blinded trials and at low risk-of-bias, effects

Table 1. Evidence Profile for Mortality in Trials of Parenteral Vitamin C.*

Outcome	Meta-analysis Results, Risk Ratio (95% CI)	Absolute Effect Estimates, No. per 1000 (95% CI)			Certainty of Evidence	Plain-Language Summary
		No Vitamin C	Vitamin C	Difference		
In-hospital mortality	0.88 (0.73 to 1.06) based on data from 2762 participants in 21 trials	307	270	37 fewer (83 fewer to 18 more)	Low, due to serious risk-of-bias,† serious imprecision,‡ and some concerns regarding inconsistency§	Parenteral vitamin C may reduce risk of in-hospital mortality
30-day mortality	0.83 (0.71-0.98) based on data from 3436 participants in 24 trials	330	274	56 fewer (96 fewer to 7 fewer)	Low, due to serious risk-of-bias† and serious inconsistency§	Parenteral vitamin C may reduce risk of 30-day mortality
Early mortality (combined in-hospital and 30-day mortality)	0.80 (0.68 to 0.93) based on data from 4366 participants in 34 trials	321	257	64 fewer (103 fewer to 22 fewer)	Low, due to serious risk-of-bias† and serious inconsistency§	Parenteral vitamin C may reduce risk of early mortality
90-day mortality	1.07 (0.94 to 1.21) based on data from 1722 participants in 5 trials	356	381	25 more (21 fewer to 75 more)	Moderate, due to serious imprecision‡	Parenteral vitamin C probably increases risk of 90-day mortality

* Risk ratio is expressed as vitamin C compared with the control. CI denotes confidence interval.

† risk-of-bias was assessed as serious due to many trials with concerns primarily related to randomization and allocation concealment.

‡ Imprecision was assessed as serious due to the 95% CI crossing the null.

§ Inconsistency was assessed as serious due to dissimilarities in point estimates, lack of overlap in CIs, and statistical evidence of heterogeneity.

Table 2. Evidence Profile for Mortality in Trials of Parenteral Vitamin C Limited to Published Blinded Full-Text Trials and at Low Risk-of-Bias.*

Outcome	Meta-analysis Results, Risk Ratio (95% CI)	Absolute Effect Estimates, No. per 1000 (95% CI)			Certainty of Evidence	Plain-Language Summary
		No Vitamin C	Vitamin C	Difference		
In-hospital mortality	1.07 (0.92 to 1.24) based on data from 1371 participants in 6 trials	310	332	22 more (25 fewer to 74 more)	Moderate, due to serious imprecision†	Parenteral vitamin C probably increases risk of in-hospital mortality
30-day mortality	0.88 (0.71 to 1.10) based on data from 2057 participants in 9 trials	313	275	38 fewer (91 fewer to 31 more)	Low, due to serious imprecision† and serious inconsistency‡	Parenteral vitamin C may reduce risk of 30-day mortality
Early mortality (combined in-hospital and 30-day mortality)	0.88 (0.73 to 1.06) based on data from 2214 participants in 11 trials	318	280	38 fewer (86 fewer to 19 more)	Low, due to serious imprecision† and some concerns regarding inconsistency‡	Parenteral vitamin C may reduce risk of early mortality
90-day mortality	1.07 (0.94 to 1.21) based on data from 1722 participants in 5 trials	356	381	25 more (21 fewer to 75 more)	Moderate, due to serious imprecision†	Parenteral vitamin C probably increases risk of 90-day mortality

* Risk ratio is expressed as vitamin C compared with the control. CI denotes confidence interval.

† Imprecision was assessed as serious due to the 95% CI crossing the null.

‡ Inconsistency was assessed as serious due to dissimilarities in point estimates, lack of overlap in CIs, and statistical evidence of heterogeneity.

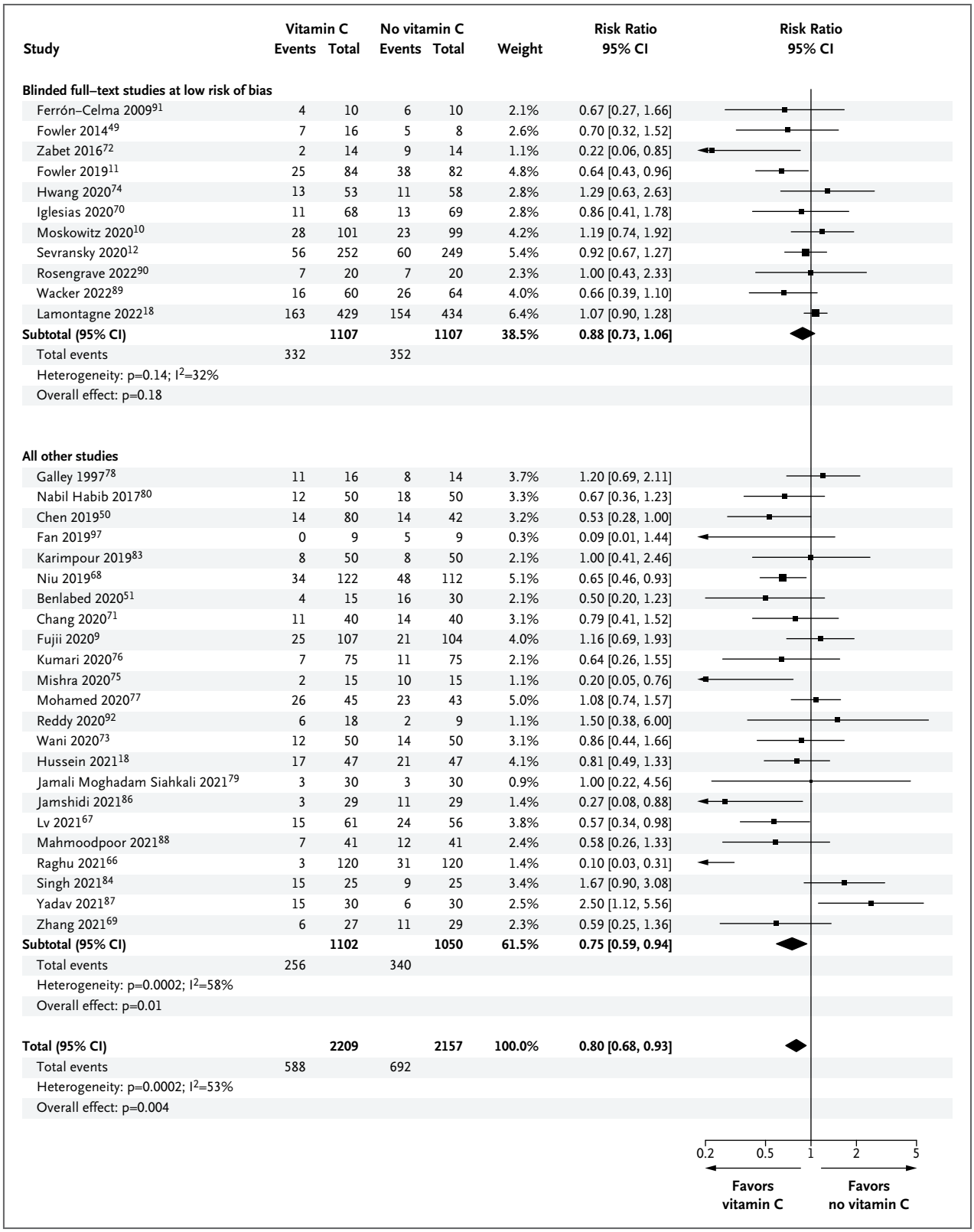

Figure 2. Effect of Parenteral Vitamin C on Early Mortality, Determined in the Hospital or at 30 Days after Randomization.

Effects are presented separately in blinded trials published in full text and at low risk-of-bias and in all other trials. Weight refers to the contribution of each trial to the estimate of the risk ratio. CI denotes confidence interval.

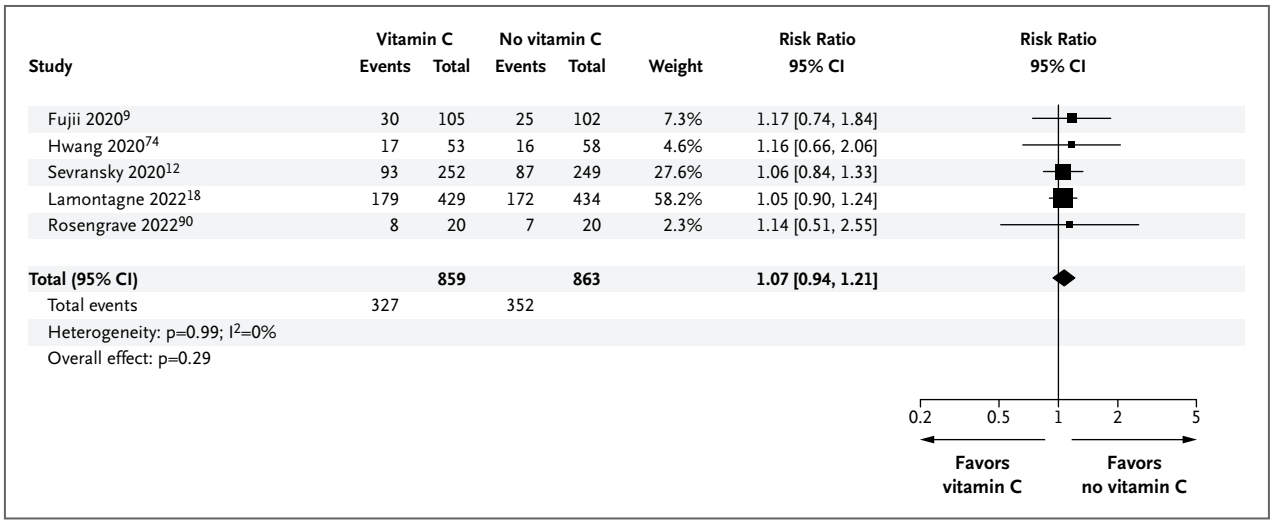

Figure 3. Effect of Parenteral Vitamin C on Mortality at 90 Days.
Weight refers to the contribution of each trial to the estimate of the risk ratio. CI denotes confidence interval.

were attenuated (hospital mortality: 6 RCTs, 1371 patients; risk ratio, 1.07 [95% CI, 0.92 to 1.24], moderate certainty; 30-day mortality: 9 RCTs, 2057 patients; risk ratio, 0.88 [95% CI, 0.71 to 1.10], low certainty; and early mortality: 11 RCTs, 2214 patients; risk ratio, 0.88 [95% CI, 0.73 to 1.06], low certainty; Fig. 2). Moderate-certainty evidence, downgraded for imprecision, suggested an increased risk of 90-day mortality (five RCTs, 1722 patients; risk ratio, 1.07 [95% CI, 0.94 to 1.21]; Fig. 3).

Secondary Outcomes

Table S5 and Figures S3 to S16 present data for secondary outcomes. Low-certainty evidence suggested that vitamin C may reduce the use of invasive mechanical ventilation (10 RCTs, 1200 patients; risk ratio, 0.91 [95% CI, 0.75 to 1.12]) and duration of ventilation (11 RCTs, 1579 patients; MD, 1.35 fewer days [95% CI, 2.91 fewer to 0.20 more]), and it may increase risks of acute kidney injury (7 RCTs, 1663 patients; risk ratio, 1.03 [95% CI, 0.93 to 1.14]) and use of renal replacement therapy (7 RCTs, 1756 patients; risk ratio, 1.06 [95% CI, 0.78 to 1.45]). Low-certainty evidence suggested little or no effect on durations of ICU stay (22 RCTs, 3125 patients; MD, 0.38 fewer days [95% CI, 2.10 fewer to 1.34 more]) and hospital stay (15 RCTs, 2820 patients; MD, 0.10 fewer days [95% CI, 3.00 fewer to 2.80 more]) and on change in SOFA score from baseline to 72 hours (16 RCTs, 2510 patients; MD, 0.30-point greater decrease from baseline [95% CI, 0.39 lesser to 0.99 greater]). The effect on time to clinical improvement was highly uncertain due to very low-certainty evidence (2 RCTs, 238 patients; MD, 1.48 fewer days [95% CI, 3.44 fewer to 0.47 more]). Moderate-certainty evidence suggested little or no effect on risks of serious adverse events leading to discontinuation (12 RCTs, 2487 patients; RD, 0.00 [95% CI, 0.00 to 0.01]) and hemolysis (2 RCTs, 1,000 patients; RD, 0.00 [95% CI, 0.00 to 0.00]), but an increased risk of hypoglycemia (1 RCT, 862 patients; risk ratio, 1.19 [95% CI, 0.69 to 2.07]).

Additional Analyses

Sensitivity analyses of SOFA scores incorporating 96-hour data and limited to trials with baseline data were similar to analyses of 72-hour data (Table S6 and Figs. S13 to S14). There were no credible subgroup effects (Table S7) related to vitamin C dose, population (severe infection due to Covid-19 or other severe infection), or cointerventions (combination therapy or monotherapy). Although the interaction P value was statistically significant for the combination therapy versus monotherapy subgroup for 30-day mortality (Fig. S17) and for early mortality (Fig. S18), residual statistical heterogeneity among trials of monotherapy was moderate to high. There was no evidence of statistical interaction in analyses of hospital and 90-day mortality. Among trials reporting 90-day mortality, a post hoc analysis showed the risk ratio of early

mortality to be 1.05 (95% CI, 0.91 to 1.21). Visual examination of funnel plots (Figs. S19 to S27) did not suggest publication bias.

Discussion

Our systematic review found low-certainty evidence suggesting that parenteral vitamin C may decrease early mortality in patients with severe infections admitted to the hospital; however, many trials had concerns related to risk-of-bias, and between-trial heterogeneity was substantial. Meta-analyses of mortality outcomes restricted to published blinded trials at low risk-of-bias showed attenuated effects that were not statistically significant at any time point. In addition, the subset of trials informing 90-day mortality was at low risk-of-bias and showed a consistent signal toward increased risk of mortality at early and 90-day follow-up. These observations suggest that treatment effects for early versus 90-day mortality reflect differences in included trials and their characteristics, rather than a true change in the effect of vitamin C over time. Subgroup analyses demonstrated no credible explanations of heterogeneity of treatment effects; however, we surmise that study design constitutes the main source. Among trials assessed at low risk-of-bias using standard methods, many had small sample sizes or were conducted in single centers, both of which are associated with larger treatment effects.[98,99] It is also possible that other factors, such as type of pathogen, explain residual heterogeneity.

Secondary outcomes were mostly informed by low-certainty evidence that suggested a possible reduction in the use of and duration of invasive ventilation as well as possible increases in the risks of acute kidney injury, renal replacement therapy, and hypoglycemia but no effects on other adverse events or short-term organ dysfunction overall. These disparate findings do not point to a comprehensive mechanistic explanation of vitamin C's effects and suggest additional hypotheses regarding populations that may experience benefit (e.g., patients with acute respiratory distress syndrome[11]) and harm (e.g., patients with diabetes or risk of renal failure). These hypotheses could be tested in a patient-level meta-analysis using available clinical trial data. The largest trial in this review found an increased risk in the primary outcome of mortality or persistent organ dysfunction at 28 days that was unexplained in analyses of biomarkers of tissue dysoxia, inflammation, and endothelial injury.[18]

Multiple systematic reviews and meta-analyses have evaluated vitamin C for patients with sepsis,[13-17,22-40] with variable conclusions regarding short-term mortality but similar findings of no effect on longer-term mortality.[14] Our review incorporates data from LOVIT, the largest published trial to date,[18] and considered patients with infections severe enough to warrant hospitalization, regardless of other criteria for sepsis. This inclusion criterion is relevant to patients with Covid-19, who are not typically described as having sepsis, and to trials of vitamin C conducted in settings where applying consensus criteria[41] to diagnose sepsis may not be done routinely. Nonetheless, a majority of included trials either reported high baseline severity of illness or a high proportion of patients receiving interventions to support organ function (Table S3), both of which would be compatible with consensus-defined sepsis. We used a comprehensive search strategy to incorporate all trials and conducted sensitivity and subgroup analyses to explore heterogeneity. The main limitation is unexplained inconsistency of effects on early mortality. Although blinded low risk-of-bias published trials showed no statistically significant effects on mortality at any time point, the point estimates differed, with corresponding changes in interpretation as informed by a minimally contextualized GRADE approach. For this review, we did not adopt a fully contextualized GRADE approach used by guideline panels, which defines thresholds for trivial, small, moderate, and large effects and considers all critical outcomes, along with explicit statements of values and preferences.

Current international guidelines provide no recommendations for use of parenteral vitamin C for patients with Covid-19,[100] a large group of acutely ill hospitalized patients for which even a small benefit of vitamin C would be of clinical relevance. We did not observe a differential effect of vitamin C in hospitalized patients with Covid-19 compared with other severe infections, but few vitamin C–treated patients with Covid-19 have been included in published trials. Data from ongoing large trials (ClinicalTrials.gov numbers NCT02735707 and NCT04401150) will be informative. In contrast, guidelines provide a weak recommendation against the use of vitamin C in patients with sepsis or septic shock based on seven trials evaluating mortality, one trial evaluating organ failure, and one trial evaluating vasopressor use.[101] Our systematic review provides more compelling evidence to support this recommendation, informed by a larger and recent body of evidence.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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