Intravenous vitamin C for patients hospitalized with COVID-19. Two harmonized randomized clinical trials

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Intravenous vitamin C for patients hospitalized with COVID-19: a prospective harmonization of two randomized clinical trials

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Key Points

Question: Does intravenous vitamin C administered to patients hospitalized with COVID-19 improve organ-support free days (a composite outcome of in-hospital mortality and duration of intensive care unit–based respiratory or cardiovascular support) up to day 21?

Findings: In two prospectively harmonized randomized clinical trials, vitamin C, compared to placebo or no vitamin C, yielded posterior probabilities of efficacy of 8.6% among 1568 critically ill patients and 2.9% among 1022 non-critically ill patients, regarding the odds of improvement in organ-support free days.

Meaning: Among hospitalized patients with COVID-19, there was a low probability that vitamin C improved organ-support free days.

Abstract

Importance: The efficacy of vitamin C for hospitalized patients with COVID-19 is uncertain.

Objective: To determine whether vitamin C improves outcomes for COVID-19 inpatients.

Design, Setting, Participants: Two prospectively harmonized randomized clinical trials enrolled critically ill patients receiving organ support in an intensive care unit (ICU, 90 sites), and non-critically ill patients (40 sites), from 23July2020 to 15July2022, in 4 continents.

Interventions: Patients were randomized to receive intravenous vitamin C or control (placebo/no vitamin C) for up to 96hr.

Main outcomes and measures: The primary outcome was a composite of organ-support free days, defined as days alive and free of ICU-based respiratory and cardiovascular organ support, up to day 21, and survival to hospital discharge. Values ranged from –1 for in-hospital death to 22 for survivors with no organ support. The primary analysis used a Bayesian cumulative logistic model. Odds ratio (OR) >1 represented efficacy (improved survival, more organ-support free days, or both), OR <1 represented harm, and OR <1.2 represented futility.

Results: Enrollment was terminated after statistical triggers for harm and futility were met. The trials enrolled 1568 critically ill patients (1041 vitamin C, 537 control; median age 60yr; 35.9% female) and 1022 non-critically ill patients (464 vitamin C; 572 control; median age 62yr, 39.6% female). Among critically ill patients, median organ-support free days (vitamin C vs. control) were 7 (interquartile range [IQR] -1, 17) vs. 10 (IQR -1, 17); OR 0.88, 95% credible interval [CrI] 0.73-1.06; posterior probabilities were 8.6% (efficacy), 91.4% (harm), and 99.9% (futility). Among non-critically ill patients, median organ-support free days (vitamin C vs. control) were 22 (IQR 18, 22) vs. 22 (IQR 21, 22); OR 0.80, 95%CrI 0.60-1.01; posterior probabilities were

2.9% (efficacy), 97.1% (harm), and >99.9% (futility). Survival to hospital discharge (vitamin C vs. control) in the critically ill was 61.9% (642/1037) vs. 64.6% (343/531) [OR 0.92 (95%CrI 0.73-1.17)] and in the non-critically ill was 85.1% (388/456) vs. 86.6% (490/566) [OR 0.86 (95%CrI 0.61-1.17)], with 24.0% and 17.8% posterior probability of efficacy, respectively. Conclusions and Relevance: In hospitalized patients with COVID-19, vitamin C did not improve organ-support free days or hospital survival.

Trial Registration: ClinicalTrials.gov identifiers: NCT04401150 (LOVIT-COVID); NCT02735707 (REMAP-CAP).

As of September 2023, World Health Organization (WHO) has reported at least 770 million cases and 6.9 million deaths due to coronavirus disease 2019 (COVID-19).[1] For hospitalized patients, immunomodulatory and anti-viral therapies are effective but imperfect,[2] and global availability remains disparate.[3]

Vitamin C is widely available and its use in septic shock increased pre-pandemic[4] until clinical trials failed to demonstrate benefit.[5-7] At the beginning of the COVID-19 pandemic, a WHO report highlighted it as a potential immunomodulatory agent.[8] Vitamin C attenuates oxidative stress and microvascular thrombosis,[9] two features of COVID-19, and hospitalized patients with COVID-19 were found to have low serum vitamin C levels.[10] A meta-analysis in patients with COVID-19 reported that vitamin C may reduce hospital mortality.[11]

We harmonized two initially separate randomized clinical trials to investigate the effect of intravenous vitamin C on need for organ support and hospital survival in hospitalized patients with COVID-19, hypothesizing that vitamin C would increase days alive and free of organ support.

Methods

Trial design

Before recruitment commenced, the investigators harmonized and decided to pool data from two clinical trials designed to evaluate the same vitamin C regimen. The Lessening Organ dysfunction with VITamin C-COVID (LOVIT-COVID) trial was initially designed as a frequentist blinded trial enrolling in Canada. The Randomized, Embedded, Multifactorial

Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial is an international, adaptive unblinded platform trial in patients with severe pneumonia;[12] this report includes patients enrolled in the COVID-19 stratum. Both trials prospectively adopted the same intervention, outcomes, statistical analysis plan, and reporting, but control groups were different: placebo in LOVIT-COVID, and no vitamin C in REMAP-CAP. Development of the harmonized trial and essential details of LOVIT-COVID and REMAP-CAP are in supplement 1 (eMethods and eTable 1); full protocols for both trials are in supplement 2. To account for observed racial and ethnic differences in outcomes during the pandemic, REMAP-CAP collected self-reported race and ethnicity from either participants or their surrogates, according to each region's standards.

The research ethics committee and regulatory authority in each jurisdiction approved the relevant trial protocol. Informed consent was obtained, either before randomization or afterwards, from all patients or their surrogates, in accordance with applicable legislation. Both trials had separate steering committees (with common co-chairs) and Data and Safety Monitoring Boards (DSMBs). Neither trial incorporated accruing data from the other in interim analyses, but their DSMBs exchanged information regarding respective trial progress.

Patients

Eligible patients were adults admitted to hospital with suspected or proven COVID-19. Patients admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support at the time of randomization were classified as critically ill and all others as non–critically ill. This prospective classification was undertaken because of previous reports

suggesting differential treatment effects in these two populations.[13-15] Respiratory support was defined by receipt of invasive ventilation, non-invasive ventilation, or high-flow nasal oxygen, and cardiovascular support by a vasopressor or inotrope infusion. In LOVIT-COVID, critically ill patients were enrolled while receiving respiratory support; cardiovascular support was an exclusion criterion. Detailed selection criteria appear in eMethods.

Randomization, interventions, and follow-up

Randomization in both trials was concealed via separate computer-based randomization systems. Patients in LOVIT-COVID were assigned in a 1:1 ratio to vitamin C or placebo. In REMAP-CAP, randomization was stratified by state (critically ill vs. non-critically ill), and patients could participate in other domains (eTable 2). The initial randomization ratio of vitamin C to no vitamin C was 1:1, with patients subsequently assigned preferentially to the arm that appeared more favorable after each adaptive analysis (protocol, supplement 2).

In both trials, patients in the intervention group received intravenous vitamin C, 50 mg/kg body weight, infused over 30-60 minutes, every 6 hours for 96 hours, up to a maximum of 16 doses. All sites used locally available vitamin C formulations (eMethods). In LOVIT-COVID, glucose monitoring for patients receiving insulin or oral hypoglycemic agents was protocolized to account for interference of vitamin C with bedside glucometers (eMethods). In REMAP-CAP, this protocol was advised for patients randomized to vitamin C. All other aspects of care were at clinicians' discretion. Patients were followed in hospital, with survivors or their relatives (all in LOVIT-COVID, and a subset in REMAP-CAP) telephoned at 6 months for additional outcomes.

Trial outcomes

The primary outcome was a composite of an ordinal measure of organ-support free days, defined as days free of respiratory and cardiovascular organ support delivered in the ICU up to day 21, and survival to hospital discharge. This hospital-based outcome is associated with 180-day survival.[16] Deaths within the hospital were assigned the worst outcome (–1). Among hospital survivors, respiratory and cardiovascular organ support-free days were calculated up to day 21; a higher number represents faster recovery. Survival to hospital discharge was censored at 90 days. Non-critically ill patients who survived without needing any organ support were assigned the best outcome (22 organ support-free days).

Secondary outcomes were pre-specified in the statistical analysis plan (supplement 2) and included death or persistent organ dysfunction[17] (receipt of invasive ventilation, a vasopressor infusion, or new kidney replacement therapy) at trial day 28, which was the primary outcome in the LOVIT trial of vitamin C in sepsis.[7]

Site investigators reported serious adverse events considered at least possibly related to a trial procedure to the coordinating center and then to the DSMB and national regulatory authorities, as required. In LOVIT-COVID, data on hemolysis and hypoglycemia were collected as safety outcomes. Additional in-hospital outcomes collected only in LOVIT-COVID and post-discharge outcomes[16] were not included in the statistical analysis plan and will be reported separately.

Statistical analysis

Following harmonization of both trials, the original fixed LOVIT-COVID sample size was replaced by the REMAP-CAP Bayesian design with no maximum sample size. Adaptive analyses were performed and response-adaptive randomization continued until reaching a pre-defined statistical trigger, initially specified as efficacy, inferiority, and equivalence.

The statistical analysis plan for the harmonized trial specified that the trial outcomes would be reported from a merged dataset created after both trials had stopped (additional details in eMethods). The analysis used Bayesian cumulative logistic models, which calculated posterior probability distributions based on accumulated trial evidence and a neutral prior distribution. Distinct treatment effects of vitamin C compared to control were estimated in critically ill and non-critically ill patients using a hierarchical prior that dynamically borrowed information between groups. The hierarchical prior distribution was centered on an overall intervention effect estimated with a prior assuming no treatment effect (standard normal prior on the log-odds ratio). The primary statistical model, used to estimate the effect of vitamin C on organ support-free days, and a similar model for hospital survival and for 28-day death or persistent organ dysfunction, adjusted for trial (LOVID-COVID vs. REMAP-CAP); other interventions, and eligibility and randomization in vitamin C domain (within REMAP-CAP); location (site, nested within country); age (categorized into six groups); sex; and time-period (two-week calendar epochs) to account for changes in clinical care and outcomes during the pandemic. Statistical models were fit using a Markov Chain Monte Carlo algorithm that drew iteratively (20,000 draws) from the joint posterior distribution. There were no terms for vitamin C interactions with other interventions. The model included patients enrolled in all other domains of REMAP-CAP, including those that remained blinded, to provide robust estimation of covariate effects. The

Statistical Analysis Committee conducted the analysis for patients with COVID-19 randomized up to July 15, 2022.

Patients were analyzed according to group assignment. Missing outcomes were not imputed. Posterior odds ratios with 95% credible intervals (CrI) were calculated, with odds ratio >1 corresponding to superiority of vitamin C to control. The probabilities of efficacy (odds ratio >1), harm (odds ratio <1), futility (odds ratio <1.2), and equivalence (odds ratio between 1/1.2 and 1.2) were calculated. For the primary outcome, an ordinal scale with 24 categories (worst category, death, and best category, alive with 21 days free of organ support), the odds ratio denotes the relative odds of being in the category $>i$ vs. $\leq i$, for i equals –1 to 21. The robustness of the proportional odds assumption was assessed for the primary ordinal regression model. For 90-day survival, an adjusted hazard ratio with 95% CrI was calculated.

The original pre-defined statistical triggers for trial conclusions were based on posterior probabilities of efficacy (>99%, odds ratio for vitamin C >1), inferiority (>99%, odds ratio <1), and equivalence (>90%, odds ratio between 1/1.2 and 1.2). After LOVIT found that vitamin C increased the risk of 28-day death or persistent organ dysfunction in sepsis,[7] statistical triggers for futility (>95%, odds ratio <1.2) and harm (>90%, odds ratio <1) were added.

Sensitivity analyses for the primary outcome and 28-day death or persistent organ dysfunction, and analyses of all secondary outcomes, used data from patients enrolled in REMAP-CAP domains that had stopped and were unblinded at the time of analysis to inform covariate adjustment. Additional sensitivity analyses with different analysis populations, and pre-specified

subgroup analyses, are in the statistical analysis plan. One such analysis included 63 patients with COVID-19 enrolled in LOVIT.[7] Data management and summaries were created using R version 4.1.2, and the primary analysis was computed in R version 4.1.3 using the rstan package version 2.21.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

The first patient was randomized in LOVIT-COVID on August 23, 2020 and in the vitamin C domain of REMAP-CAP on July 23, 2020. Both trials stopped recruitment on July 15, 2022 as advised by their DSMBs, as statistical triggers for futility and harm had been met for both critically ill and non-critically ill strata in REMAP-CAP. Interim analysis reports of both trials are in eResults, and response-adaptive randomization proportions over time in REMAP-CAP are shown in eFigure 1.

Of 2613 randomized patients, 7 were assessed as non-eligible, 15 withdrew consent for follow-up, and one critically ill patient in the control group contributed baseline data but had a missing primary outcome (Figure 1 and eFigures 2-3). The population for the primary statistical model included 2590 randomized and evaluable patients, with 1493 patients assigned to vitamin C and 1097 assigned to control. There were 1568 critically ill patients from 90 sites and 1022 non-critically ill patients from 40 sites, with 2206 enrolled in the vitamin C domain of REMAP-CAP and 384 in LOVIT-COVID. Two critically ill patients included in the analysis withdrew consent for follow-up but allowed for collected data to be used; their last known status was carried

forward for the primary outcome. Accrual rates over time are shown in eFigures 4-5. Covariate effects were estimated from 9771 patients from any REMAP-CAP domain and LOVIT-COVID.

Baseline characteristics are reported in Table 1 and eTables 3-8. Patients were recruited from Asia (34.7%), North America (28.5%), Europe (27.7%), and Australia (9.2%). Among critically ill patients, respiratory support at enrollment included invasive ventilation (28.0%), non-invasive ventilation (36.2%), and high-flow nasal oxygen (35.1%). Among non-critically ill patients, most were receiving no respiratory support or low-flow oxygen (90.7%). Most patients received corticosteroids (96.4%). In LOVIT-COVID, 96.1% of patients received ≥90% of scheduled doses (eTable 9); in REMAP-CAP, 95.2% of patients had no treatment delivery-related deviation (eTable 10).

Primary outcome

Among critically ill patients, median organ-support free days were 7 (interquartile range [IQR] –1, 17) in the vitamin C group vs. 10 (IQR –1, 17) in the control group (Table 2; Figure 2). The odds ratio for vitamin C was 0.88 (95%CrI 0.73-1.06), yielding posterior probabilities of 8.6% for efficacy, 91.4% for harm, and 99.9% for futility. Among non-critically ill patients, median organ-support free days were 22 (IQR 18, 22) in the vitamin C group vs. 22 (IQR 21, 22) in the control group (Table 3; Figure 3). The odds ratio for vitamin C was 0.80 (95%CrI 0.60-1.01), yielding posterior probabilities of 2.9% for efficacy, 97.1% for harm, and >99.9% for futility.

Among critically ill patients, survival to hospital discharge was 61.9% (642/1037) in the vitamin C group vs. 64.6% (343/531) in the control group. The odds ratio for vitamin C was 0.92

(95%CrI 0.73-1.17), with posterior probabilities of 24.0% for efficacy, 76.0% for harm, and 98.4% for futility. Among non-critically ill patients, survival to hospital discharge was 85.1% (388/456) in the vitamin C group vs. 86.6% (490/566) patients in the control group. The odds ratio for vitamin C was 0.86 (95%CrI 0.61-1.17), with posterior probabilities of 17.8% for efficacy, 82.2% for harm, and 98.1% for futility.

Secondary outcomes

Among critically ill patients, 90-day survival was 59.8% (617/1032) in the vitamin C group vs. 62.1% (328/528) in the control group (Table 2; Figure 2). The hazard ratio for vitamin C was 0.94 (95%CrI 0.80-1.11), with 22.4% posterior probability for efficacy. Among non-critically ill patients, 90-day survival was 81.5% (370/454) in the vitamin C group vs. 82.8% (466/563) patients in the control group (Table 3; Figure 3). The odds ratio for vitamin C was 0.93 (95%CrI 0.74-1.19), with 27.2% posterior probability of efficacy. Survival to 28 days without persistent organ dysfunction was similar in critically ill patients (Table 2; odds ratio for vitamin C, 0.90 (95% CrI 0.72-1.12; 16.4% probability of efficacy) and in non-critically ill patients (Table 3; odds ratio for vitamin C, 0.92 (95% CrI 0.68-1.23; 26.6% probability of efficacy)

Posterior probabilities of superiority of vitamin C vs. control were less than 33% for all other secondary outcomes (Tables 2-3; eFigures 6-7). Serious adverse events were reported in 1.8% (27/1493) patients assigned to vitamin C and 0.8% (9/1098) assigned to control (eTable 11). There were four serious adverse events possibly or probably related to vitamin C, including one patient with methemoglobinemia, two with hypoglycemia, and one with hemolytic anemia subsequently discovered to have glucose-6-phosphate dehydrogenase deficiency.

Sensitivity, subgroup, and exploratory analyses

Sensitivity analyses of organ support-free days, hospital survival, and 28-day mortality or persistent organ dysfunction using different analysis populations were consistent with the primary analyses (eTables 12-14). Credible intervals were wider in LOVIT-COVID compared to REMAP-CAP, with no convincing evidence of divergent effect estimates (eTable 15). There were no differential effects among subgroups (eTable 16). Exploratory analyses showed that the in-hospital mortality rates by group in REMAP-CAP shifted over time (eFigure 8), with the effect of vitamin C on organ support-free days varying over successive periods defined by randomization ratio (eTable 17). *Post hoc* analyses of treatment effect by continent and by dominant SARS-CoV-2 strain by month in each country of enrollment did not explain this variation (eTables 18-19).

Discussion

In this large, harmonized, multinational randomized trial, vitamin C administered to hospitalized patients with COVID-19 did not improve organ-support-free days or hospital survival. On the contrary, there were high posterior probabilities (>90% for organ support-free days and >75% for hospital survival) that vitamin C worsened both outcomes in critically ill and non-critically ill patients. These effects were consistent across predefined subgroups and in sensitivity analyses.

The regimen of vitamin C was based on a previous trial in sepsis showing sustained elevation of serum vitamin C levels over the treatment course, in addition to lower mortality, a secondary outcome.[18] The current results, from a critically ill population with mainly COVID-19

respiratory failure and a non-critically ill population, are consistent with the LOVIT trial among septic patients treated with vasopressors.[7] Existing analyses do not elucidate mechanisms of harm, and while future biomarker analyses from LOVIT-COVID may be informative,[19] the same biomarkers measured in LOVIT were comparable between vitamin C and placebo groups.[7] A previous meta-analysis of nine trials, with the largest randomizing 100 patients, found a reduced odds of mortality in COVID-19 patients receiving vitamin C.[11] These divergent results may be explained by more extreme effects observed in small trials.[20]

Several methodological issues are noteworthy. First, the initial decision to limit statistical stopping triggers to efficacy, inferiority, and equivalence facilitated investigation of a small treatment benefit. Although the current results do not exclude the possibility of any beneficial effect of vitamin C in COVID-19, it is more likely that vitamin C is ineffective or harmful. Second, this report provides separate effects of vitamin C in critically ill and non-critically ill patients, consistent with the design. An alternative approach would have included all randomized patients and generated a more precise overall treatment effect, with testing for a subgroup effect. Nonetheless, the current model allowed for statistical borrowing between critically ill and non-critically ill strata, thus mitigating the loss of statistical power. Third, treatment effects are presented in relative terms, rather than as absolute effects better suited for shared decision-making. The difference of 1.5 organ-support free days is considered minimally important by the Food and Drug Administration,[21] but patients' views are unknown. Finally, response-adaptive randomization in REMAP-CAP, designed to favor assignment to the group with superior outcomes at interim analyses, led to 69% of critically ill patients assigned to vitamin C, despite lack of efficacy in both strata. This situation arose because early results in critically ill patients

favored vitamin C, without reaching a statistical trigger, with the final adaptive analysis conducted 10 months after the penultimate one due to implementation of new processes for international data flow. During this period, over 50% of enrollment occurred, without changes to domain selection criteria or trial procedures. This analysis reported a reversed direction of treatment effect, unexplained *post hoc*, underscoring the early instability of treatment effect estimates in trials.[22-24] Because the inferiority trigger was never reached, the trial may have continued, even with more frequent analyses, until harm and futility triggers were introduced due to external evidence.[7] Options for avoiding this situation include frequent adaptive analyses or forcing the randomization ratio to remain closer to 1:1.[25,26]

Strengths of this report include selection of a vitamin C regimen based on promising initial evaluations,[18,27] excellent treatment adherence and follow-up, and enhanced generalizability based on a broad geographical enrollment.[28]

Limitations

This report combines data from two trials, initially designed differently, in an attempt to improve efficiency and reduce waste in pandemic research.[29] Fewer patients were enrolled in the placebo-controlled LOVIT-COVID trial, with differential post-randomization care possible for patients enrolled in the open-label REMAP-CAP trial. Analyses showing comparable treatment effects in these two trials were underpowered. Data on individual participants' vaccination status, vitamin C product received, and baseline vitamin C levels were unavailable to inform subgroup analyses, although a subgroup analysis by baseline vitamin C level in LOVIT was uninformative.[7]

In conclusion, in hospitalized patients with COVID-19, treatment with vitamin C did not improve organ support-free days or hospital survival.

Author contributions:

Drs Adhikari and Lamontagne had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Adhikari and Lamontagne are joint first and joint senior authors.

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References

1. WHO COVID-19 Dashboard. World Health Organization. Accessed 30 March, 2023. https://covid19.who.int/
2. Lamontagne F, Agarwal A, Rochwerg B, et al. A living WHO guideline on drugs for covid-19. *BMJ*. Sep 4 2020;370:m3379. doi:10.1136/bmj.m3379
3. Usher AD. The global COVID-19 treatment divide. *Lancet*. Feb 26 2022;399(10327):779-782. doi:10.1016/S0140-6736(22)00372-5
4. Vail EA, Wunsch H, Pinto R, Bosch NA, Walkey AJ, Lindenauer PK, Gershengorn HB. Use of Hydrocortisone, Ascorbic Acid, and Thiamine in Adults with Septic Shock. *Am J Respir Crit Care Med*. Dec 1 2020;202(11):1531-1539. doi:10.1164/rccm.202005-1829OC
5. Fujii T, Luethi N, Young PJ, et al. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA*. Feb 4 2020;323(5):423-431. doi:10.1001/jama.2019.22176
6. Sevransky JE, Rothman RE, Hager DN, et al. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial. *JAMA*. Feb 23 2021;325(8):742-750. doi:10.1001/jama.2020.24505
7. Lamontagne F, Masse MH, Menard J, et al. Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit. *N Engl J Med*. Jun 23 2022;386(25):2387-2398. doi:10.1056/NEJMoa2200644
8. World Health Organization. *A coordinated global research roadmap: 2019 novel coronavirus*. 2020:1-68. https://www.who.int/publications/m/item/a-coordinated-global-research-roadmap
9. Carr AC, Rowe S. The Emerging Role of Vitamin C in the Prevention and Treatment of COVID-19. *Nutrients*. Oct 27 2020;12(11)doi:10.3390/nu12113286
10. Chiscano-Camon L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O, Ferrer R. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Crit Care*. Aug 26 2020;24(1):522. doi:10.1186/s13054-020-03249-y
11. Olczak-Pruc M, Swieczkowski D, Ladny JR, et al. Vitamin C Supplementation for the Treatment of COVID-19: A Systematic Review and Meta-Analysis. *Nutrients*. Oct 10 2022;14(19)doi:10.3390/nu14194217
12. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. *Ann Am Thorac Soc*. Jul 2020;17(7):879-891. doi:10.1513/AnnalsATS.202003-192SD
13. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. Feb 25 2021;384(8):693-704. doi:10.1056/NEJMoa2021436
14. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med*. Aug 26 2021;385(9):790-802. doi:10.1056/NEJMoa2105911
15. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med*. Aug 26 2021;385(9):777-789. doi:10.1056/NEJMoa2103417

16. Writing Committee for the REMAP-CAP Investigators, Higgins AM, Berry LR, et al. Long-term (180-Day) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial. *JAMA*. Jan 3 2023;329(1):39-51. doi:10.1001/jama.2022.23257
17. Heyland DK, Muscedere J, Drover J, Jiang X, Day AG, Canadian Critical Care Trials Group. Persistent organ dysfunction plus death: a novel, composite outcome measure for critical care trials. *Crit Care*. 2011;15(2):R98. doi:10.1186/cc10110
18. Fowler AA, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *JAMA*. Oct 1 2019;322(13):1261-1270. doi:10.1001/jama.2019.11825
19. Fish M, Rynne J, Jennings A, et al. Coronavirus disease 2019 subphenotypes and differential treatment response to convalescent plasma in critically ill adults: secondary analyses of a randomized clinical trial. *Intensive Care Med*. Nov 2022;48(11):1525-1538. doi:10.1007/s00134-022-06869-w
20. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ*. Apr 24 2013;346:f2304. doi:10.1136/bmj.f2304
21. Laterre PF, Berry SM, Blemings A, et al. Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial. *JAMA*. Oct 15 2019;322(15):1476-1485. doi:10.1001/jama.2019.14607
22. Canner PL. The Coronary Drug Project. Monitoring of the data for evidence of adverse or beneficial treatment effects. *Control Clin Trials*. Dec 1983;4(4):467-83. doi:10.1016/0197-2456(83)90029-6
23. Abraham E, Reinhart K, Opal S, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA*. Jul 9 2003;290(2):238-47. doi:10.1001/jama.290.2.238
24. Wheatley K, Clayton D. Be skeptical about unexpected large apparent treatment effects: the case of an MRC AML12 randomization. *Control Clin Trials*. Feb 2003;24(1):66-70. doi:10.1016/s0197-2456(02)00273-8
25. Bhatt DL, Mehta C. Adaptive Designs for Clinical Trials. *N Engl J Med*. Jul 7 2016;375(1):65-74. doi:10.1056/NEJMra1510061
26. Granholm A, Kaas-Hansen BS, Lange T, et al. An overview of methodological considerations regarding adaptive stopping, arm dropping, and randomization in clinical trials. *J Clin Epidemiol*. Jan 2023;153:45-54. doi:10.1016/j.jclinepi.2022.11.002
27. Fowler AA, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med*. Jan 31 2014;12:32. doi:10.1186/1479-5876-12-32
28. Ramanan M, Tong SYC, Kumar A, Venkatesh B. Geographical Representation of Low- and Middle-Income Countries in Randomized Clinical Trials for COVID-19. *JAMA Netw Open*. Feb 1 2022;5(2):e220444. doi:10.1001/jamanetworkopen.2022.0444
29. Glasziou PP, Sanders S, Hoffmann T. Waste in covid-19 research. *BMJ*. May 12 2020;369:m1847. doi:10.1136/bmj.m1847
30. WHO Working Group on the Clinical Characterisation and Management of COVID-19 Infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. Aug 2020;20(8):e192-e197. doi:10.1016/S1473-3099(20)30483-7

Table 1 Baseline characteristics

	Critically ill		Non-critically ill	
	Vitamin C (n = 1037)	**Control (n = 532)**	**Vitamin C (n = 456)**	**Control (n = 566)**
Age in years, median (IQR)	60.0 (49.0-69.0)	61.0 (50.0-72.0)	63.0 (51.0-73.0)	62.0 (51.0-72.0)
Age category, n (%)				
18-49	268 (25.8)	122 (22.9)	97 (21.3)	132 (23.3)
50-69	512 (49.4)	253 (47.6)	204 (44.7)	258 (45.6)
70+	257 (24.8)	157 (29.5)	155 (34.0)	176 (31.1)
Female sex, n (%)	382 (36.8)	182 (34.2)	189 (41.4)	216 (38.2)
Male sex, n (%)	655 (63.2)	350 (65.8)	267 (58.6)	350 (61.8)
Body mass index, median (IQR)[a]	29.6 (25.7-35.3) (n=837)	29.6 (26.0-35.1) (n=437)	28.4 (25.0-33.8) (n=358)	28.4 (25.1-32.5) (n=435)
Continent, n (%)				
Asia	373 (36.0)	134 (25.2)	156 (34.2)	235 (41.5)
Australia	136 (13.1)	65 (12.2)	15 (3.3)	22 (3.9)
Europe	365 (35.2)	180 (33.8)	74 (16.2)	98 (17.3)
North America	163 (15.7)	153 (28.8)	211 (46.3)	211 (37.3)
Race / Ethnicity,[b] n / N (%)				
Asian	32/417 (7.7)	10/219 (4.6)	3/123 (2.4)	4/133 (3.0)
Black	16/417 (3.8)	12/219 (5.5)	14/123 (11.4)	13/133 (9.8)
Mixed or multiple	6/417 (1.4)	1/219 (0.5)	0/123 (0.0)	0/133 (0.0)
White	298/417 (71.5)	159/219 (72.6)	97/123 (78.9)	108/133 (81.2)
Other	65/417 (15.6)	37/219 (16.9)	9/123 (7.3)	8/133 (6.0)
APACHE II score,[c] median (IQR)	12.0 (8.0-18.0) (n=1031)	14.0 (8.0-21.0) (n=531)	8.0 (5.0-12.0) (n=278)	8.0 (5.0-11.0) (n=358)
Clinical Frailty Score,[d] median (IQR)	3.0 (2.0-3.0) (n=979)	3.0 (2.0-3.0) (n=492)	3.0 (2.0-3.0) (n=358)	3.0 (2.0-3.0) (n=463)
Preexisting condition,[e] n / N (%)				
Diabetes	323 (31.1)	159 (29.9)	133 (29.2)	138 (24.4)
Respiratory disease	167/1006 (16.6)	89/505 (17.6)	75/386 (19.4)	86/495 (17.4)
Kidney disease	68/919 (7.4)	46/446 (10.3)	24/371 (6.5)	37/488 (7.6)
Severe cardiovascular disease	42 (4.1)	32 (6.0)	25/455 (5.5)	35/565 (6.2)
Any immunosuppressive condition	35/998 (3.5)	33/496 (6.7)	21/367 (5.7)	20/468 (4.3)
Time to enrollment, median (IQR)				
From hospital admission, days[f]	1.1 (0.8-2.7)	1.1 (0.8-2.5)	1.0 (0.7-2.1)	1.0 (0.7-2.1)
From ICU admission, hours[g]	15.0 (8.5-19.9) (n=1034)	15.2 (8.8-20.0) (n=531)	15.6 (9.6-20.1) (n=219)	15.0 (7.2-21.0) (n=283)
Acute respiratory support,[h] n / N (%)				
Invasive mechanical ventilation	287/1036 (27.7)	151/531 (28.4)	0 (0.0)	0 (0.0)
Noninvasive ventilation only	393/1036 (37.9)	175/531 (33.0)	6 (1.3)	8 (1.4)
High-flow nasal oxygen	350/1036 (33.8)	200/531 (37.7)	35 (7.7)	46 (8.1)
None or low-flow oxygen	6/1036 (0.6)	5/531 (0.9)	415 (91.0)	512 (90.5)
Vasopressor support, n / N (%)	152/1036 (14.7)	76/531 (14.3)		

Concomitant therapies, n / N (%)[i]				
Remdesivir	403/974 (41.4)	174/463 (37.6)	211/355 (59.4)	267/471 (56.7)
Corticosteroids	990/1035 (95.7)	518/531 (97.6)	420 (92.1)	531/564 (94.1)
Tocilizumab or sarilumab	296/974 (30.4)	151/463 (32.6)	30/355 (8.5)	52/471 (11.0)

APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range.
Control patients include all patients randomized to control who were also eligible to be randomized to vitamin C, i.e., direct concurrent controls.
Trial-specific baseline characteristics may be found in eTables 5-8.

Percentages may not sum to 100 because of rounding.

[a] The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
[b] Collection of ethnicity data was approved in UK, Australia, and USA only, and data were not collected in LOVIT-COVID. "Other" includes any other racial or ethnic group reported.
[c] Acute Physiology and Chronic Health Evaluation II scores range from 0 to 71, with higher scores indicating greater severity of illness and higher risk of death.
[d] Scores on the Clinical Frailty Scale range from 1 to 9, with higher scores indicating greater frailty.
[e] Kidney disease was determined from the most recent serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 130 μmol/L or greater (1.5 mg/dL) for males or 100 μmol/L or greater (1.1 mg/dL) for females not previously receiving dialysis. Cardiovascular disease was defined as New York Heart Association class IV symptoms. In LOVIT-COVID, immunosuppressive conditions included receipt of recent chemotherapy or chronic immunosuppressive medications (excluding steroids), neutropenia, solid organ or stem cell transplantation, or human immunodeficiency virus positive status. In REMAP-CAP, these conditions included acquired immunodeficiency syndrome, metastatic cancer, specific hematological malignancies or other hematological conditions, or other inherited, primary, or secondary immune deficiencies.
[f] In LOVIT-COVID, hospital admission was recorded when the patient left the Emergency Department or when care in the Emergency Department was assumed by an inpatient service, depending on the hospital. In REMAP-CAP, time to enrolment from hospital admission explicitly includes all time spent in the Emergency Department.
[g] Patients in an intensive care unit but not receiving respiratory or cardiovascular organ support were prospectively classified as non-critically ill.
[h] Non-invasive ventilation and high-flow nasal oxygen delivered outside an intensive care unit did not fulfil the trial definition of critical illness.
[i] Concomitant therapies were given at baseline or within 48 hours of randomization (REMAP-CAP), or at baseline or on the day of or the day after randomization (LOVIT-COVID). Data on remdesivir and tocilizumab or sarilumab were specifically collected in REMAP-CAP, but could be recorded under 'antiviral' or 'immunomodulator' in LOVIT-COVID.

Table 2. Primary and secondary outcomes in critically ill participants

	Intravenous vitamin C	Control	Adjusted proportional Odds Ratio (95% CrI)[a]	Probability of efficacy / harm, %
Primary outcome				
Organ support-free days to day 21[b]	Median (q1, q3) [N=1037] 7 (–1 to 17)	Median (q1,q3) [N=532] 10 (–1 to 17)	0.88 (0.73, 1.06)	8.6 / 91.4[c]
Component of primary outcome				
Survival to hospital discharge	No. of patients/total no. (%) 642/1037 (61.9)	No. of patients/total no. (%) 343/531 (64.6)	0.92 (0.73, 1.17)	24.0 / 76.0[d]
Secondary outcomes				
Survival without persistent organ dysfunction at day 28[e]	No. of patients/total no. (%) 592/1037 (57.1)	No. of patients/total no. (%) 323/532 (60.7)	0.90 (0.72, 1.12)	16.4 / 83.6
Vasopressor/inotrope-free days through day 28	Median (q1, q3) [N=1037] 26 (-1, 28)	Median (q1, q3) [n=532] 27 (-1, 28)	0.84 (0.75, 0.94)	0.9 / 99.1
Respiratory support-free days through day 28	Median (q1, q3) [N=1037] 13 (-1, 24)	Median (q1, q3) [N=531] 16 (-1, 24)	0.89 (0.73, 1.01)	3.2 / 96.8
Endotracheal intubation through day 28	No. of patients/total no. (%) 266/750 (35.5)	No. of patients/total no. (%) 124/381 (32.5)	0.74 (0.56, 0.99)	2.1 / 97.9
Extracorporeal support through day 28[f]	No. of patients/total no. (%) 12/1034 (1.2)	No. of patients/total no. (%) 7/532 (1.3)		
Survival to day 28	No. of patients/total no. (%) 671/1032 (65.0)	No. of patients/total no. (%) 356/530 (67.2)	0.94 (0.75, 1.19)	31.2 / 68.8
Discharge alive from the ICU[g]			0.96 (0.84, 1.10)	28.4 / 71.6
Discharge alive from the hospital[g]			0.93 (0.82, 1.05)	12.1 / 87.9
90-day survival[h]	No. of patients/total no. (%) 617/1032 (59.8)	No. of patients/total no. (%) 328/528 (62.1)	0.94 (0.80, 1.11)	22.4 / 77.6
WHO ordinal scale at day 14[i]			0.89 (0.75, 1.07)	11.0 / 89.0

CrI, credible interval; ICU, intensive care unit; IQR, interquartile range; WHO, World Health Organization

[a] The odds ratio is for vitamin C relative to control.
[b] The model assigns hospital decedents a value of –1 organ support-free days.
[c] The probability of futility was 99.9%.
[d] The probability of futility was 98.4%.
[e] The outcome is the complement of 28-day mortality or persistent organ dysfunction to preserve the interpretation of odds ratio >1 denoting superiority of vitamin C.
[f] No model was constructed for this outcome, as per the statistical analysis plan.
[g] Crude results are not provided because the model assigns hospital decedents a length of stay of 90 days.
[h] The 90-day survival proportions exclude from the denominator patients censored alive prior to 90 days (8 critically ill patients were censored).
[i] The WHO ordinal scale measures the patient's overall status at day 14; range: 0-8, where 0 denotes no illness, 1-7 denote increasing level of care, and 8 denotes death.[30] In this analysis, categories 0, 1, and 2 have been condensed into one category for all patients discharged from hospital. In LOVIT-COVID, states 3 and 4 were collapsed into one category.

Table 3. Primary and secondary outcomes in non-critically ill participants

	Intravenous vitamin C	Control	Adjusted proportional Odds Ratio (95% CrI)[a]	Probability of efficacy / harm, %
Primary outcome				
Organ support-free days to day 21[b]	Median (q1, q3) [N=456] 22 (18 to 22)	Median (q1,q3) [N=566] 22 (21 to 22)	0.80 (0.60, 1.01)	2.9 / 97.1[c]
Component of primary outcome				
Survival to hospital discharge	No. of patients/total no. (%) 388/456 (85.1)	No. of patients/total no. (%) 490/566 (86.6)	0.86 (0.61, 1.17)	17.8 / 82.2[d]
Secondary outcomes				
Survival without persistent organ dysfunction at day 28[e]	No. of patients/total no. (%) 381/456 (83.6)	No. of patients/total no. (%) 477/566 (84.3)	0.92 (0.68, 1.23)	26.6 / 73.4
Vasopressor/inotrope-free days through day 28	Median (q1, q3) [N=456] 28 (28, 28)	Median (q1, q3) [n=566] 28 (28, 28)	0.77 (0.65, 0.90)	0.5 / 99.5
Respiratory support-free days through day 28	Median (q1, q3) [N=456] 28 (26, 28)	Median (q1, q3) [N=566] 28 (27, 28)	0.83 (0.64, 0.99)	1.9 / 98.1
Endotracheal intubation through day 28	No. of patients/total no. (%) 63/456 (13.8)	No. of patients/total no. (%) 50/566 (8.8)	0.59 (0.38, 0.83)	0.1 / 99.9
Extracorporeal support through day 28[f]	No. of patients/total no. (%) 2/456 (0.4)	No. of patients/total no. (%) 4/566 (0.7)		
Survival to day 28	No. of patients/total no. (%) 385/454 (84.8)	No. of patients/total no. (%) 480/563 (85.3)	0.94 (0.68, 1.26)	32.9 / 67.1
Discharge alive from the hospital[g]			0.92 (0.81, 1.05)	10.6 / 89.4
90-day survival[h]	No. of patients/total no. (%) 370/454 (81.5)	No. of patients/total no. (%) 466/563 (82.8)	0.93 (0.74, 1.19)	27.2 / 72.8
WHO ordinal scale at day 14[i]			0.89 (0.71, 1.12)	15.6 / 84.4

CrI, credible interval; ICU, intensive care unit; IQR, interquartile range; WHO, World Health Organization

[a] The odds ratio is for vitamin C relative to control.
[b] The model assigns hospital decedents a value of –1 organ support-free days.
[c] The probability of futility was >99.9%.
[d] The probability of futility was 98.1%.
[e] The outcome is the complement of 28-day mortality or persistent organ dysfunction to preserve the interpretation of odds ratio >1 denoting superiority of vitamin C.
[f] No model was constructed for this outcome, as per the statistical analysis plan.
[g] Crude results are not provided because the model assigns hospital decedents a length of stay of 90 days.
[h] The 90-day survival proportions exclude from the denominator patients censored alive prior to 90 days (4 non-critically ill patients were censored).
[i] The WHO ordinal scale measures the patient's overall status at day 14; range: 0-8, where 0 denotes no illness, 1-7 denote increasing level of care, and 8 denotes death.[30] In this analysis, categories 0, 1, and 2 have been condensed into one category for all patients discharged from hospital. In LOVIT-COVID, states 3 and 4 were collapsed into one category.

Figure 1 Flow of patients through the harmonized trial. Additional details are provided in Figures S2 and S3. ITT, intention to treat; SC, steering committee. SDM: Surrogate decision maker.

[a] Other reasons why patients were excluded in LOVIT-COVID: 7 Had known G6PD deficiency; 3 Had known sickle cell anemia, 2 Had known allergy to vitamin C, 17 Had known kidney stones within the past 1 year, 1 Received IV vitamin C (not incorporated into parenteal nutrition).
[b] Other reasons why eligible patients were not enrolled in LOVIT-COVID: 12 Had SDM that was unable to be reached, 18 Were missed (off-business hours), 1 Was enrolled in a trial for which co-enrollment was not allowed, and 129 for: 74 had no reason, 33 were diabetic patients (glucose monitoring requiring too much work for the nursing staff), 5 were asymptomatic COVID patients hospitalized for another reason, 4 were discharged before the responsible physician get back to the research team on patient's eligibility, 2 were disoriented or had dementia and no SDM, 2 were palliative or deemed palliative, 2 had a language barrier, 1 had passive decline, 1 was being discharged, 1 was transferred to another hospital after intubation, 1 had acute kidney injury, 1 had planned renal transplant, 1 was not enrolled due to research team workload, 1 was due for several interventions with no possibility of approach within 24 hours.
[c] Patients could meet more than one ineligibility criterion.
[d] Other reasons in Vitamin C Domain active and not enrolled in another domain: 10 Received IV vitamin C during this hospital admission, 5 Patients randomized to another trial of vitamin C.
[e] Other reasons in Vitamin C Domain active: 19 Patients randomized to another trial of vitamin C, 12 Reveal of allocation not completed, 1 Other.
[f] Randomization was stratified by site in LOVIT-COVID and by population (critically ill vs. non-critically ill) in REMAP-CAP.
[g] The principal investigators designed both LOVIT-COVID and the vitamin C domain of REMAP-CAP, and with support of the respective steering committees, *a priori* decided to use a common vitamin C treatment regimen, collect a set of common outcomes, and conduct a merged analysis after both trials had completed recruitment.

Figure 2 Critically ill patients. Panel A: The cumulative proportion (y-axis) for vitamin C (blue line) or control (red line) by day (x-axis) of organ support-free days, with death listed first. Curves that rise more slowly indicate a more favorable distribution in the number of days alive and free of organ support. Panel B: Organ support-free days as horizontally stacked proportions by intervention group. Red represents worse outcomes and blue represents better outcomes. The median adjusted odds ratio from the primary analysis was 0.88 (95% credible interval, 0.73 to 1.06), yielding 8.6% probability of vitamin C being superior to control. Panel C: 90-day survival. There were 415/1032 deaths (40.2%) in the vitamin C group and 200/528 deaths (37.9%) in the control group. Denominators exclude censored patients. The blue line represents vitamin C and the red line represents control. Data was available on all patients through death or 90 days except for 8 patients that were censored alive prior to 90 days.

Figure 3 Non-critically ill patients. Panel A: The cumulative proportion (y-axis) for vitamin C (blue line) or control (red line) by day (x-axis) of organ support-free days, with death listed first. Curves that rise more slowly indicate a more favorable distribution in the number of days alive and free of organ support. Panel B: Organ support-free days as horizontally stacked proportions by intervention group. Red represents worse outcomes and blue represents better outcomes. The median adjusted odds ratio from the primary analysis was 0.80 (95% credible interval, 0.60 to 1.01), yielding 2.9% probability of vitamin C being superior to control. Panel C: 90-day survival. There were 84/454 deaths (18.5%) in the vitamin C group and 97/563 deaths (17.2%) in the control group. Denominators exclude censored patients. The blue line represents vitamin C and the red line represents control. Data was available on all patients through death or 90 days except for 4 patients that were censored alive prior to 90 days.