Vitamin C reduces COVID-19 risk: real-time meta analysis of 75 studies

@CovidAnalysis, July 2025, Version 83
https://c19early.org/cmeta.html

Abstract

Significantly lower risk is seen for mortality, ICU admission, hospitalization, and recovery. 26 studies from 26 independent teams in 13 countries show significant benefit.

Meta analysis using the most serious outcome reported shows 21% [15-28%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Clinical outcomes suggest benefit while viral and case outcomes do not, consistent with an intervention that aids the immune system or recovery but may have limited antiviral effects. Early treatment is more effective than late treatment.

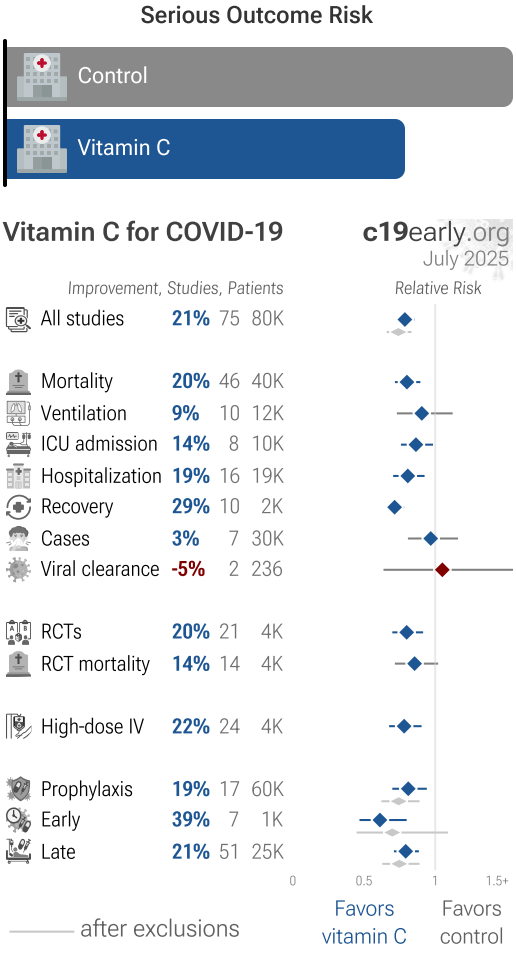
Results are robust — in exclusion sensitivity analysis 32 of 75 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

6 RCTs with 1,420 patients have not reported results (up to 4 years late).

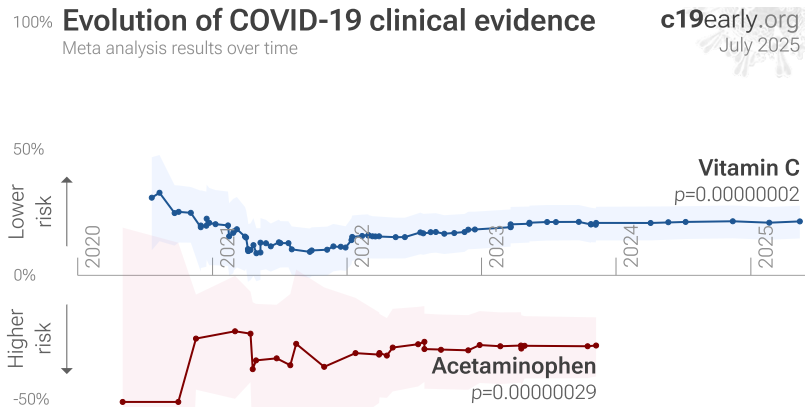
The European Food Safety Authority has found evidence for a causal relationship between the intake of vitamin C and optimal immune system function [1,2].

Early cessation of high-dose IV treatment may result in a detrimental rebound effect [3]. Ongoing treatment is more effective than early cessation: 33% [22-42%] vs. 16% [-31-46%].

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. Dietary sources may be preferred. The quality of non-prescription supplements varies widely and the quantity of the active ingredient may be significantly lower than stated [4-6]. High doses may increase the risk of kidney stones [7], with risk depending on formulation, predisposition, diet, and hydration [8]. All data and sources to reproduce this analysis are in the appendix.



7 other meta analyses show significant improvements with vitamin C for mortality [9-13], progression [14], severity [9,13], and cases [15].



VITAMIN C FOR COVID-19 — HIGHLIGHTS

Vitamin C reduces risk with very high confidence for mortality, hospitalization, recovery, and in pooled analysis, high confidence for ICU admission, and low confidence for progression.

Early treatment is more effective than late treatment.

6th treatment shown effective in September 2020, now with $p = 0.00000002$ from 75 studies, recognized in 22 countries.

Real-time updates and corrections with a consistent protocol for 172 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

75 vitamin C COVID-19 studies

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	Improvement, RR [CI]			Treatment	Control
Su	-135%	2.35 [0.67-8.27]	progression	n/a	n/a
Thomas (RCT)	-204%	3.04 [0.13-72.9]	death	1/48	0/50
Zhao (PSM)	72%	0.28 [0.08-0.93]	progression	4/55	12/55
Ried (RCT)	31%	0.69 [0.54-0.89]	no recov.	69/162	46/75
Usanma Koban	33%	0.67 [0.07-5.38]	viral+	31 (n)	95 (n)
Madamombe	53%	0.47 [0.31-0.71]	death	672 (all patients)	
Rahman	40%	0.60 [0.47-0.76]	hosp.	128/476	56/124
Early treatment	39%	0.61 [0.47-0.80]		202/772	114/399

$Tau^2 = 0.04$, $I^2 = 40.2\%$, p = 0.00035

	Improvement, RR [CI]			Treatment	Control
Krishnan	31%	0.69 [0.47-0.92]	death	40/79	52/73
Zhang (RCT)	50%	0.50 [0.20-1.50]	death	6/27	11/29
Yüksel (ICU)	19%	0.81 [0.66-0.99]	death	31/42	40/44
Patel	29%	0.71 [0.43-1.14]	death	22/96	26/80
Kumari (RCT)	36%	0.64 [0.26-1.55]	death	7/75	11/75
Darban (RCT)	33%	0.67 [0.14-3.17]	progression	2/10	3/10
Jang	51%	0.49 [0.23-1.01]	no recov.	5/12	6/7
JamaliMo.. (RCT)	0%	1.00 [0.22-4.56]	death	3/30	3/30
Gao	86%	0.14 [0.03-0.72]	death	1/46	5/30
Hamidi-A.. (RCT)	44%	0.56 [0.20-1.51]	death	5/40	9/40
Al Sulaiman (PSM)	15%	0.85 [0.61-1.12]	death	46/142	59/142
Mulhem	-32%	1.32 [1.07-1.62]	death	157/794	359/2,425
Gadhiya	-1%	1.01 [0.48-1.91]	death	19/55	36/226
Hakamifard (RCT)	46%	0.54 [0.14-2.08]	ICU	3/38	5/34
Elhadi (ICU)	-12%	1.12 [0.96-1.31]	death	175/277	106/188
Suna	21%	0.79 [0.44-1.41]	death	17/153	24/170
Pourhoseingholi	13%	0.87 [0.63-1.19]	death	54/199	285/2,269
Li (ICU)	-11%	1.11 [0.79-1.54]	death	7/8	19/24
Vishnuram	54%	0.46 [0.24-0.86]	death	164/8,634	10/241
Özgünay (ICU)	9%	0.91 [0.63-1.30]	death	17/32	75/128
Tan	25%	0.75 [0.10-2.98]	death/int.	1/46	14/115
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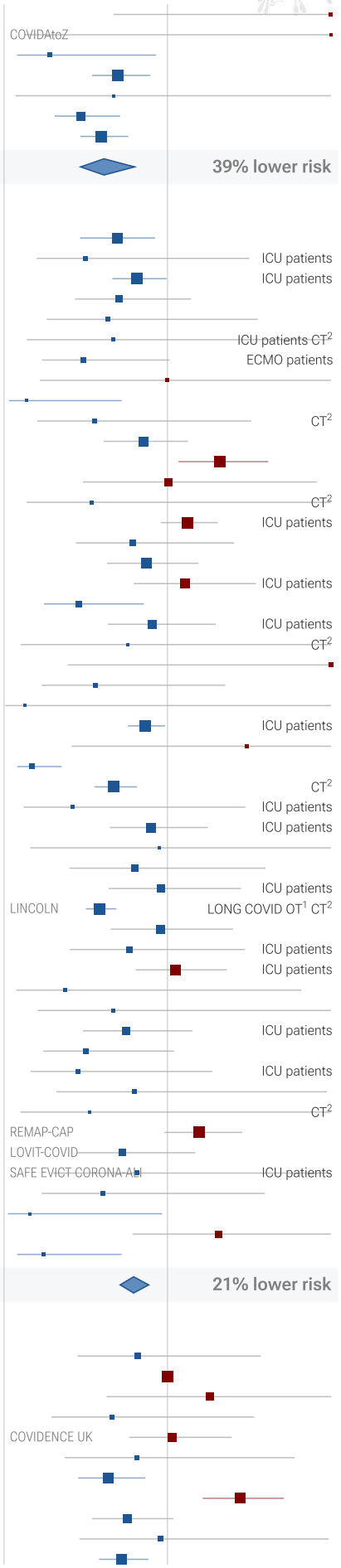
Simsek	44%	0.56 [0.23-1.35]	death	6/58	15/81
Tehrani (RCT)	87%	0.13 [0.01-2.25]	death	0/18	4/26
Majidi (DB RCT)	14%	0.86 [0.76-0.98]	death	26/31	67/69
Baguma	-48%	1.48 [0.41-4.70]	death	385 (n)	96 (n)
Tu	83%	0.17 [0.08-0.35]	death	8/116	26/64
Yang (RCT)	33%	0.67 [0.55-0.81]	recov. time	10 (n)	10 (n)
Gavrielatou (ICU)	58%	0.42 [0.12-1.48]	death	2/10	49/103
Salehi (ICU)	10%	0.90 [0.65-1.25]	death	22/40	52/85
Coppock (RCT)	5%	0.95 [0.16-7.84]	progression	4/44	2/22
Hess (PSW)	20%	0.80 [0.40-1.60]	death	10/25	37/75
Zangeneh (ICU)	4%	0.96 [0.64-1.45]	death	n/a	n/a
Izzo	41%	0.59 [0.50-0.69]	recovery	869 (n)	521 (n)
Fogleman (DB RCT)	4%	0.96 [0.65-1.40]	recovery	32 (n)	34 (n)
Kumar (DB RCT)	23%	0.77 [0.40-1.47]	death	10/30	13/30
Özgültekin (ICU)	-5%	1.05 [0.81-1.36]	death	18/21	18/22
Doocy	63%	0.37 [0.08-1.82]	death	2/64	22/80
Labbani-.. (DB RCT)	33%	0.67 [0.20-2.17]	death	4/37	6/37
Coskun (ICU)	25%	0.75 [0.48-1.15]	death	17/38	24/40
Kyagambiddwa	50%	0.50 [0.24-1.04]	death	246 (all patients)	
Rana (DB RCT)	55%	0.45 [0.16-1.27]	death	5/139	11/139
Mousaviasl (DB RCT)	20%	0.80 [0.32-1.98]	death	8/201	10/200
Seely (DB RCT)	48%	0.52 [0.10-2.71]	progression	2/42	4/44
Adhikari (RCT)	-19%	1.19 [0.98-1.46]	death	1,303 (n)	903 (n)
Adhikari (DB RCT)	28%	0.72 [0.45-1.17]	death	190 (n)	194 (n)
Fowler (DB RCT)	19%	0.81 [0.30-2.19]	death	5/22	7/25
Corrao	39%	0.61 [0.23-1.60]	death	9/104	6/42
Uz	84%	0.16 [0.02-0.97]	death	41 (n)	46 (n)
Dinoi	-32%	1.32 [0.79-2.20]	death	case control	
Bepouka	76%	0.24 [0.08-0.72]	death	185 (n)	225 (n)
Late treatment	21%	0.79 [0.71-0.89]		952/14,960	1,538/9,920

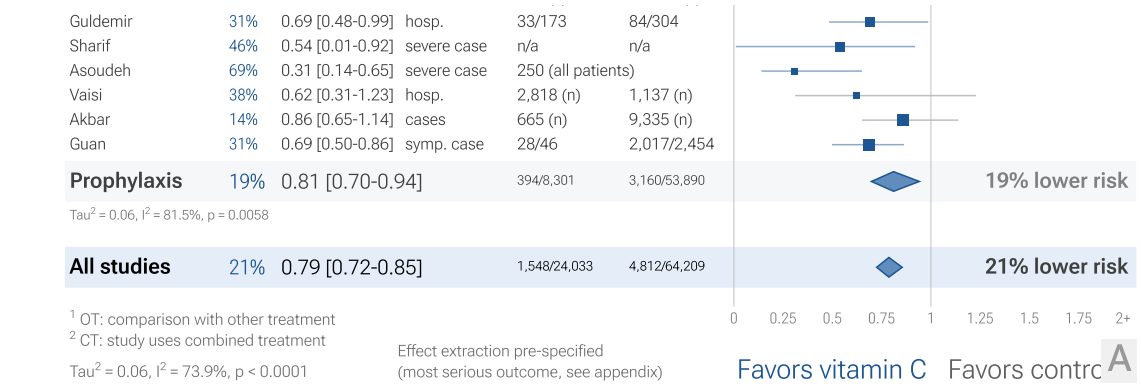
$Tau^2 = 0.07$, $I^2 = 65.4\%$, p < 0.0001

	Improvement, RR [CI]			Treatment	Control
Behera	18%	0.82 [0.45-1.57]	cases	case control	
Louca	0%	1.00 [0.97-1.04]	cases	population-based cohort	
Mahto	-26%	1.26 [0.63-2.28]	IgG+	34/140	59/549
Bejan	34%	0.66 [0.29-1.53]	death	569 (n)	8,637 (n)
Holt	-3%	1.03 [0.77-1.39]	cases	49/1,580	397/13,647
Abdulateef	19%	0.81 [0.37-1.78]	hosp.	8/132	22/295
Aldwihi	36%	0.64 [0.45-0.86]	hosp.	142/505	95/233
Mohseni	-44%	1.44 [1.22-1.71]	cases	34/43	307/560
Nimer	25%	0.75 [0.54-1.04]	hosp.	52/651	167/1,497
Shehab	4%	0.96 [0.46-1.99]	severe case	14/139	12/114
Loucera	28%	0.72 [0.58-0.88]	death	840 (n)	15,128 (n)



Early treatment 39% lower risk

Late treatment 21% lower risk



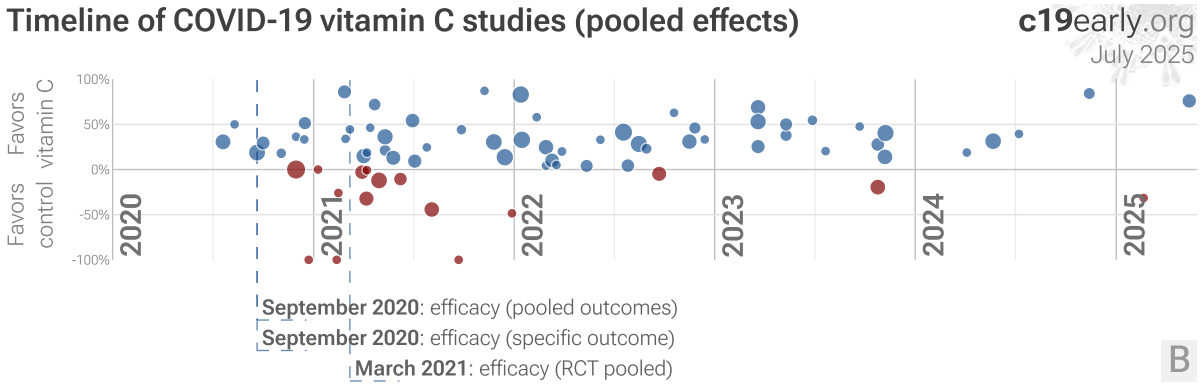


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in vitamin C studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, and pooled outcomes in RCTs. Efficacy based on RCTs only was delayed by 5.6 months, compared to using all studies.

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury[17-29] and cognitive deficits[20,25], cardiovascular complications[30-34], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[35]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

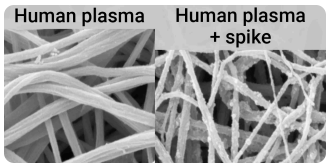


***Figure 2.* SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[16].**

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,36-43], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[44], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research

Vitamin C has been identified by the European Food Safety Authority (EFSA) as having sufficient evidence for a causal relationship between intake and optimal immune system function[1,2,45]. Vitamin C plays a key role in the immune system, supporting the production and function of leukocytes, or white blood cells, which defend against infection

and disease, including the production of lymphocytes, which make antibodies, and enhancing phagocytosis, the process by which immune system cells ingest and destroy viruses and infected cells. Vitamin C is an antioxidant, protecting cells from damage caused by free radicals. Vitamin C inhibits SARS-CoV-2 $3CL^{pro}$ [46,47], inhibits SARS-CoV-2 infection by reducing ACE2 levels in a dose-dependent manner [48], and may limit COVID-19 induced cardiac damage by acting as an antioxidant and potentially reducing the reactive oxygen species (ROS) production induced by the spike protein that contributes to the activation of profibrotic pathways [31]. Vitamin C reduces inflammation, oxidative stress, and NETosis, supporting immune function and vascular protection [49]. Intracellular levels of vitamin C decline during COVID-19 hospitalization suggesting ongoing utilization and depletion of vitamin C [50]. Threonic acid, a metabolite of vitamin C, is lower in mild and severe cases, consistent with increased need for and metabolization of vitamin C with moderate infection, but more limited ability to produce threonic acid in severe infection due to depletion or existing lower levels of vitamin C [51]. Symptomatic COVID-19 is associated with a lower frequency of natural killer (NK) cells, and vitamin C has been shown to improve NK cell numbers and functioning [52,53].

Other infections

Studies have shown efficacy with vitamin C for the common cold [54,55] and acute respiratory tract infections [56].

Analysis

We analyze all significant controlled studies of vitamin C for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, peer-reviewed studies, Randomized Controlled Trials (RCTs), and higher quality studies.

Treatment timing

Figure 3 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

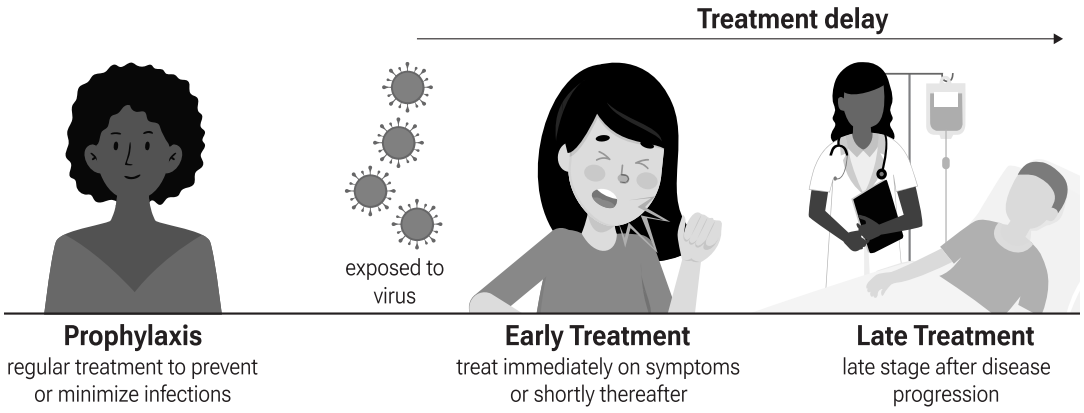


Figure 3. Treatment stages.

Preclinical Research

Vitamin C inhibits SARS-CoV-2 $3CL^{pro}$ [46,47], inhibits SARS-CoV-2 infection by reducing ACE2 levels in a dose-dependent manner [48], and may limit COVID-19 induced cardiac damage by acting as an antioxidant and potentially reducing the reactive oxygen species (ROS) production induced by the spike protein that contributes to the activation of profibrotic pathways [31].

8 *In Silico* studies support the efficacy of vitamin C [47,57-63].

8 *In Vitro* studies support the efficacy of vitamin C [31,46-48,57,64-66].

An *In Vivo* animal study supports the efficacy of vitamin C [48].

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, high-dose IV studies, high-dose IV RCTs with early cessation vs. ongoing treatment, sufficiency studies, peer reviewed studies, non-symptomatic vs. symptomatic results, and long COVID.

	Relative Risk	Studies	Patients
All studies	0.79 [0.72-0.85] ****	75	80K
After exclusions	0.74 [0.66-0.83] ****	44	50K
Peer-reviewed	0.77 [0.71-0.85] ****	68	80K
RCTs	0.80 [0.70-0.91] **	21	4,605
Mortality	0.80 [0.72-0.90] ***	46	40K
Ventilation	0.91 [0.73-1.12]	10	10K
ICU admission	0.86 [0.76-0.98] *	8	10K
Hospitalization	0.81 [0.70-0.93] **	16	10K
Recovery	0.71 [0.65-0.78] ****	10	2,182
Cases	0.97 [0.81-1.16]	7	30K
Viral	1.05 [0.64-1.73]	2	236
RCT mortality	0.86 [0.72-1.02]	14	4,038
RCT hospitalization	0.91 [0.76-1.09]	8	856

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	Late treatment	Prophylaxis
All studies	0.61 [0.47-0.80] ***	0.79 [0.71-0.89] ****	0.81 [0.70-0.94] **
After exclusions	0.70 [0.45-1.09]	0.75 [0.63-0.89] **	0.74 [0.62-0.89] **
Peer-reviewed	0.61 [0.47-0.80] ***	0.77 [0.67-0.87] ****	0.81 [0.70-0.94] **
RCTs	0.70 [0.54-0.90] **	0.81 [0.70-0.94] **	
Mortality	0.60 [0.18-2.05]	0.82 [0.74-0.92] ***	0.71 [0.58-0.87] **
Ventilation		0.92 [0.73-1.15]	0.75 [0.35-1.62]
ICU admission		0.87 [0.74-1.01]	0.85 [0.43-1.69]
Hospitalization	0.60 [0.47-0.76] ****	0.90 [0.76-1.06]	0.71 [0.62-0.82] ****
Recovery	0.75 [0.63-0.90] **	0.71 [0.64-0.79] ****	
Cases			0.97 [0.81-1.16]
Viral	1.05 [0.64-1.73]		
RCT mortality	3.04 [0.13-72.89]	0.85 [0.71-1.02]	
RCT hospitalization	0.69 [0.12-3.98]	0.91 [0.76-1.10]	

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. ** p<0.01 *** p<0.001 **** p<0.0001.

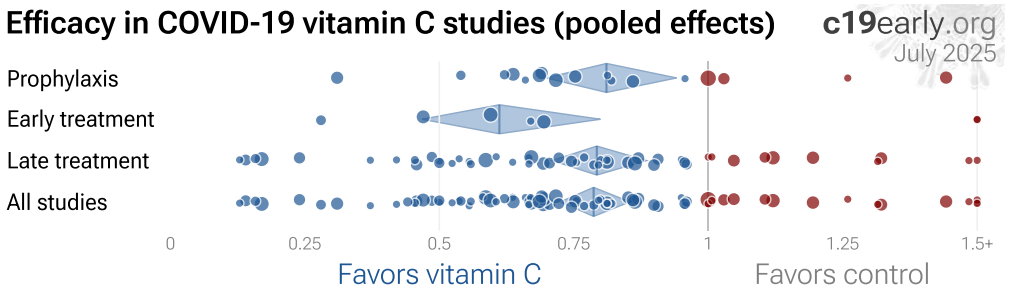


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

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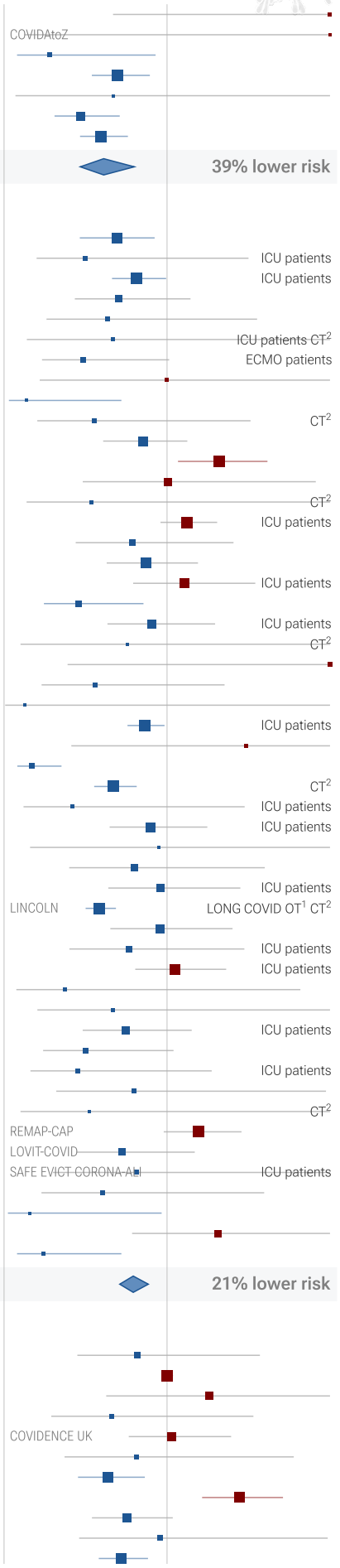
Kyagambiddwa	50%	0.50 [0.24-1.04]	death	246 (all patients)	
Rana (DB RCT)	55%	0.45 [0.16-1.27]	death	5/139	11/139
Mousaviasl (DB RCT)	20%	0.80 [0.32-1.98]	death	8/201	10/200
Seely (DB RCT)	48%	0.52 [0.10-2.71]	progression	2/42	4/44
Adhikari (RCT)	-19%	1.19 [0.98-1.46]	death	1,303 (n)	903 (n)
Adhikari (DB RCT)	28%	0.72 [0.45-1.17]	death	190 (n)	194 (n)
Fowler (DB RCT)	19%	0.81 [0.30-2.19]	death	5/22	7/25
Corrao	39%	0.61 [0.23-1.60]	death	9/104	6/42
Uz	84%	0.16 [0.02-0.97]	death	41 (n)	46 (n)
Dinoi	-32%	1.32 [0.79-2.20]	death	case control	
Bepouka	76%	0.24 [0.08-0.72]	death	185 (n)	225 (n)
Late treatment	21%	0.79 [0.71-0.89]		952/14,960	1,538/9,920

$Tau^2 = 0.07$, $I^2 = 65.4\%$, p < 0.0001

	Improvement, RR [CI]			Treatment	Control
Behera	18%	0.82 [0.45-1.57]	cases	case control	
Louca	0%	1.00 [0.97-1.04]	cases	population-based cohort	
Mahto	-26%	1.26 [0.63-2.28]	IgG+	34/140	59/549
Bejan	34%	0.66 [0.29-1.53]	death	569 (n)	8,637 (n)
Holt	-3%	1.03 [0.77-1.39]	cases	49/1,580	397/13,647
Abdulateef	19%	0.81 [0.37-1.78]	hosp.	8/132	22/295
Aldwihi	36%	0.64 [0.45-0.86]	hosp.	142/505	95/233
Mohseni	-44%	1.44 [1.22-1.71]	cases	34/43	307/560
Nimer	25%	0.75 [0.54-1.04]	hosp.	52/651	167/1,497
Shehab	4%	0.96 [0.46-1.99]	severe case	14/139	12/114
Loucera	28%	0.72 [0.58-0.88]	death	840 (n)	15,128 (n)



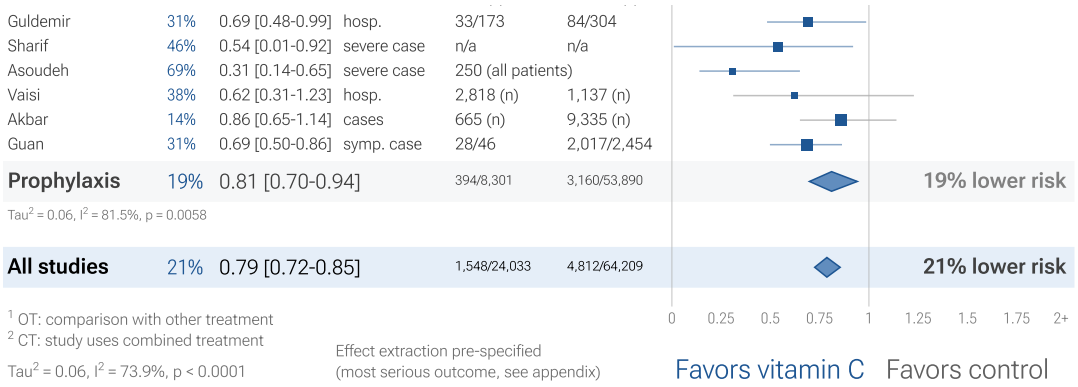


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

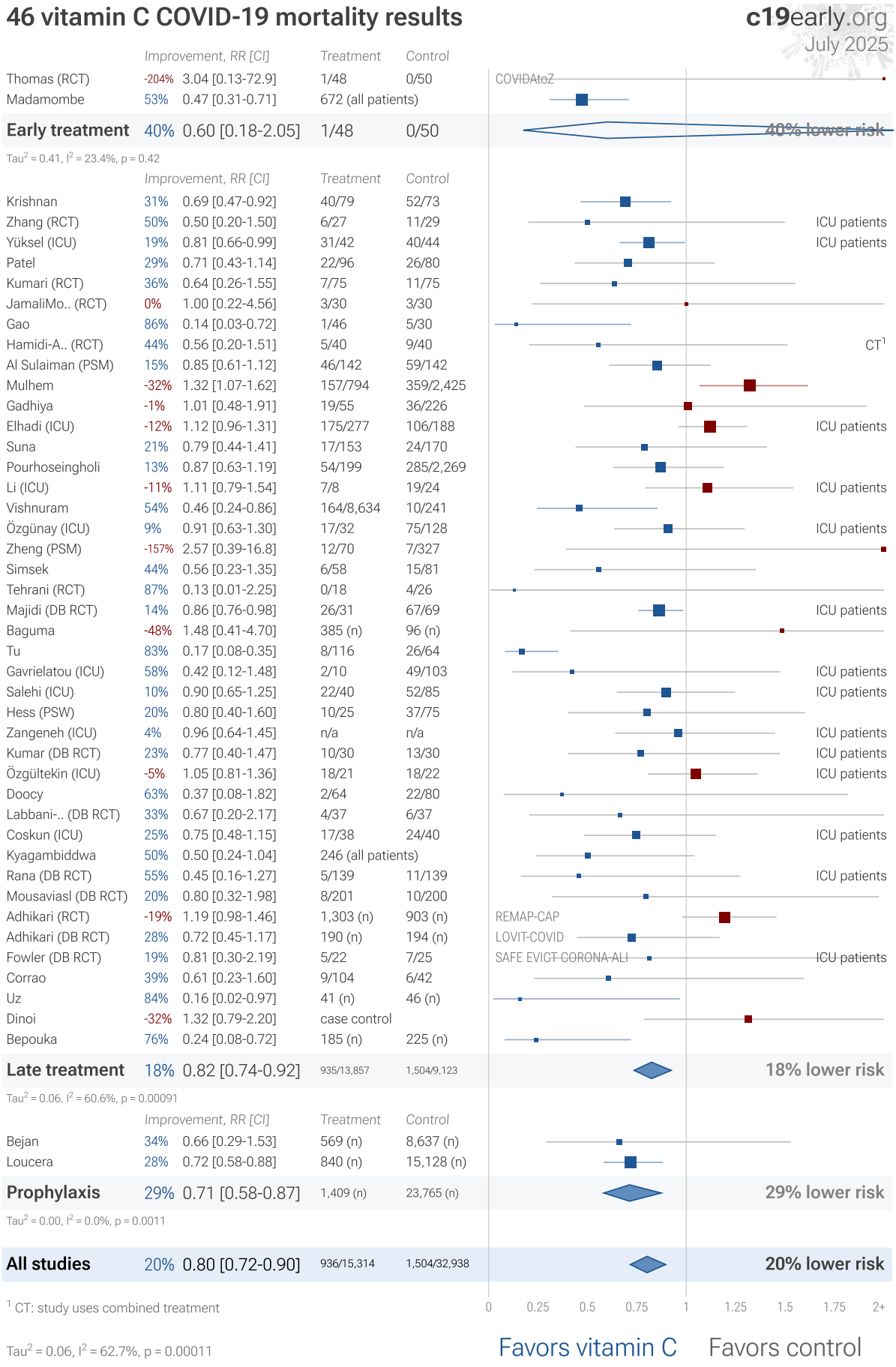


Figure 6. Random effects meta-analysis for mortality results.

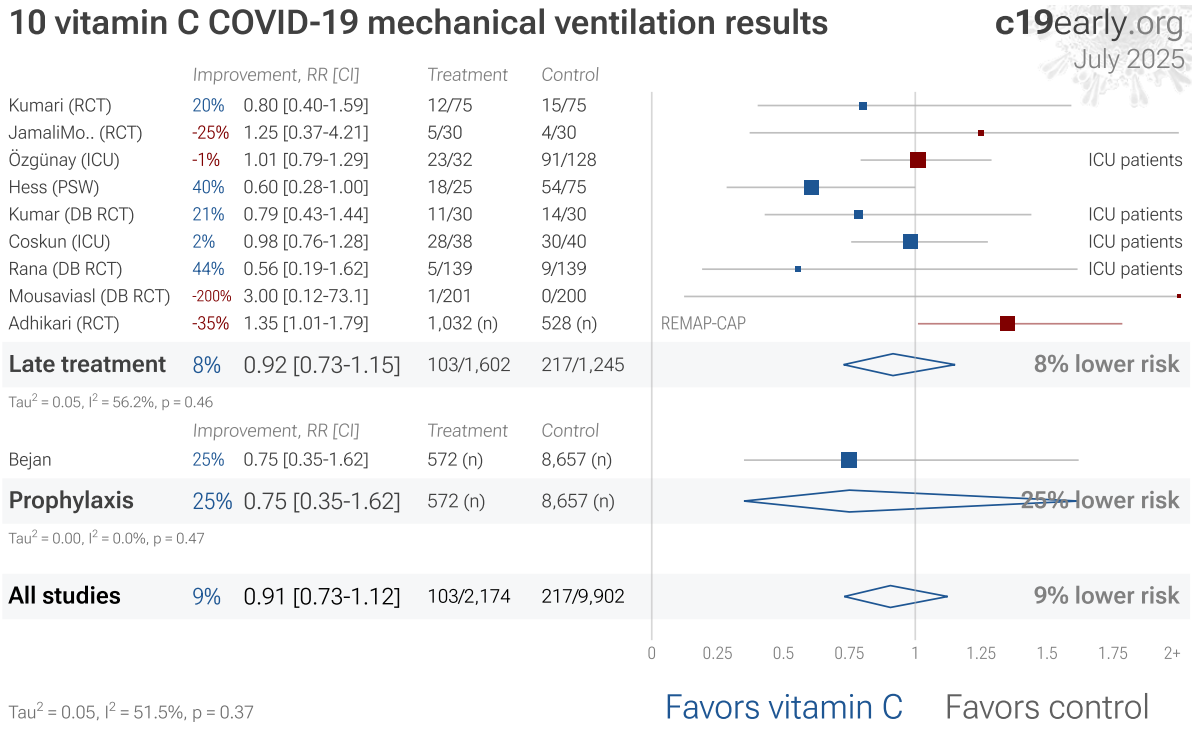


Figure 7. Random effects meta-analysis for ventilation.

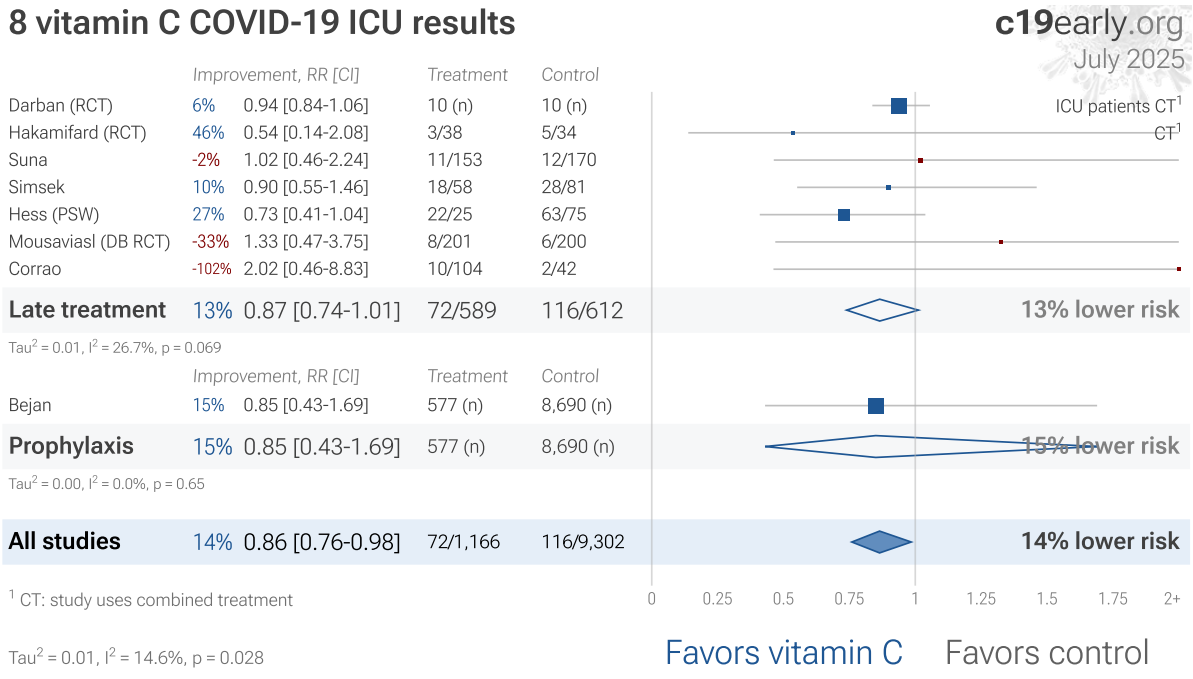


Figure 8. Random effects meta-analysis for ICU admission.

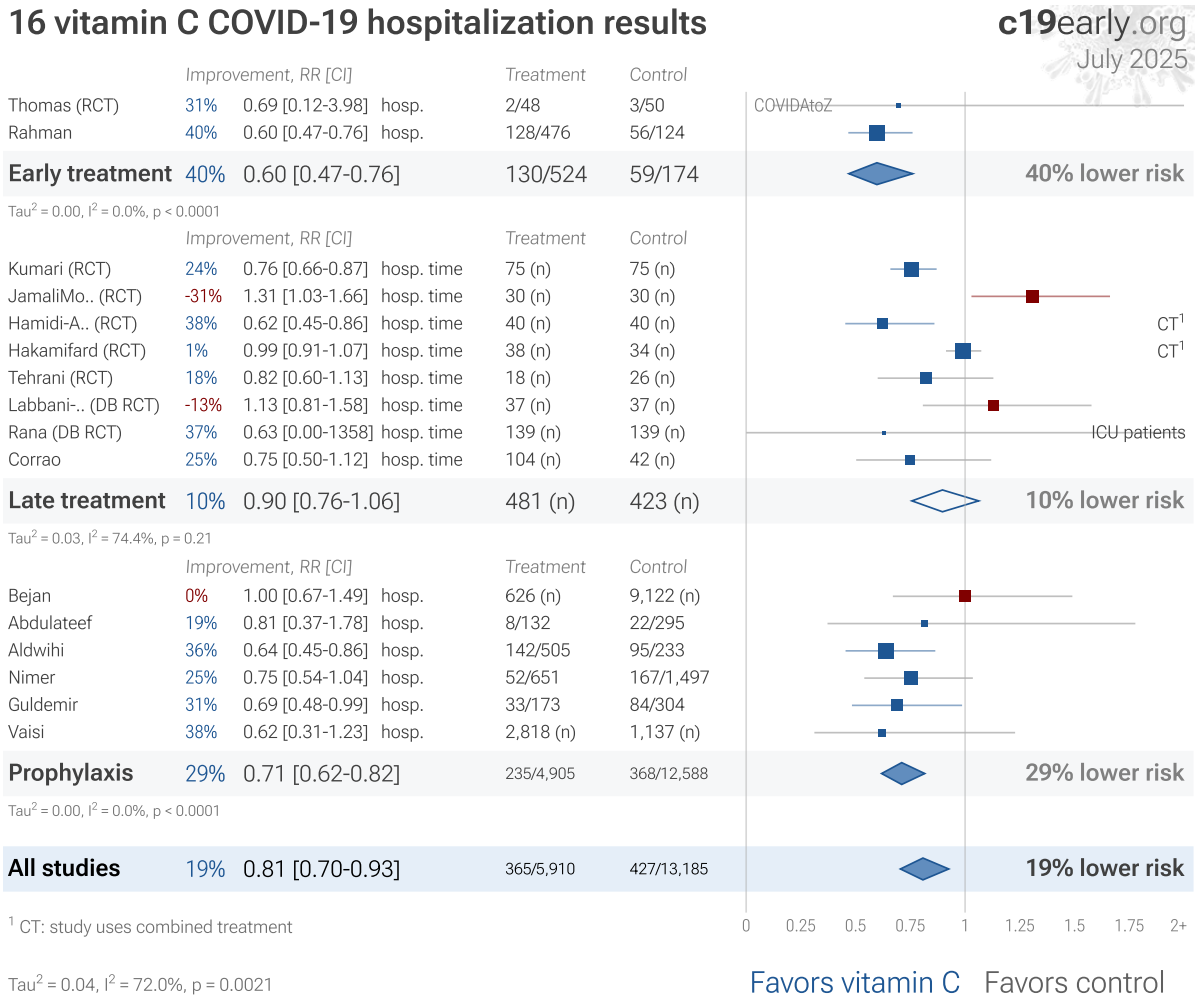


Figure 9. Random effects meta-analysis for hospitalization.

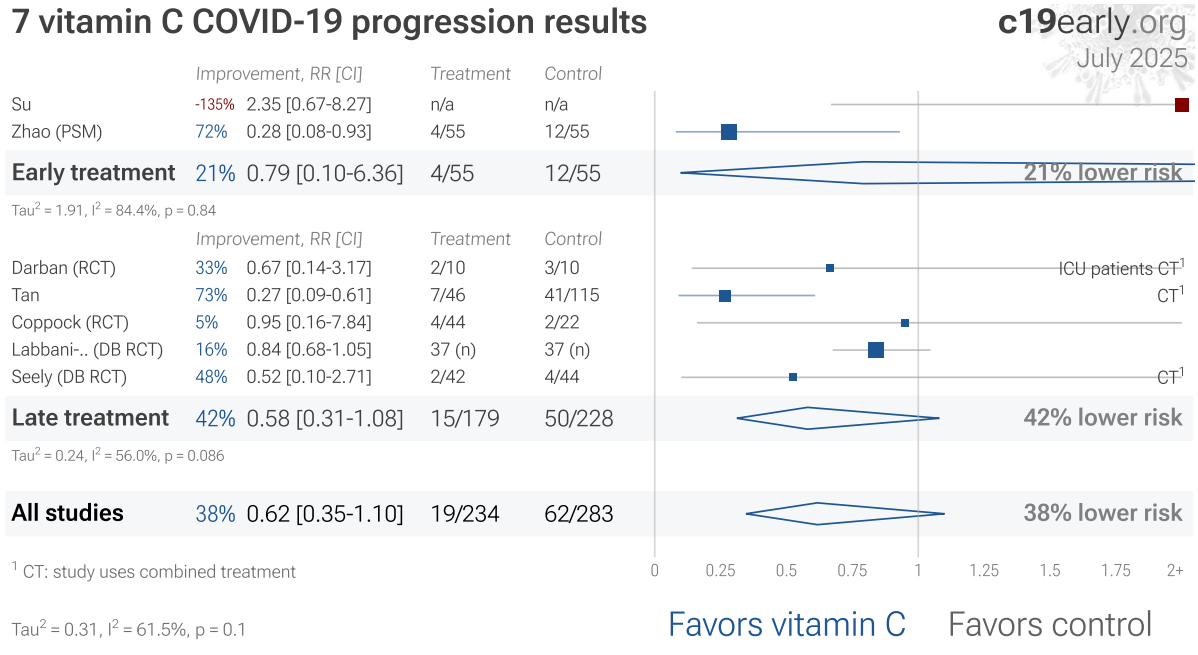


Figure 10. Random effects meta-analysis for progression.

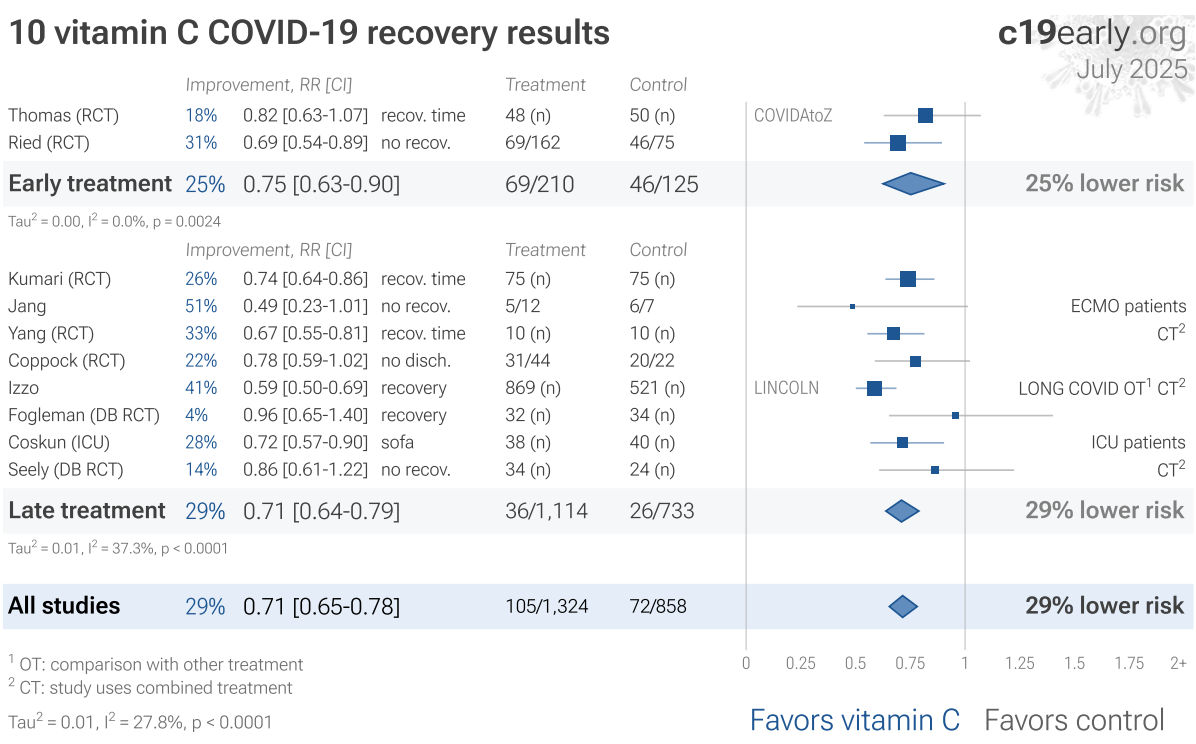


Figure 11. Random effects meta-analysis for recovery.

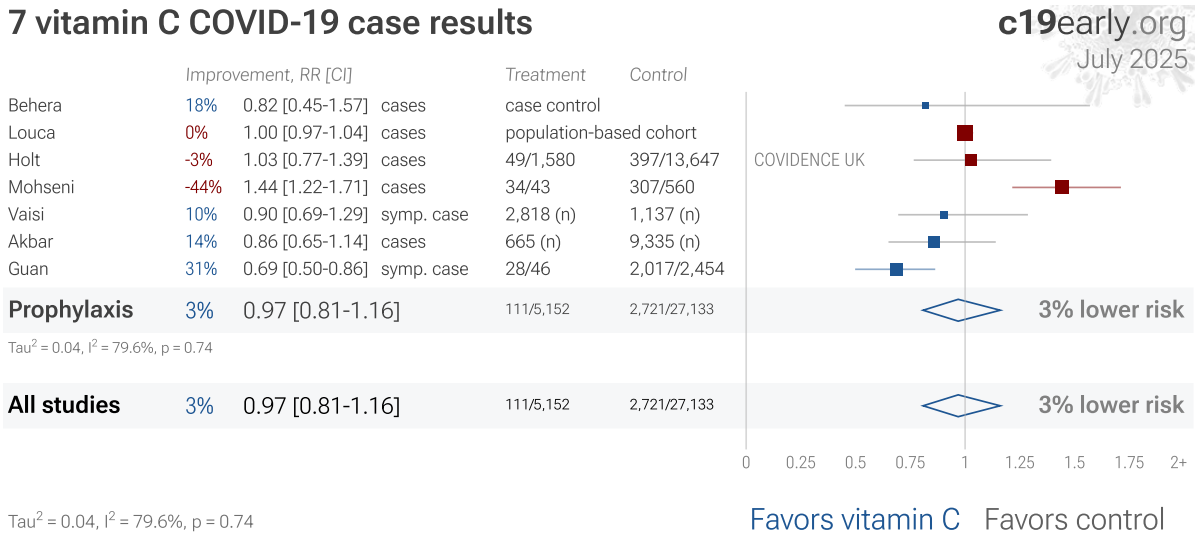


Figure 12. Random effects meta-analysis for cases.

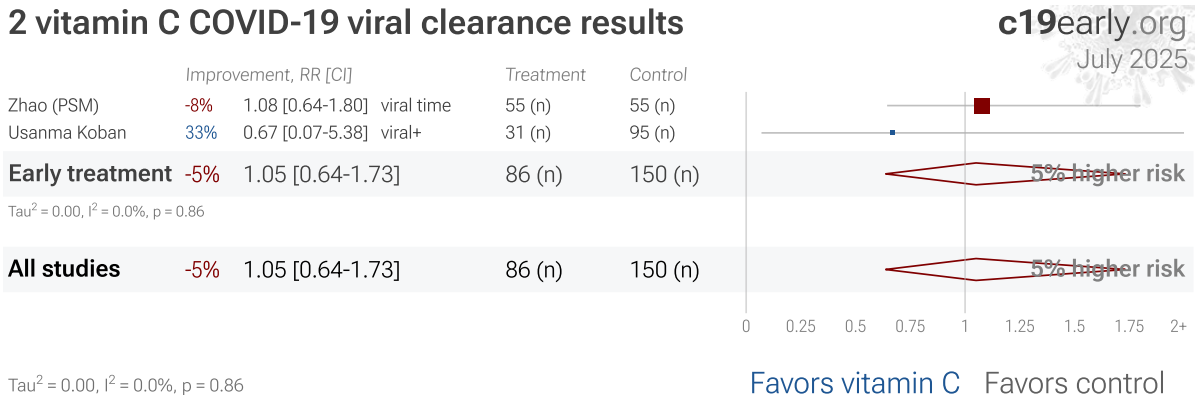


Figure 13. Random effects meta-analysis for viral clearance.

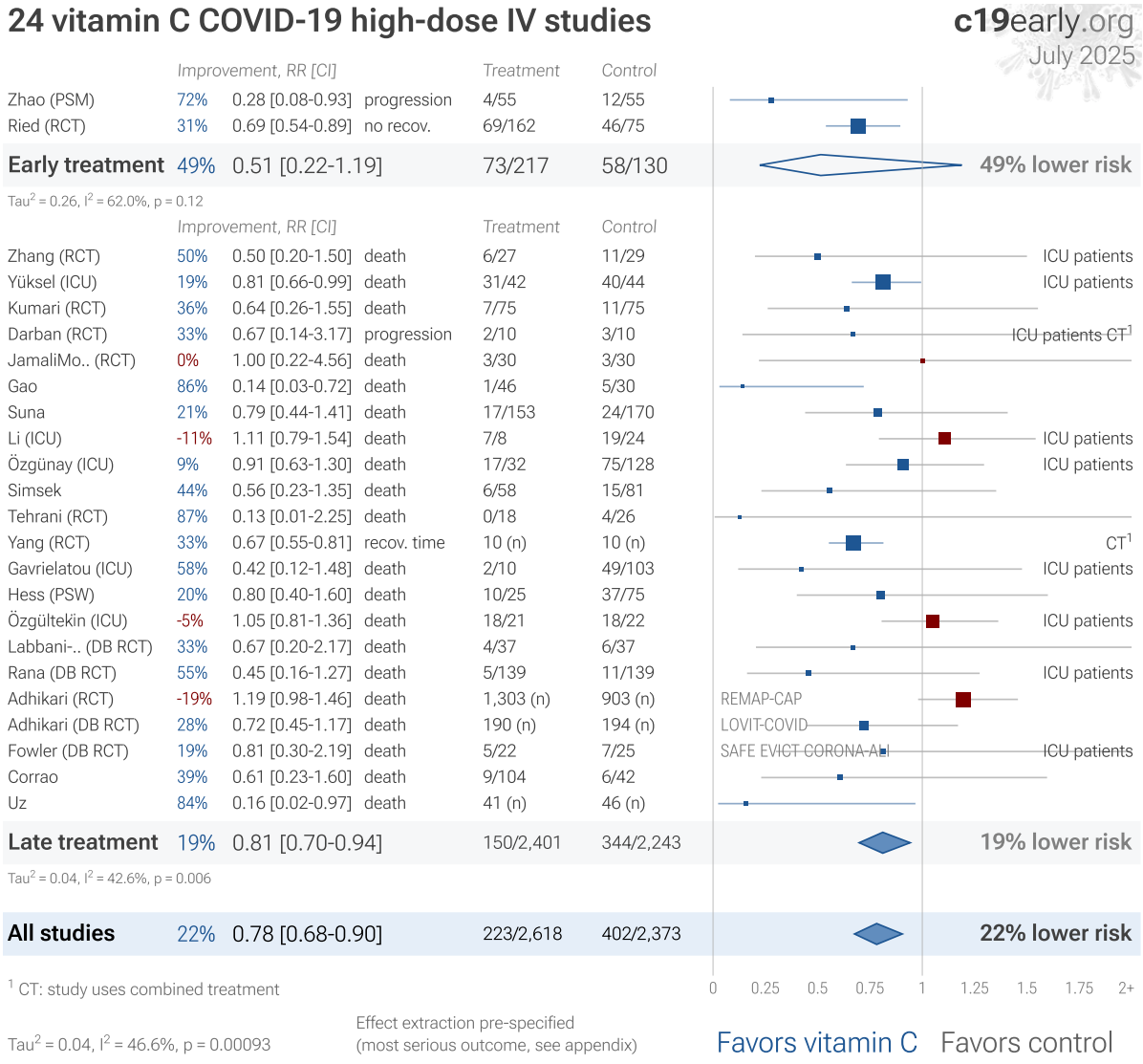


Figure 14. **Random effects meta-analysis for high-dose IV studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

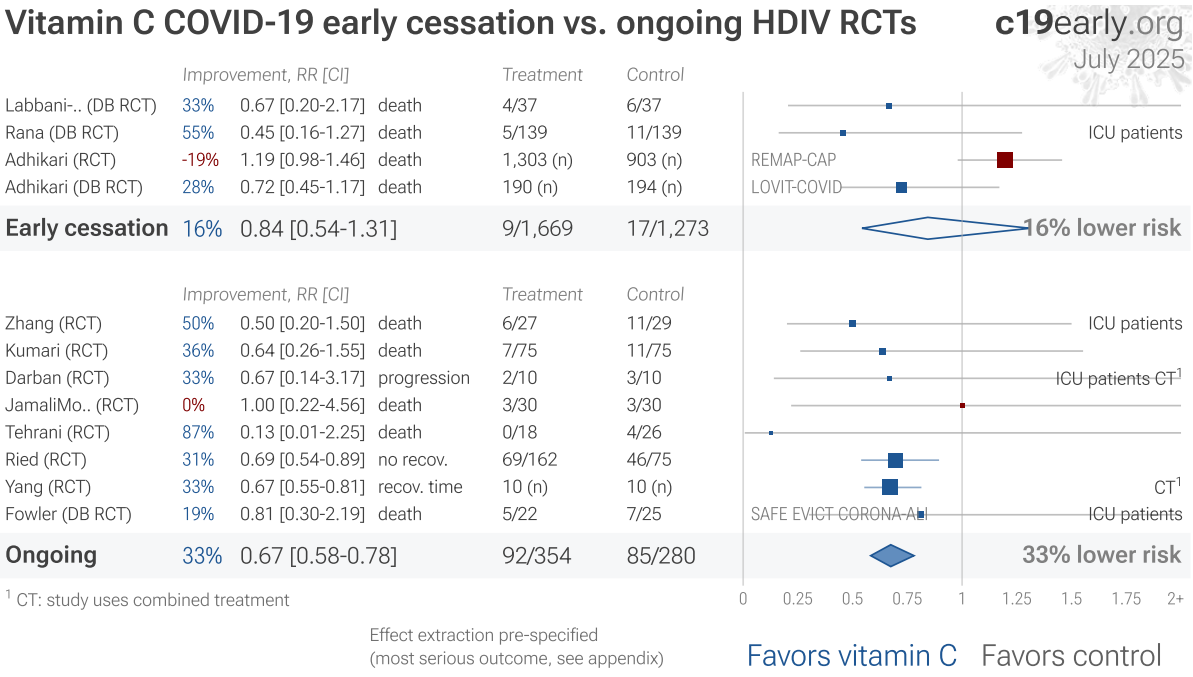


Figure 15. **Random effects meta-analysis for high-dose IV RCTs with early cessation vs. ongoing treatment.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

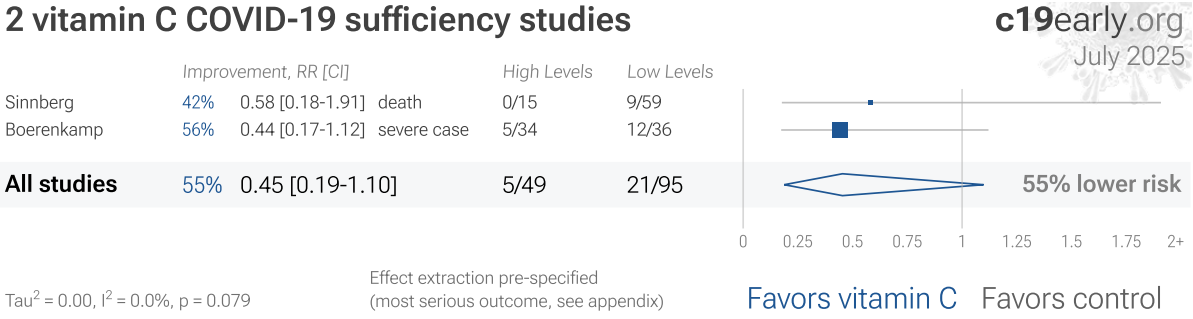


Figure 16. **Random effects meta-analysis for sufficiency studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

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	Improvement, RR [CI]			Treatment	Control	
Su	-135%	2.35 [0.67-8.27]	progression	n/a	n/a	
Thomas (RCT)	-204%	3.04 [0.13-72.9]	death	1/48	0/50	COVIDAtoZ
Zhao (PSM)	72%	0.28 [0.08-0.93]	progression	4/55	12/55	
Ried (RCT)	31%	0.69 [0.54-0.89]	no recov.	69/162	46/75	
Usanma Koban	33%	0.67 [0.07-5.38]	viral+	31 (n)	95 (n)	
Madamombe	53%	0.47 [0.31-0.71]	death	672 (all patients)		
Rahman	40%	0.60 [0.47-0.76]	hosp.	128/476	56/124	
Early treatment	39%	0.61 [0.47-0.80]		202/772	114/399	**39% lower risk**

$Tau^2 = 0.04$, $I^2 = 40.2\%$, p = 0.00035

	Improvement, RR [CI]			Treatment	Control	
Krishnan	31%	0.69 [0.47-0.92]	death	40/79	52/73	
Zhang (RCT)	50%	0.50 [0.20-1.50]	death	6/27	11/29	ICU patients
Patel	29%	0.71 [0.43-1.14]	death	22/96	26/80	
Kumari (RCT)	36%	0.64 [0.26-1.55]	death	7/75	11/75	
Darban (RCT)	33%	0.67 [0.14-3.17]	progression	2/10	3/10	ICU patients CT[2]
Jang	51%	0.49 [0.23-1.01]	no recov.	5/12	6/7	ECMO patients
Gao	86%	0.14 [0.03-0.72]	death	1/46	5/30	
Hamidi-A.. (RCT)	44%	0.56 [0.20-1.51]	death	5/40	9/40	CT[2]
Mulhem	-32%	1.32 [1.07-1.62]	death	157/794	359/2,425	
Gadhiya	-1%	1.01 [0.48-1.91]	death	19/55	36/226	
Hakamifard (RCT)	46%	0.54 [0.14-2.08]	ICU	3/38	5/34	CT[2]
Elhadi (ICU)	-12%	1.12 [0.96-1.31]	death	175/277	106/188	ICU patients
Suna	21%	0.79 [0.44-1.41]	death	17/153	24/170	
Li (ICU)	-11%	1.11 [0.79-1.54]	death	7/8	19/24	ICU patients
Vishnuram	54%	0.46 [0.24-0.86]	death	164/8,634	10/241	
Özgünay (ICU)	9%	0.91 [0.63-1.30]	death	17/32	75/128	ICU patients
Tan	25%	0.75 [0.10-2.98]	death/int.	1/46	14/115	CT[2]
Zheng (PSM)	-157%	2.57 [0.39-16.8]	death	12/70	7/327	
Simsek	44%	0.56 [0.23-1.35]	death	6/58	15/81	
Tehrani (RCT)	87%	0.13 [0.01-2.25]	death	0/18	4/26	
Majidi (DB RCT)	14%	0.86 [0.76-0.98]	death	26/31	67/69	ICU patients
Tu	83%	0.17 [0.08-0.35]	death	8/116	26/64	
Yang (RCT)	33%	0.67 [0.55-0.81]	recov. time	10 (n)	10 (n)	CT[2]
Gavrielatou (ICU)	58%	0.42 [0.12-1.48]	death	2/10	49/103	ICU patients
Coppock (RCT)	5%	0.95 [0.16-7.84]	progression	4/44	2/22	
Hess (PSW)	20%	0.80 [0.40-1.60]	death	10/25	37/75	
Zangeneh (ICU)	4%	0.96 [0.64-1.45]	death	n/a	n/a	ICU patients
Izzo	41%	0.59 [0.50-0.69]	recovery	869 (n)	521 (n)	LINCOLN LONG COVID OT[1] CT[2]
Fogleman (DB RCT)	4%	0.96 [0.65-1.40]	recovery	32 (n)	34 (n)	
Kumar (DB RCT)	23%	0.77 [0.40-1.47]	death	10/30	13/30	ICU patients
Özgültekin (ICU)	-5%	1.05 [0.81-1.36]	death	18/21	18/22	ICU patients
Doocy	63%	0.37 [0.08-1.82]	death	2/64	22/80	
Labbani-.. (DB RCT)	33%	0.67 [0.20-2.17]	death	4/37	6/37	
Coskun (ICU)	25%	0.75 [0.48-1.15]	death	17/38	24/40	ICU patients
Kyagambiddwa	50%	0.50 [0.24-1.04]	death	246 (all patients)		
Rana (DB RCT)	55%	0.45 [0.16-1.27]	death	5/139	11/139	ICU patients
Mousaviasl (DB RCT)	20%	0.80 [0.32-1.98]	death	8/201	10/200	
Seely (DB RCT)	48%	0.52 [0.10-2.71]	progression	2/42	4/44	CT[2]
Adhikari (RCT)	-19%	1.19 [0.98-1.46]	death	1,303 (n)	903 (n)	REMAP-CAP
Adhikari (DB RCT)	28%	0.72 [0.45-1.17]	death	190 (n)	194 (n)	LOVIT-COVID
Corrao	39%	0.61 [0.23-1.60]	death	9/104	6/42	
Uz	84%	0.16 [0.02-0.97]	death	41 (n)	46 (n)	
Dinoi	-32%	1.32 [0.79-2.20]	death	case control		
Bepouka	76%	0.24 [0.08-0.72]	death	185 (n)	225 (n)	
Late treatment	23%	0.77 [0.67-0.87]		791/14,100	1,092/7,229	**23% lower risk**

$Tau^2 = 0.09$, $I^2 = 70.0\%$, p < 0.0001

	Improvement, RR [CI]			Treatment	Control	
Behera	18%	0.82 [0.45-1.57]	cases	case control		
Louca	0%	1.00 [0.97-1.04]	cases	population-based cohort		
Mahto	-26%	1.26 [0.63-2.28]	IgG+	34/140	59/549	
Bejan	34%	0.66 [0.29-1.53]	death	569 (n)	8,637 (n)	
Holt	-3%	1.03 [0.77-1.39]	cases	49/1,580	397/13,647	COVIDENCE UK
Abdulateef	19%	0.81 [0.37-1.78]	hosp.	8/132	22/295	
Aldwihi	36%	0.64 [0.45-0.86]	hosp.	142/505	95/233	
Mohseni	-44%	1.44 [1.22-1.71]	cases	34/43	307/560	
Nimer	25%	0.75 [0.54-1.04]	hosp.	52/651	167/1,497	
Shehab	4%	0.96 [0.46-1.99]	severe case	14/139	12/114	
Loucera	28%	0.72 [0.58-0.88]	death	840 (n)	15,128 (n)	
Guldemir	31%	0.69 [0.48-0.99]	hosp.	33/173	84/304	
Sharif	46%	0.54 [0.01-0.92]	severe case	n/a	n/a	
Asoudeh	69%	0.31 [0.14-0.65]	severe case	250 (all patients)		
Vaisi	38%	0.62 [0.31-1.23]	hosp.	2,818 (n)	1,137 (n)	
Akbar	14%	0.86 [0.65-1.14]	cases	665 (n)	9,335 (n)	
Guan	31%	0.69 [0.50-0.86]	symp. case	28/46	2,017/2,454	

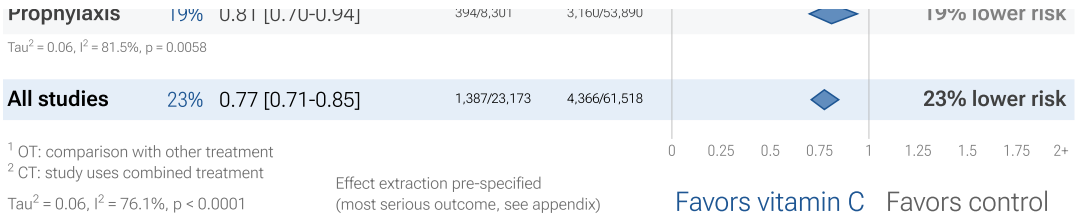

Figure 17. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

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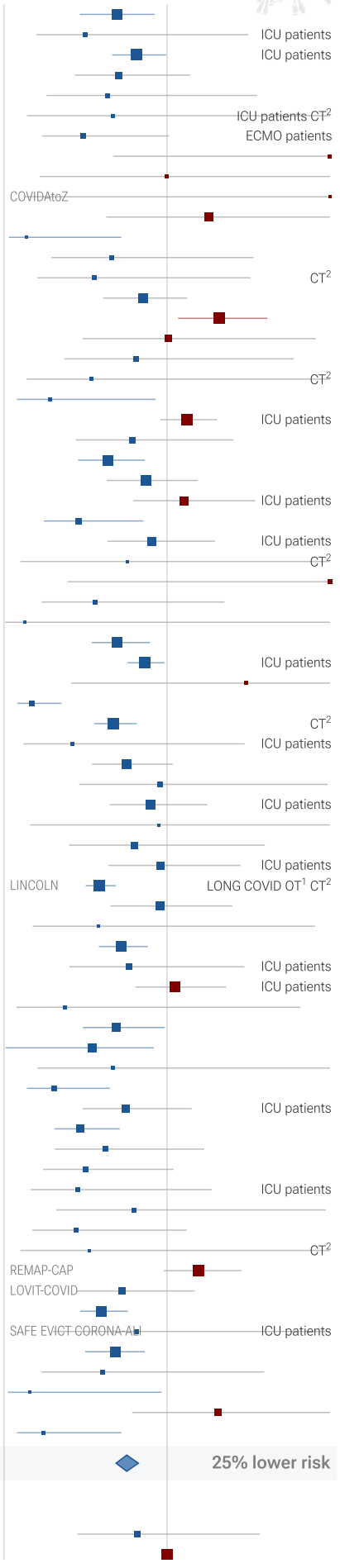
	Improvement, RR [CI]			Treatment	Control
Krishnan	31%	0.69 [0.47-0.92]	death	40/79	52/73
Zhang (RCT)	50%	0.50 [0.20-1.50]	death	6/27	11/29
Yüksel (ICU)	19%	0.81 [0.66-0.99]	death	31/42	40/44
Patel	29%	0.71 [0.43-1.14]	death	22/96	26/80
Kumari (RCT)	36%	0.64 [0.26-1.55]	death	7/75	11/75
Darban (RCT)	33%	0.67 [0.14-3.17]	progression	2/10	3/10
Jang	51%	0.49 [0.23-1.01]	no recov.	5/12	6/7
Su	-135%	2.35 [0.67-8.27]	progression	n/a	n/a
JamaliMo.. (RCT)	0%	1.00 [0.22-4.56]	death	3/30	3/30
Thomas (RCT)	-204%	3.04 [0.13-72.9]	death	1/48	0/50
Mahto	-26%	1.26 [0.63-2.28]	IgG+	34/140	59/549
Gao	86%	0.14 [0.03-0.72]	death	1/46	5/30
Bejan	34%	0.66 [0.29-1.53]	death	569 (n)	8,637 (n)
Hamidi-A.. (RCT)	44%	0.56 [0.20-1.51]	death	5/40	9/40
Al Sulaiman (PSM)	15%	0.85 [0.61-1.12]	death	46/142	59/142
Mulhem	-32%	1.32 [1.07-1.62]	death	157/794	359/2,425
Gadhiya	-1%	1.01 [0.48-1.91]	death	19/55	36/226
Abdulateef	19%	0.81 [0.37-1.78]	hosp.	8/132	22/295
Hakamifard (RCT)	46%	0.54 [0.14-2.08]	ICU	3/38	5/34
Zhao (PSM)	72%	0.28 [0.08-0.93]	progression	4/55	12/55
Elhadi (ICU)	-12%	1.12 [0.96-1.31]	death	175/277	106/188
Suna	21%	0.79 [0.44-1.41]	death	17/153	24/170
Aldwihi	36%	0.64 [0.45-0.86]	hosp.	142/505	95/233
Pourhoseingholi	13%	0.87 [0.63-1.19]	death	54/199	285/2,269
Li (ICU)	-11%	1.11 [0.79-1.54]	death	7/8	19/24
Vishnuram	54%	0.46 [0.24-0.86]	death	164/8,634	10/241
Özgünay (ICU)	9%	0.91 [0.63-1.30]	death	17/32	75/128
Tan	25%	0.75 [0.10-2.98]	death/int.	1/46	14/115
Zheng (PSM)	-157%	2.57 [0.39-16.8]	death	12/70	7/327
Simsek	44%	0.56 [0.23-1.35]	death	6/58	15/81
Tehrani (RCT)	87%	0.13 [0.01-2.25]	death	0/18	4/26
Ried (RCT)	31%	0.69 [0.54-0.89]	no recov.	69/162	46/75
Majidi (DB RCT)	14%	0.86 [0.76-0.98]	death	26/31	67/69
Baguma	-48%	1.48 [0.41-4.70]	death	385 (n)	96 (n)
Tu	83%	0.17 [0.08-0.35]	death	8/116	26/64
Yang (RCT)	33%	0.67 [0.55-0.81]	recov. time	10 (n)	10 (n)
Gavrielatou (ICU)	58%	0.42 [0.12-1.48]	death	2/10	49/103
Nimer	25%	0.75 [0.54-1.04]	hosp.	52/651	167/1,497
Shehab	4%	0.96 [0.46-1.99]	severe case	14/139	12/114
Salehi (ICU)	10%	0.90 [0.65-1.25]	death	22/40	52/85
Coppock (RCT)	5%	0.95 [0.16-7.84]	progression	4/44	2/22
Hess (PSW)	20%	0.80 [0.40-1.60]	death	10/25	37/75
Zangeneh (ICU)	4%	0.96 [0.64-1.45]	death	n/a	n/a
Izzo	41%	0.59 [0.50-0.69]	recovery	869 (n)	521 (n)
Fogleman (DB RCT)	4%	0.96 [0.65-1.40]	recovery	32 (n)	34 (n)
Sinnberg	42%	0.58 [0.18-1.91]	death	0/15	9/59
Loucera	28%	0.72 [0.58-0.88]	death	840 (n)	15,128 (n)
Kumar (DB RCT)	23%	0.77 [0.40-1.47]	death	10/30	13/30
Özgültekin (ICU)	-5%	1.05 [0.81-1.36]	death	18/21	18/22
Doocy	63%	0.37 [0.08-1.82]	death	2/64	22/80
Guldemir	31%	0.69 [0.48-0.99]	hosp.	33/173	84/304
Sharif	46%	0.54 [0.01-0.92]	severe case	n/a	n/a
Labbani-.. (DB RCT)	33%	0.67 [0.20-2.17]	death	4/37	6/37
Asoudeh	69%	0.31 [0.14-0.65]	severe case	250 (all patients)	
Coskun (ICU)	25%	0.75 [0.48-1.15]	death	17/38	24/40
Madamombe	53%	0.47 [0.31-0.71]	death	672 (all patients)	
Vaisi	38%	0.62 [0.31-1.23]	hosp.	2,818 (n)	1,137 (n)
Kyagambiddwa	50%	0.50 [0.24-1.04]	death	246 (all patients)	
Rana (DB RCT)	55%	0.45 [0.16-1.27]	death	5/139	11/139
Mousaviasl (DB RCT)	20%	0.80 [0.32-1.98]	death	8/201	10/200
Boerenkamp	56%	0.44 [0.17-1.12]	severe case	5/34	12/36
Seely (DB RCT)	48%	0.52 [0.10-2.71]	progression	2/42	4/44
Adhikari (RCT)	-19%	1.19 [0.98-1.46]	death	1,303 (n)	903 (n)
Adhikari (DB RCT)	28%	0.72 [0.45-1.17]	death	190 (n)	194 (n)
Rahman	40%	0.60 [0.47-0.76]	hosp.	128/476	56/124
Fowler (DB RCT)	19%	0.81 [0.30-2.19]	death	5/22	7/25
Guan	31%	0.69 [0.50-0.86]	symp. case	28/46	2,017/2,454
Corrao	39%	0.61 [0.23-1.60]	death	9/104	6/42
Uz	84%	0.16 [0.02-0.97]	death	41 (n)	46 (n)
Dinoi	-32%	1.32 [0.79-2.20]	death	case control	
Bepouka	76%	0.24 [0.08-0.72]	death	185 (n)	225 (n)
Symptomatic	25%	0.75 [0.69-0.82]		1,470/21,763	4,129/40,667

$Tau^2 = 0.07$, $I^2 = 65.1\%$, $p < 0.0001$

	Improvement, RR [CI]			Treatment	Control
Behera	18%	0.82 [0.45-1.57]	cases	case control	
Louca	0%	1.00 [0.97-1.04]	cases	population-based cohort	



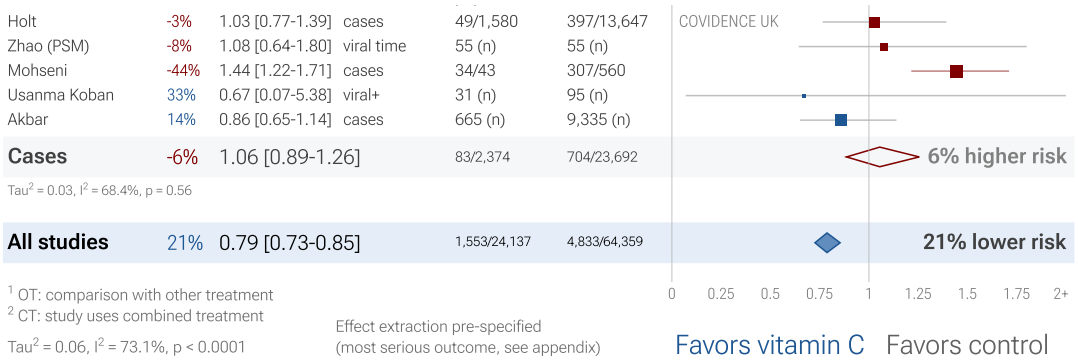


Figure 18. **Random effects meta-analysis for non-symptomatic vs. symptomatic results.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

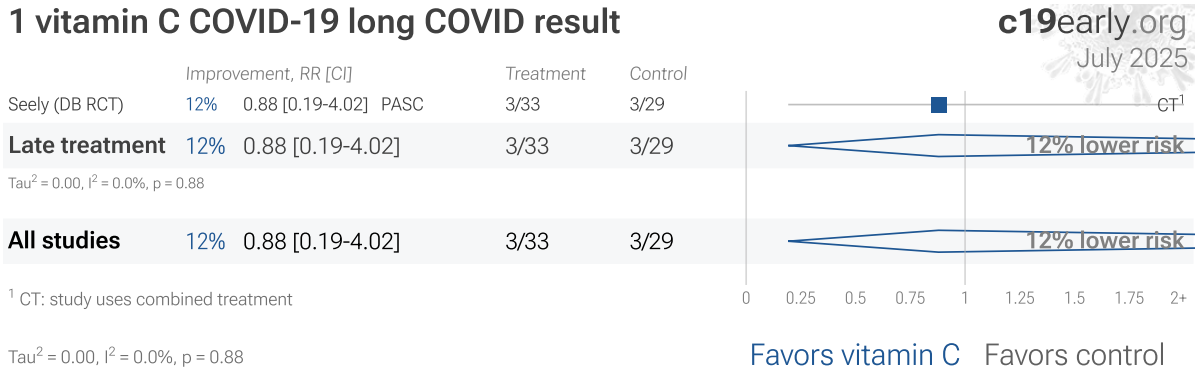


Figure 19. **Random effects meta-analysis for long COVID.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Figure 20 shows a comparison of results for RCTs and observational studies. Figure 21, 22, and 23 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

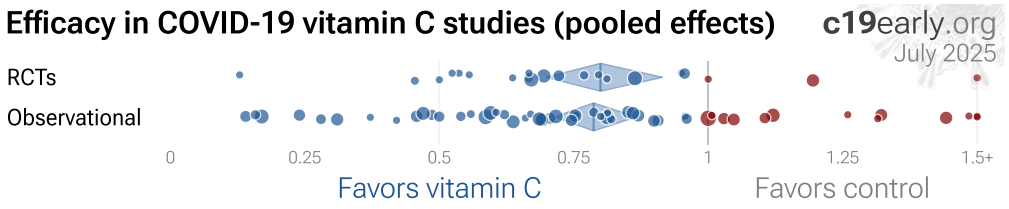


Figure 20. **Results for RCTs and observational studies.**

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases[69], and analysis of double-blind RCTs has identified extreme levels of bias[70]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases;

errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs

RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment

High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 172 treatments we have analyzed, 67% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

RCT bias for widely available treatments

RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for vitamin C are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Observational studies have been shown to be reliable

Evidence shows that observational studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* analyzed reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. We performed a similar analysis across the 172 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.98 [0.92-1.05][75]. Similar results are found for all low-cost treatments, RR 1.00 [0.91-1.09]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the supplementary data. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases.

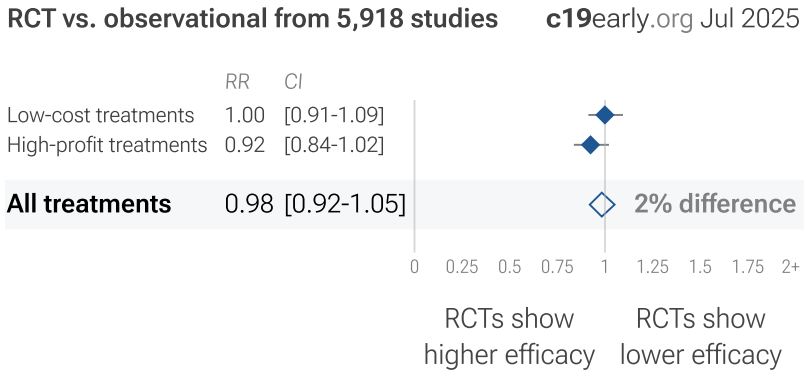


Figure 24. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[72].**

Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or remote survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [77,78].

Using all studies identifies efficacy 8+ months faster (9+ months for low-cost treatments)

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 58% have been confirmed in RCTs, with a mean delay of 7.7 months (64% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

Summary

We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

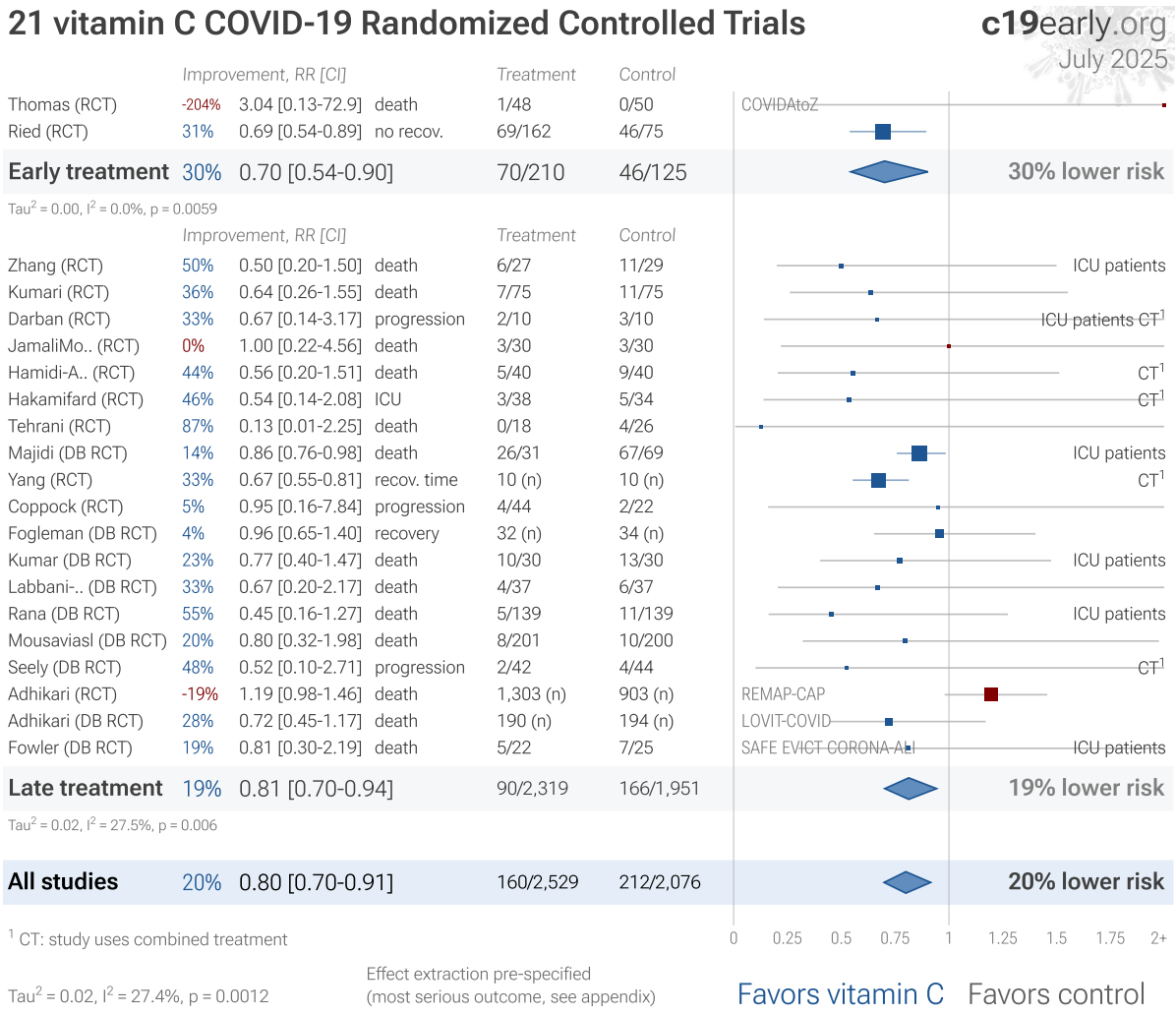


Figure 21. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

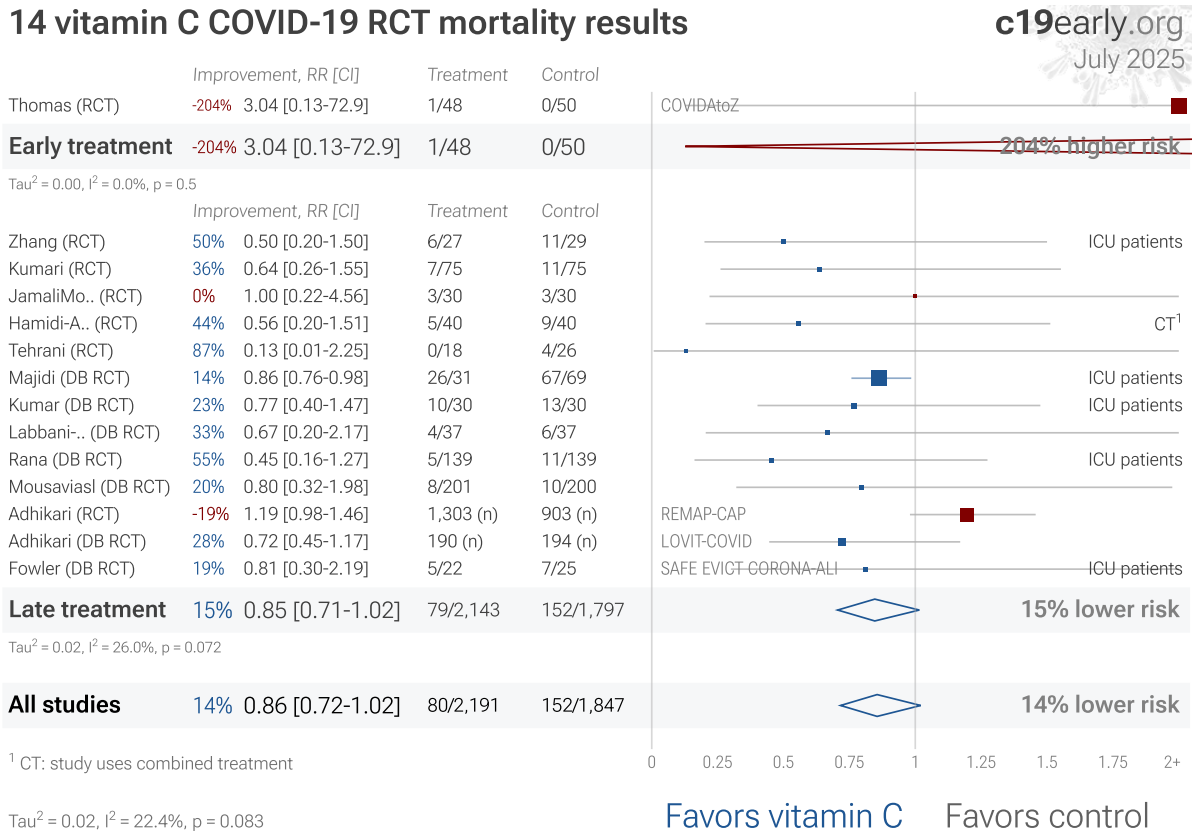


Figure 22. Random effects meta-analysis for RCT mortality results.

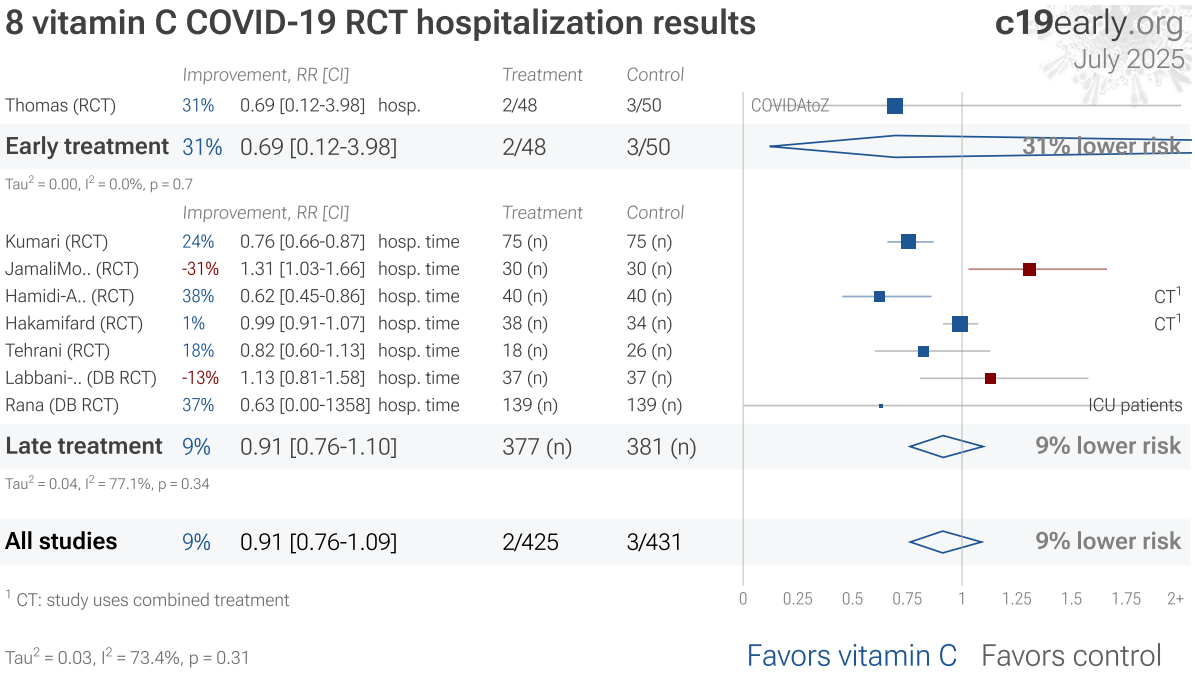


Figure 23. Random effects meta-analysis for RCT hospitalization results.

NIH

NIH provides an analysis of vitamin C for COVID-19[79], concluding that there is insufficient evidence to recommend for or against use. However, they appear to have not examined the majority of the evidence. For example, considering RCTs providing clinical results for COVID-19 and vitamin C, they reference only[80-85], and appear not to know about 15 other RCTs[86-100] as shown in Figure 25. Notably, the NIH selection does not correspond to the most relevant and highest quality studies, for example including *Zhang et al.*, with very late treatment of ICU patients. Authors do not reference any of the 54 observational studies. For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[72].

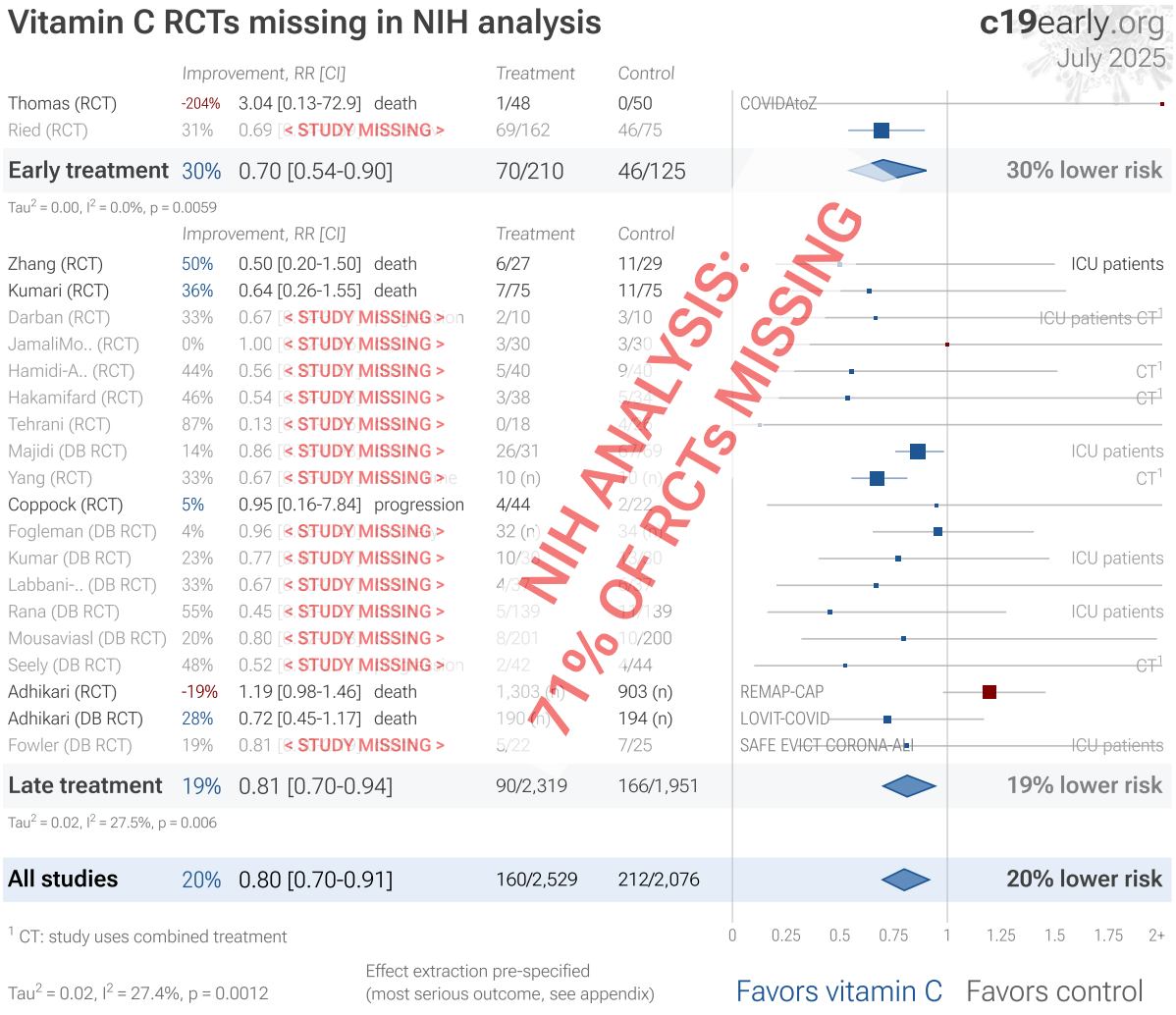


Figure 25. **Analysis by NIH is missing 15 RCTs.**

Unreported RCTs

6 vitamin C RCTs have not reported results[101-106]. The trials report a total of 1,420 patients, with 3 trials having actual enrollment of 602, and the remainder estimated. The results are delayed from 2 years to over 4 years.

Exclusions

To avoid bias in the selection of studies, we analyze all non-retracted studies. Here we show the results after excluding studies with major issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on analysis of each study and identifying when there is a significant chance that limitations will substantially change the outcome of the study. We believe this can be more valuable than checklist-based approaches such as Cochrane GRADE, which can be easily influenced by potential bias, may ignore or underemphasize serious issues not captured in the checklists, and may overemphasize issues unlikely to alter outcomes in specific cases (for example certain specifics of randomization with a very large effect size and well-matched baseline characteristics).

The studies excluded are as below. Figure 26 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Abdulateef, unadjusted results with no group details.

Coskun, very late stage, ICU patients.

Darban, very late stage, ICU patients.

Elhadi, unadjusted results with no group details; very late stage, ICU patients.

Fowler, very late stage, ICU patients.

Gadhiya, substantial unadjusted confounding by indication likely.

Gavrielatou, very late stage, ICU patients.

Guldemir, unadjusted results with no group details.

Holt, significant unadjusted confounding possible.

Jang, very late stage, ECMO patients.

Krishnan, unadjusted results with no group details.

Kumar (B), very late stage, ICU patients.

Li, very late stage, ICU patients.

Majidi, very late stage, ICU patients.

Mohseni, unadjusted results with no group details.

Mulhem, substantial unadjusted confounding by indication likely; substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

Rahman, unadjusted results with no group details; significant unadjusted confounding possible.

Rana, very late stage, ICU patients.

Salehi, unadjusted results with no group details; very late stage, ICU patients.

Shehab, unadjusted results with no group details.

Suna, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

Tu, unadjusted results with no group details.

Vishnuram, unadjusted results with no group details; minimal details of groups provided.

Yang (B), combined treatments may contribute significantly to the effect seen.

Yüksel, very late stage, ICU patients.

Zangeneh, very late stage, ICU patients.

Zhang, very late stage, ICU patients.

Zhao, substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

Zheng, substantial unadjusted confounding by indication likely; immortal time bias may significantly affect results; treatment start times unknown, treatment may not have started at baseline.

Özgültekin, very late stage, ICU patients.

Özgünay, substantial unadjusted confounding by indication likely; very late stage, ICU patients.

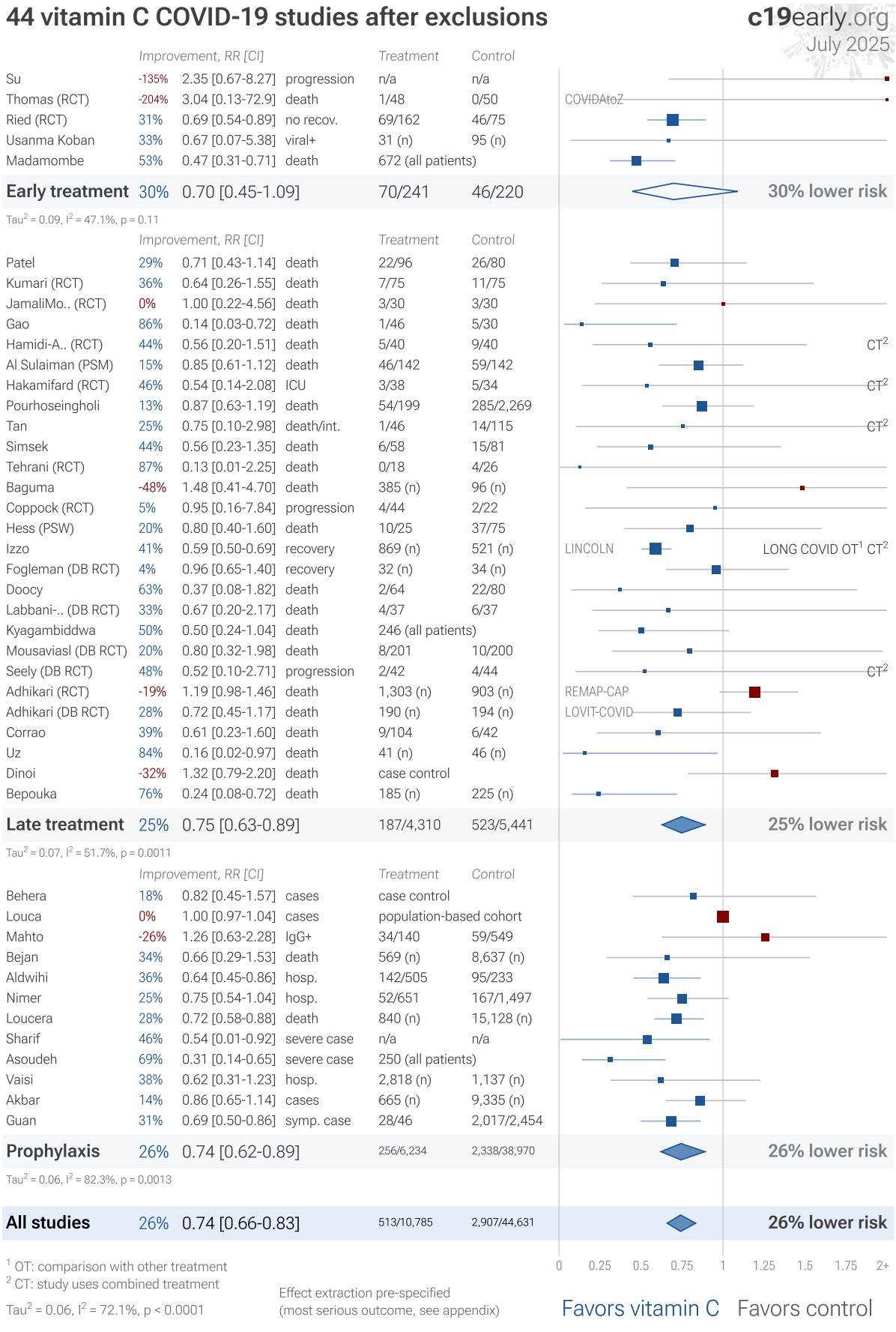


Figure 26. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours [131,132]. Baloxavir marboxil studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar (C) et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases [133]
<24 hours	-33 hours symptoms [134]
24-48 hours	-13 hours symptoms [134]
Inpatients	-2.5 hours to improvement [135]

Table 3. **Studies of baloxavir marboxil for influenza show that early treatment is more effective.**

Figure 27 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

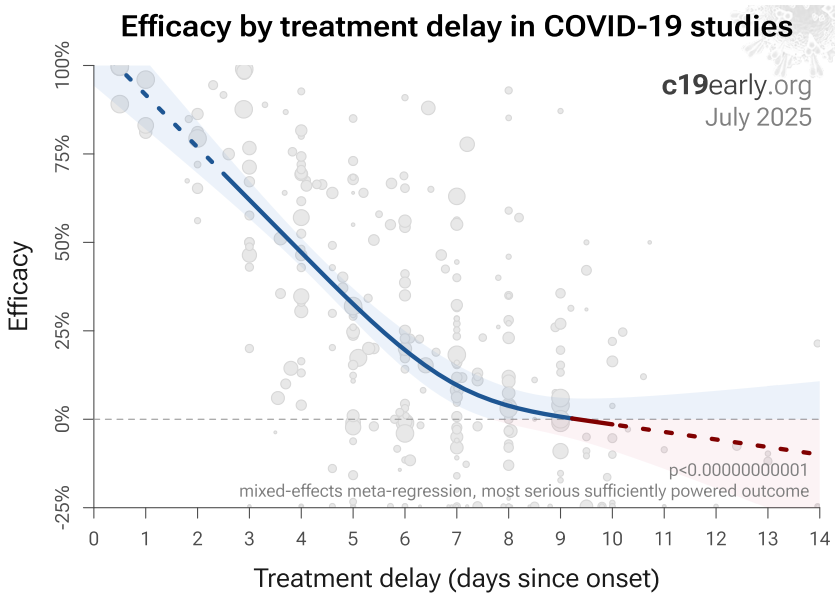


Figure 27. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results, for example as in *López-Medina et al.*

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [137], for example the Gamma variant shows significantly different characteristics [138-141]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants [142,143].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu (B) et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer. Non-prescription supplements may show very wide variations in quality [4,5].

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic [146-162], therefore efficacy may depend strongly on combined treatments.

Effect measured

Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta analysis

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Pooled effects are no longer required to show efficacy as of September 2020

This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however pooled effects are no longer required for vitamin C as of September 2020. Efficacy is now known based on specific outcomes.

Combining studies is required

For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. *"The studies reported different outcomes"* is not a good reason for disregarding results. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Ethical and practical issues limit high-risk trials

Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster and safer collection of evidence.

Validating pooled outcome analysis for COVID-19

For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Analysis of the the association between different outcomes across studies from all 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 28 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 29 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 30 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.000000082$ to $p = 0.0000000033$.

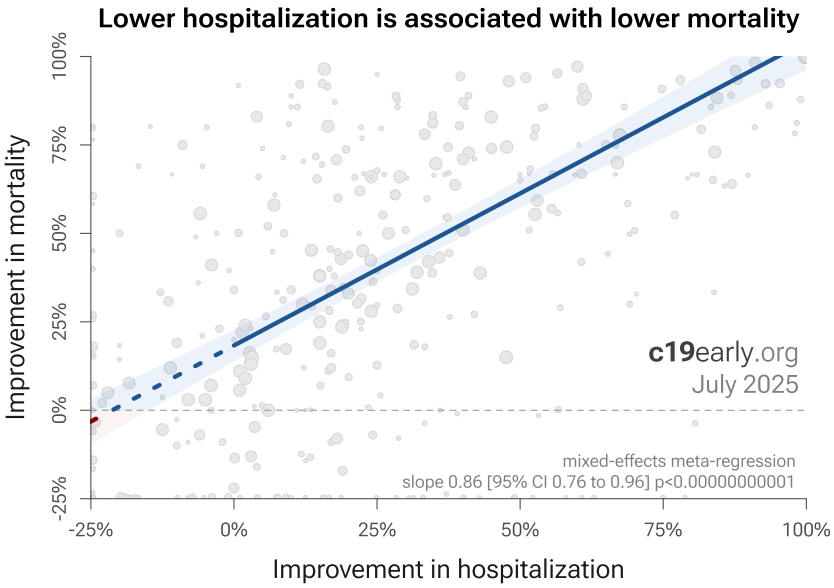


Figure 28. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

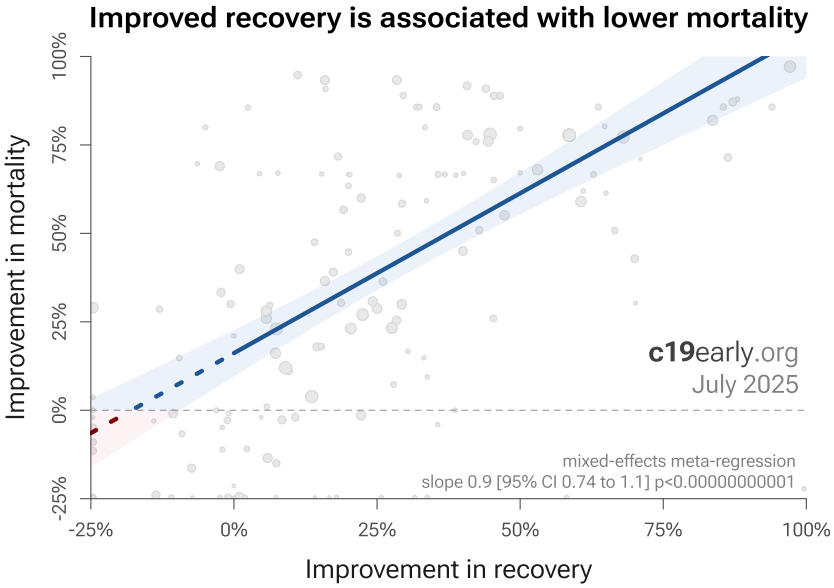


Figure 29. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

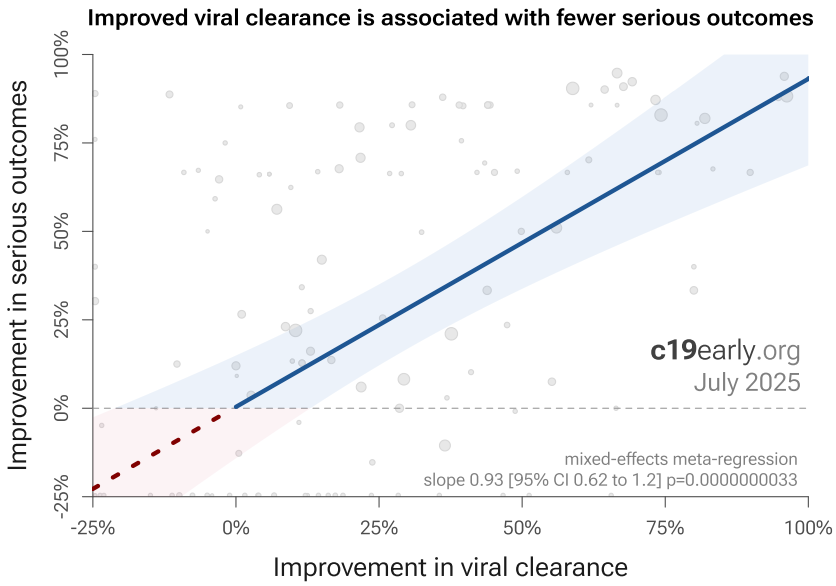


Figure 28. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 31 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

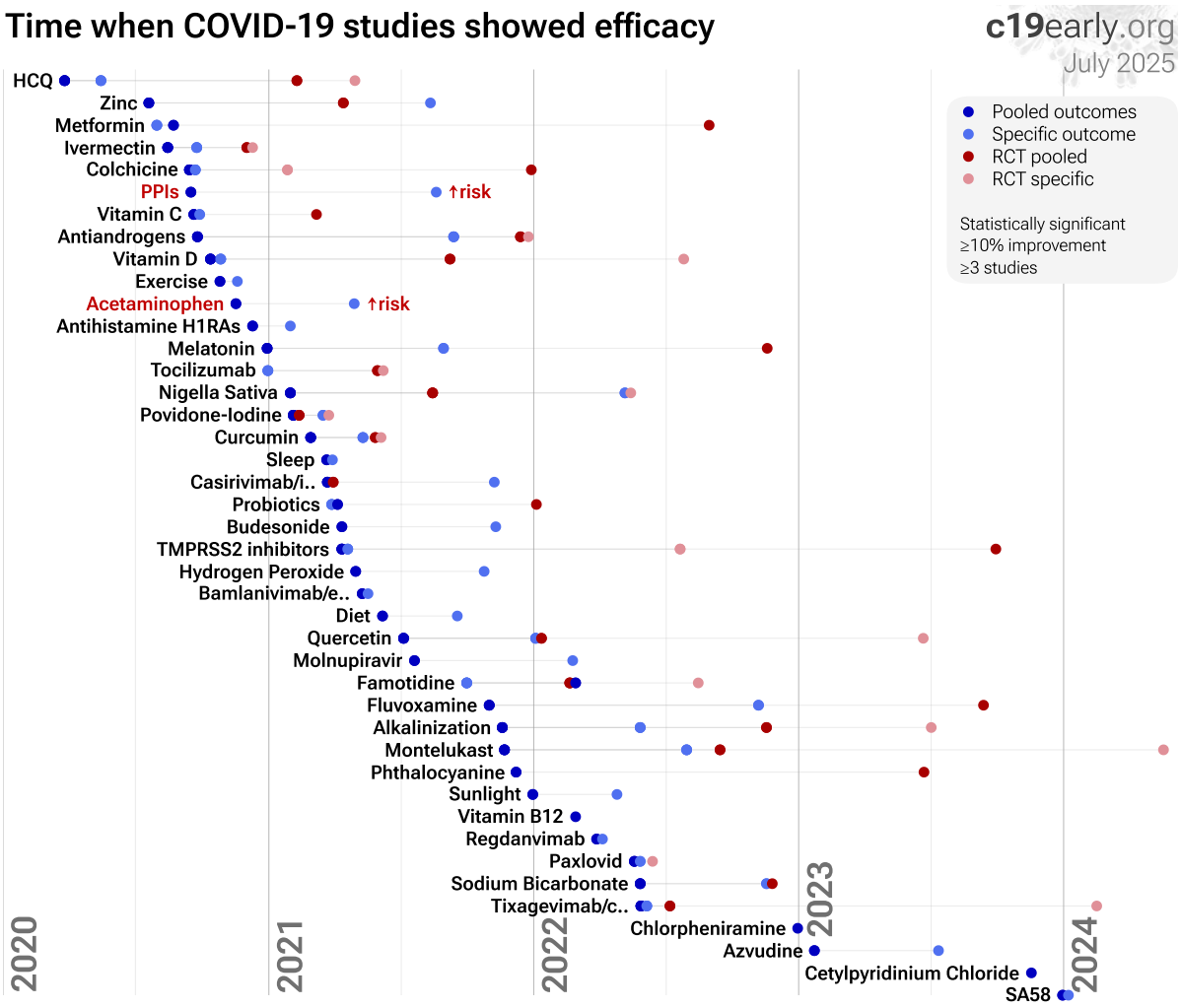


Figure 31. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations

Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary

Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Kidney Stones

High doses of vitamin C may increase the risk of kidney stones[7], with doses exceeding around 1,000 mg per day elevating risk, and a clearer association with over 2,000 mg per day. Vitamin C metabolization produces oxalate, a key component of calcium oxalate kidney stones, which are the most common type. The risk depends on individual predisposition (e.g., history of kidney stones, dehydration, or metabolic conditions), total oxalate intake from the diet, and hydration levels.

Risk depends on the formulation. Liposomal vitamin C enhances absorption and may allow lower effective doses, potentially reducing oxalate production compared to equivalent doses of ascorbic acid. Time-release formulations spread absorption over time, which may lower peak oxalate levels. Natural sources (e.g., fruit) also contain other compounds (like citrate in citrus fruits) that may inhibit stone formation. Dietary intake is less commonly associated with increased risk. Risk may also be reduced with hydration—adequate water intake dilutes urinary oxalate and calcium, reducing stone formation.

Discussion

Results for other infections

Studies have also shown efficacy with vitamin C for the common cold [54,55] and acute respiratory tract infections [56].

Publication bias

Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results [164-167].

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 32 shows a scatter plot of results for prospective and retrospective treatment studies. Prospective studies show 20% [8-30%] improvement in meta analysis, compared to 22% [13-30%] for retrospective studies, showing no significant difference.

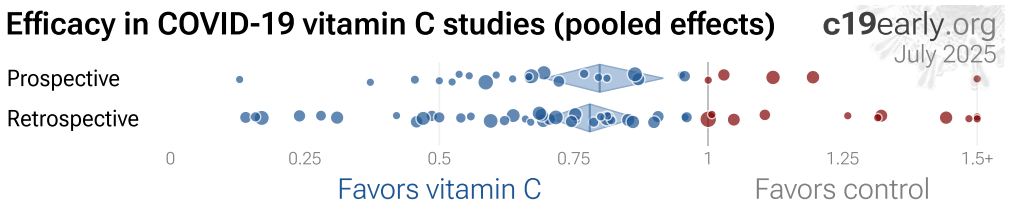


Figure 32. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Late treatment bias

Studies for vitamin C were mostly late treatment studies, in contrast with typical high-profit drugs that were more likely to be tested with early treatment.

Funnel plot analysis

Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 34 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ [168-175]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex —

each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

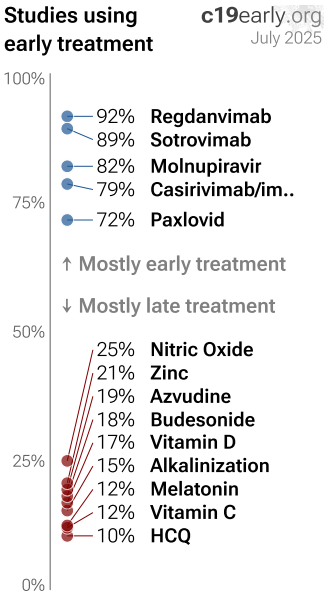


Figure 33. Early treatment was more common for high-profit drugs.

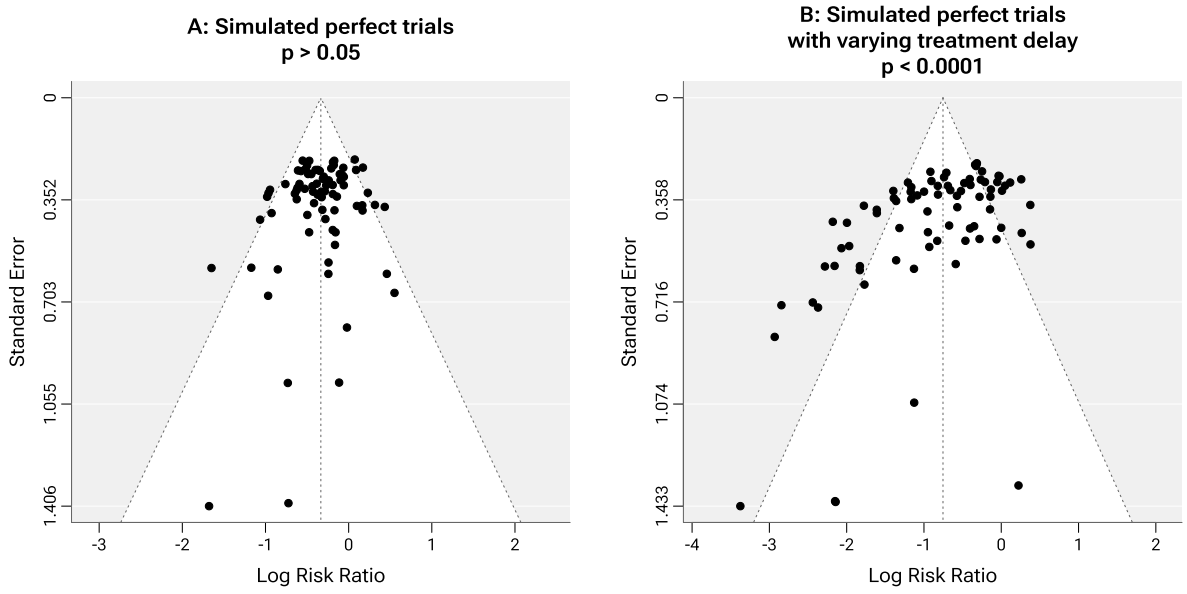


Figure 34. Example funnel plot analysis for simulated perfect trials.

Conflicts of interest

Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Vitamin C for COVID-19 lacks this because it is an inexpensive and widely available supplement. In contrast, most COVID-19 vitamin C trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all vitamin C trials represent the optimal conditions for efficacy.

Limitations

Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and

we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone [146-162]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes

1 of the 75 studies compare against other treatments, which may reduce the effect seen. 7 of 75 studies combine treatments. The results of vitamin C alone may differ. 5 of 21 RCTs use combined treatment. 7 other meta analyses show significant improvements with vitamin C for mortality [9-13], progression [14], severity [9,13], and cases [15].

Reviews

Many reviews cover vitamin C for COVID-19, presenting additional background on mechanisms and related results, including [3,49,176-189].

Other studies

Additional preclinical or review papers suggesting potential benefits of vitamin C for COVID-19 include [227-239]. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors [36-43], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [44], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary

complications. Figure 35 shows an overview of the results for vitamin C in the context of multiple COVID-19 treatments, and Figure 36 shows a plot of efficacy vs. cost for COVID-19 treatments.

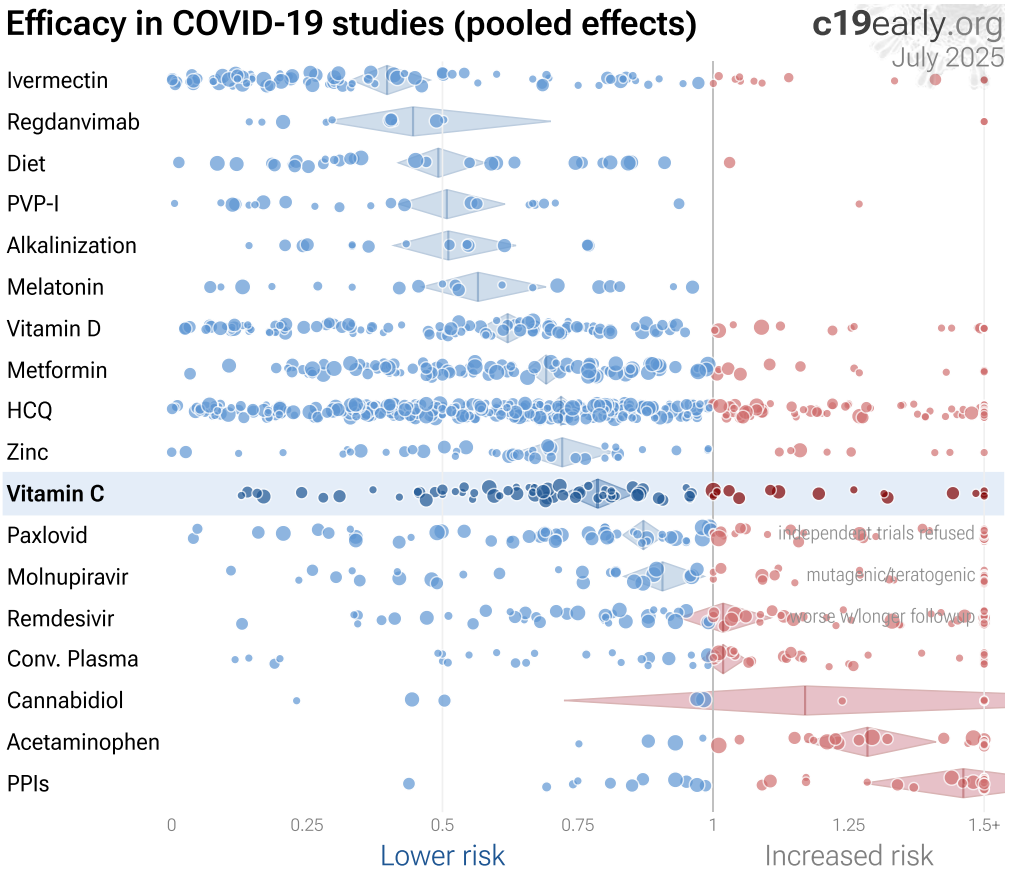


Figure 35. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy[240].

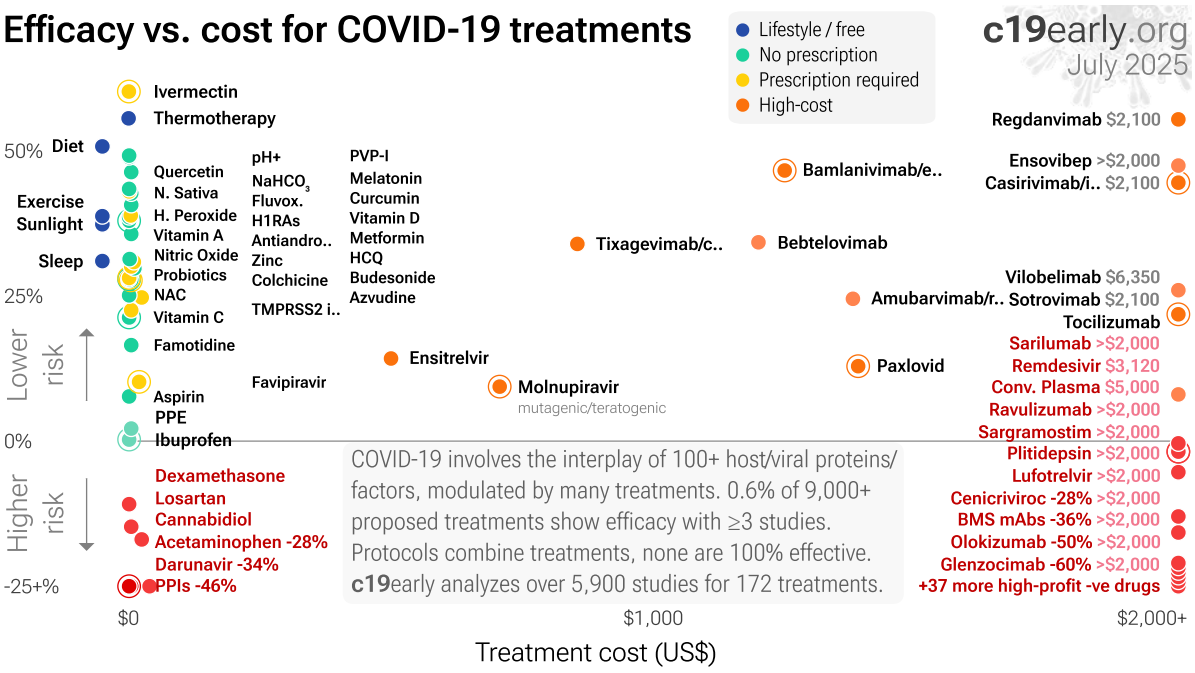


Figure 36. **Efficacy vs. cost for COVID-19 treatments.**

Conclusion

Vitamin C is an effective treatment for COVID-19. Significantly lower risk is seen for mortality, ICU admission, hospitalization, and recovery. 26 studies from 26 independent teams in 13 countries show significant benefit. Meta analysis using the most serious outcome reported shows 21% [15-28%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Clinical outcomes suggest benefit while viral and case outcomes do not, consistent with an intervention that aids the immune system or recovery but may have limited antiviral effects. Early treatment is more effective than late treatment. 2 sufficiency studies analyze outcomes based on serum levels, showing 55% [-10-81%] lower risk for patients with higher vitamin C levels. Results are robust — in exclusion sensitivity analysis 32 of 75 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

The European Food Safety Authority has found evidence for a causal relationship between the intake of vitamin C and optimal immune system function[1,2].

Early cessation of high-dose IV treatment may result in a detrimental rebound effect[3]. Ongoing treatment is more effective than early cessation: 33% [22-42%] vs. 16% [-31-46%].

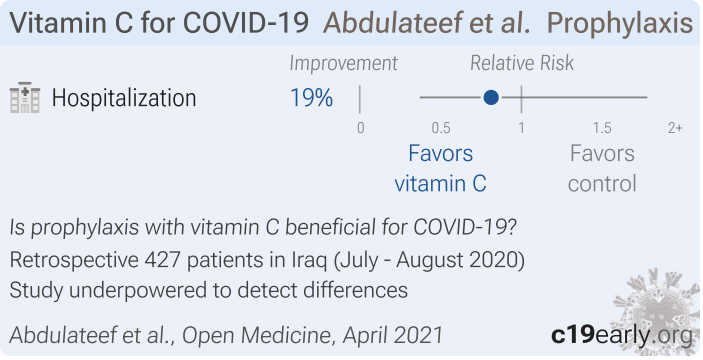
7 other meta analyses show significant improvements with vitamin C for mortality[9-13], progression[14], severity[9,13], and cases[15].

Studies have also shown efficacy with vitamin C for the common cold[54,55] and acute respiratory tract infections[56].

High doses may increase the risk of kidney stones[7], with risk depending on formulation, predisposition, diet, and hydration[8].

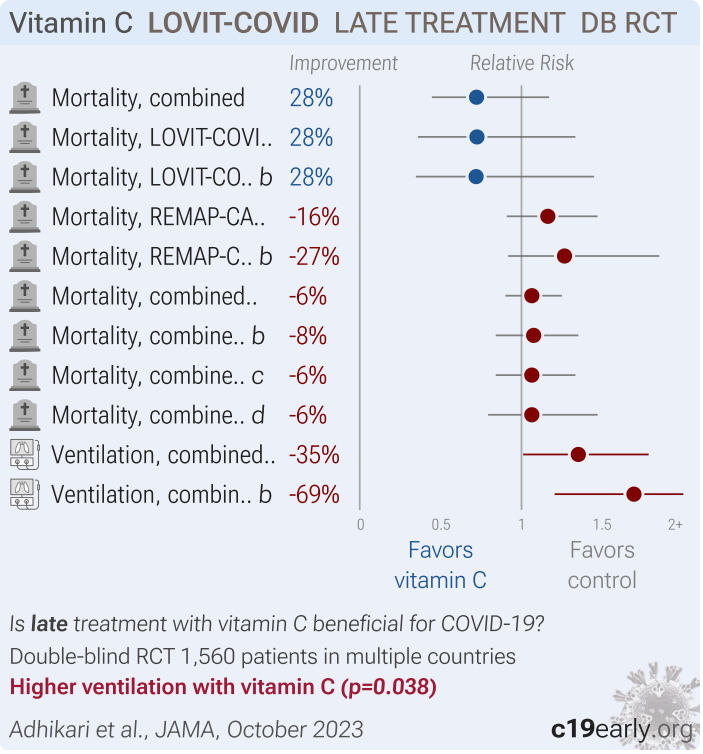
Study Notes

Abdulateef



Survey of 428 recovered COVID-19 patients in Iraq, showing fewer hospital visits for patients on prophylactic vitamin C or D. Hospitalization was lower for those on vitamin C, D, or zinc, without statistical significance.

Adhikari



Very late stage (APACHE II 8 and 12 for non-critical and critical) RCT with publication delayed over a year showing higher ventilation and no significant difference in mortality with vitamin C.

Authors have combined what was to be two separate trials into one trial, however there are very large differences between the trials. The results for each source trial are shown separately here[84,85].

eTable 15 shows that results in LOVIT-COVID were substantially better than those in REMAP-CAP. eTable 13 shows improved survival for LOVIT-COVID and worse survival for REMAP-CAP (authors provide mortality breakdown only for hospital survival):

LOVIT-COVID shows 85% and 82% probability of superiority of vitamin C (critical and non-critical).
REMAP-CAP shows 12% and 7% probability of superiority of vitamin C.

Notably, LOVIT-COVID patients were blinded, while REMAP-CAP was open-label, introducing additional opportunity for bias on this highly politicized treatment. REMAP-CAP had more patients and dominates the combined results.

eFigure 8b also shows that the REMAP-CAP results were initially positive, switching to negative around September 2021. Authors note that they were unable to explain this reversal. The overall negative result is only due to the larger number of patients in the REMAP-CAP later time period.

Results for intubation are much worse than mortality, with statistically significant higher intubation for the treatment group. Hypothetically, if the actual risk matched other trials (~20% lower risk in meta analysis of 18 RCTs at the time), and there was something causing biased intubation of treatment patients in this mostly open-label trial, we may get the observed results whereby intubation is significantly worse due to the bias, but this has a muted effect on mortality which may reflect the change in risk due to intubation combined with that due to treatment.

Results varied dramatically over time. For example, during 22 Jan - 21 Apr 2021, the probability of superiority for vitamin C was 1.0 for critical and 0.97 for non-critical (eTable 17).

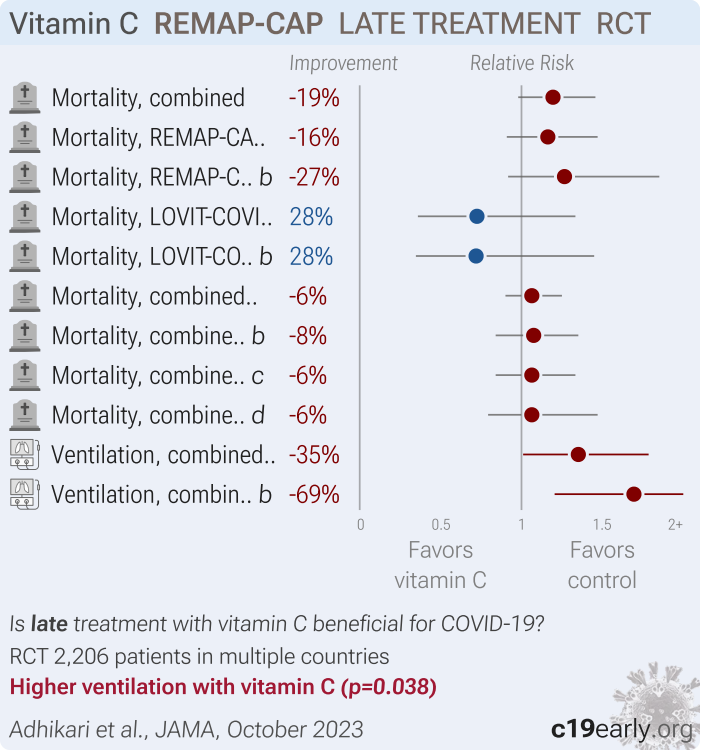
There were dramatic changes in randomization proportions and in overall clinical outcomes over time, leading to potential issues and inaccuracies in the attempted adjustment for confounding by time.

The very long delay between the end of the trial and publication also raises questions.

See also *Hemilä et al.* which shows that the poor results may be explained by a rebound effect due to the abrupt termination of treatment after 4 days.

NCT04401150 (LOVIT-COVID) and NCT02735707 (REMAP-CAP). 50mg/kg vitamin C administered intravenously over 30-60 minutes every 6 hours for 4 days.

Adhikari



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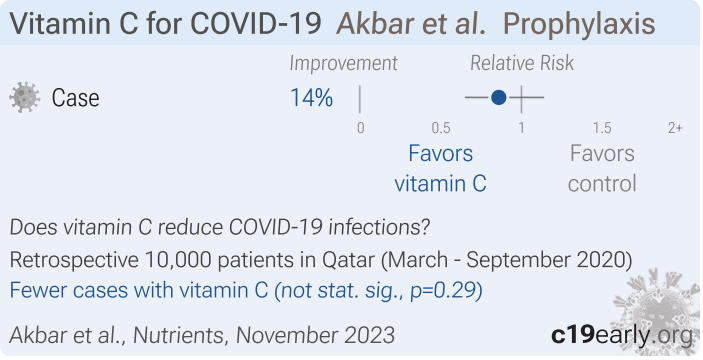
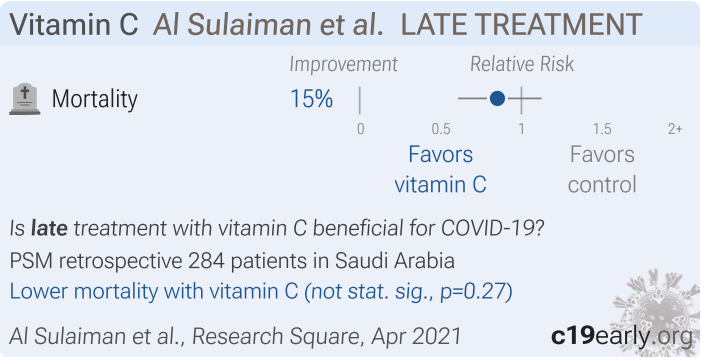
Akbar



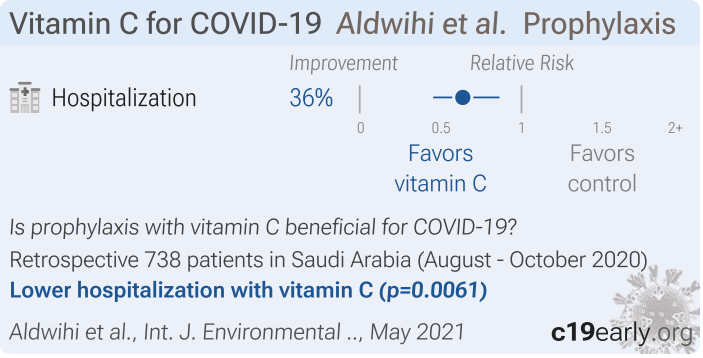
Retrospective 10,000 adults in Qatar, showing lower risk of COVID-19 cases with vitamin C supplementation, without statistical significance. Authors do not analyze COVID-19 severity.

Al Sulaiman



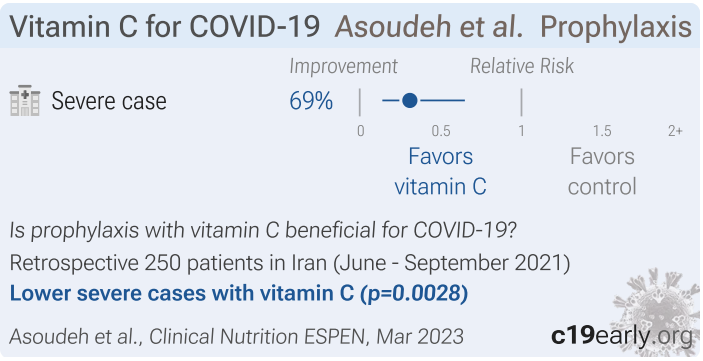
Retrospective 158 critically ill patients receiving vitamin C and propensity matched controls, showing mortality OR 0.77 [0.48-1.23], and statistically significantly lower thrombosis, OR 0.42 [0.18-0.94]. 1000mg of vitamin C was given daily.

Aldwihi



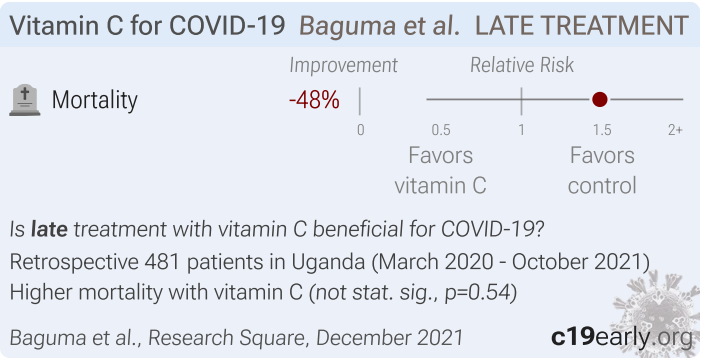
Retrospective survey-based analysis of 738 COVID-19 patients in Saudi Arabia, showing lower hospitalization with vitamin C, turmeric, zinc, and nigella sativa, and higher hospitalization with vitamin D. For vitamin D, most patients continued prophylactic use. For vitamin C, the majority of patients continued prophylactic use. For nigella sativa, the majority of patients started use during infection. Authors do not specify the fraction of prophylactic use for turmeric and zinc.

Asoudeh



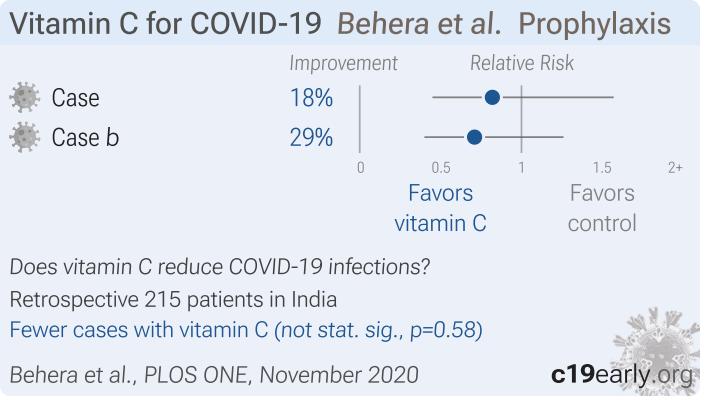
Retrospective 250 recovered COVID-19 patients, showing lower risk of severe cases with higher vitamin C intake.

Baguma



Retrospective COVID+ hospitalized patients in Uganda, 385 patients receiving vitamin C treatment, showing higher mortality with treatment, without statistical significance.

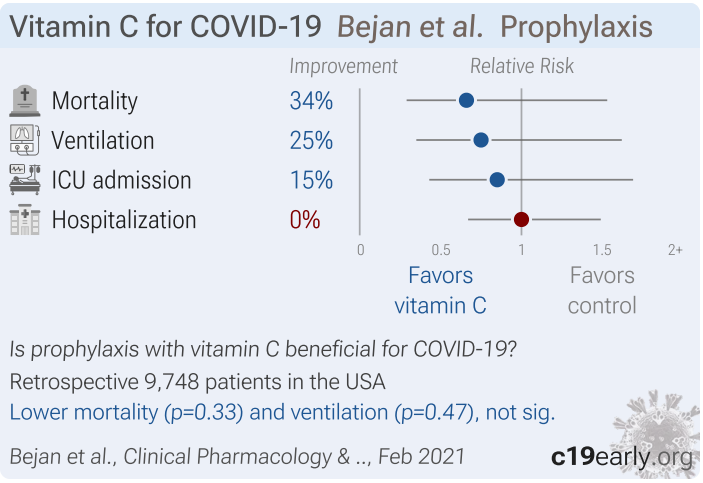
Behera



Retrospective matched case-control prophylaxis study for HCQ, ivermectin, and vitamin C with 372 healthcare workers, showing lower COVID-19 incidence for all treatments, with statistical significance reached for ivermectin.

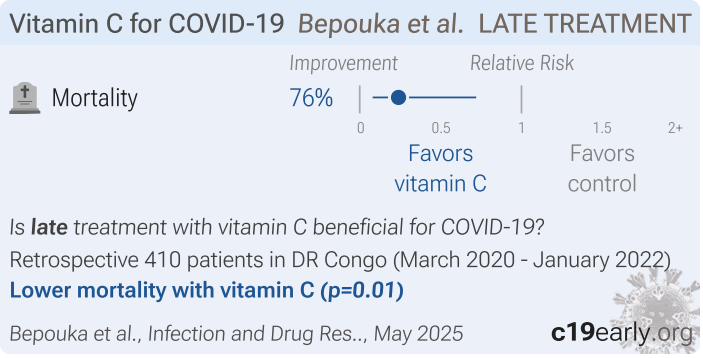
HCQ OR 0.56, p = 0.29
Ivermectin OR 0.27, p < 0.001
Vitamin C OR 0.82, p = 0.58

Bejan



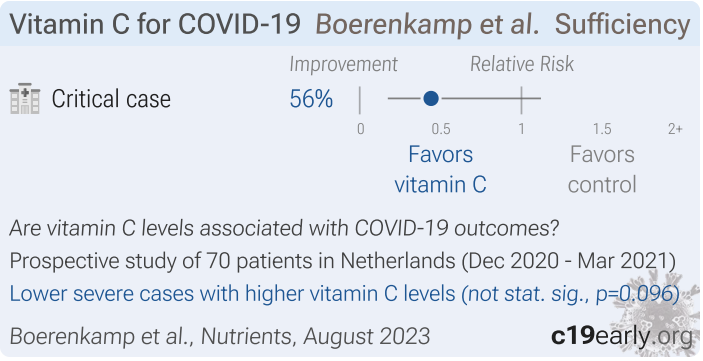
Retrospective 9,748 COVID-19 patients in the USA showing lower risk of mortality, ventilation, and ICU admission with vitamin C prophylaxis, without statistical significance.

Bepouka



Retrospective 410 hospitalized COVID-19 patients in the Democratic Republic of Congo showing significantly lower mortality with vitamin C treatment.

Boerenkamp



Analysis of serum and intracellular vitamin C levels in hospitalized COVID-19 patients. Low vitamin C levels were common with 36% having serum levels <26 µmol/L and 15% <11 µmol/L.

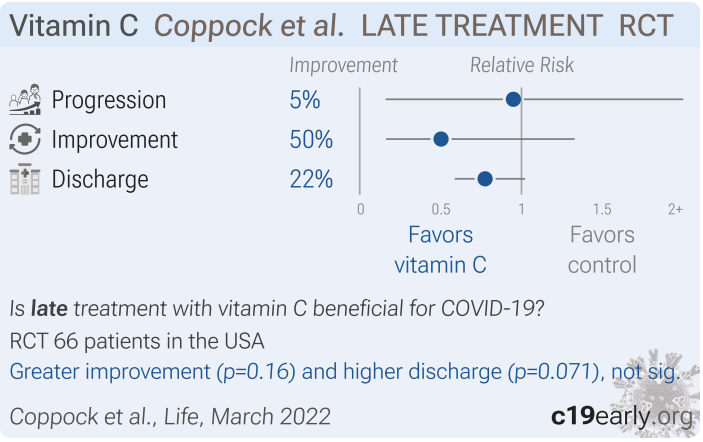
Intracellular vitamin C levels in peripheral blood mononuclear cells (PBMCs) were low at admission and declined during hospitalization, suggesting ongoing utilization and depletion of vitamin C stores.

Critical patients had higher odds of low serum vitamin C levels. There was a weak negative correlation between serum vitamin C levels and severity, without statistical significance.

Boukef

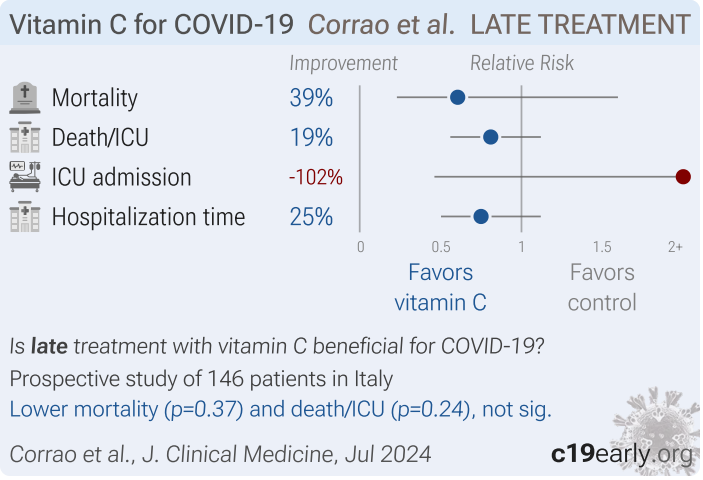
150 patient vitamin C early treatment RCT with results not reported over 2 years after completion.

Coppock



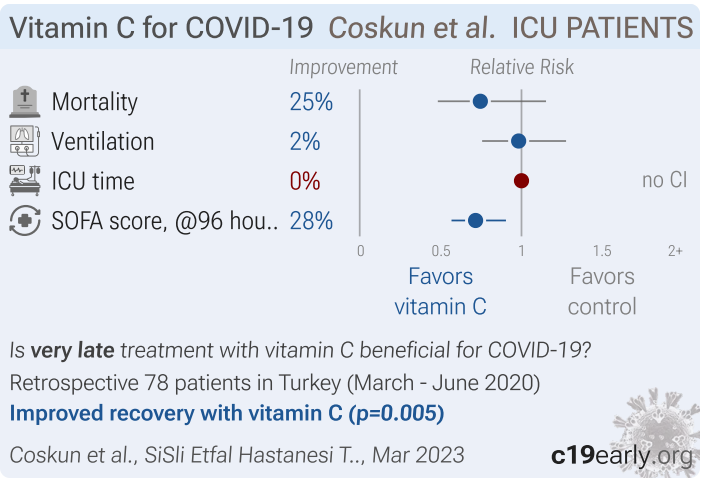
RCT with 66 very late stage (8 days from symptom onset) hospitalized patients, 44 treated with vitamin C and 22 control patients, showing no significant differences with treatment.

Corrao



Prospective study of 146 hospitalized COVID-19 patients showing shorter hospitalization with high-dose intravenous vitamin C. 104 patients received 10g of vitamin C intravenously daily for 3 days and 42 patients received only standard care. Mortality was lower with treatment (8.7% vs 14.3%) without statistical significance. Treatment was associated with significantly shorter hospitalization in multivariable analysis (−4.95, p=0.041). No adverse events were reported in the vitamin C group.

Coskun

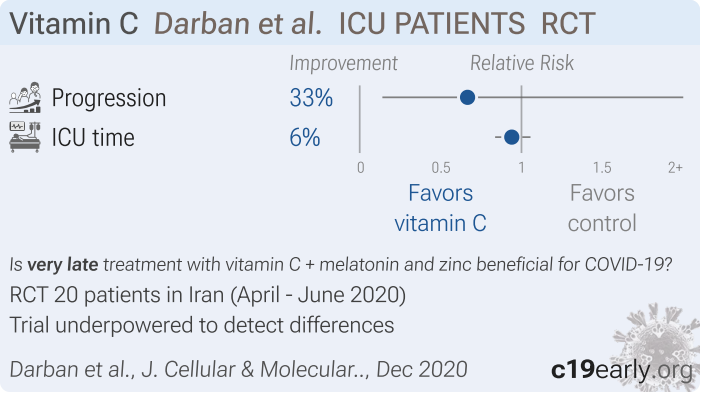


Retrospective 78 ICU patients in Turkey, showing lower mortality with high-dose vitamin C treatment, without statistical significance. The SOFA score was significantly better with treatment at day 4.

Authors incorrectly state that "HDVC treatment did not reduce the short-term mortality...". Mortality was lower with treatment, although not statistically significant given the sample size.

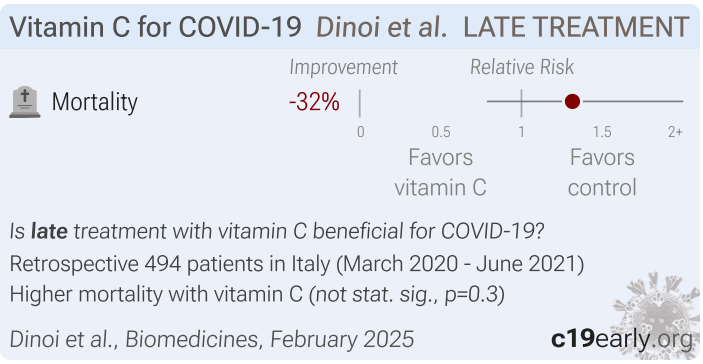
6g of vitamin C daily in 4 equal doses every 6h, for a total of 96h.

Darban



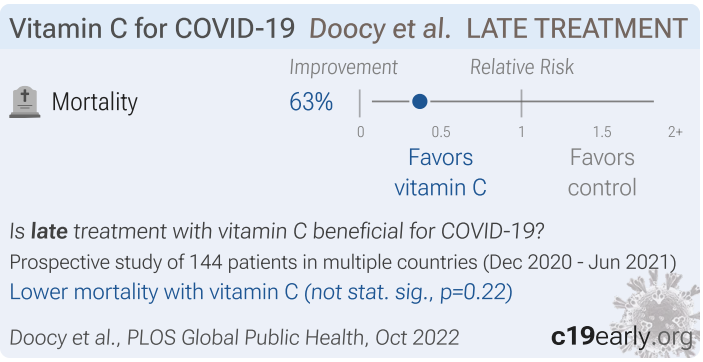
Small RCT in Iran with 20 ICU patients, 10 treated with high-dose vitamin C, melatonin, and zinc, not showing significant differences.

Dinoi



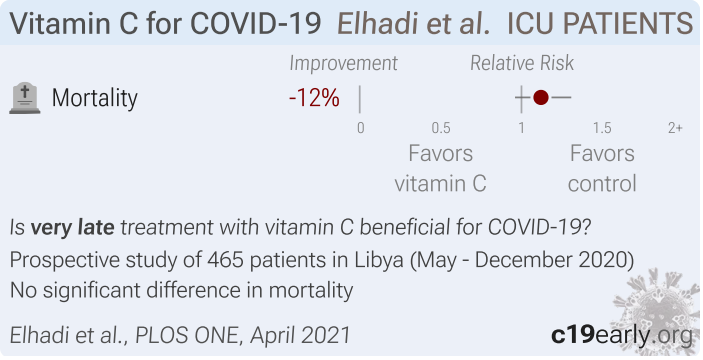
Retrospective 247 non-survivors and 247 matched survivors in hospitalized COVID-19 patients in Italy showing results for several treatments.

Doocy



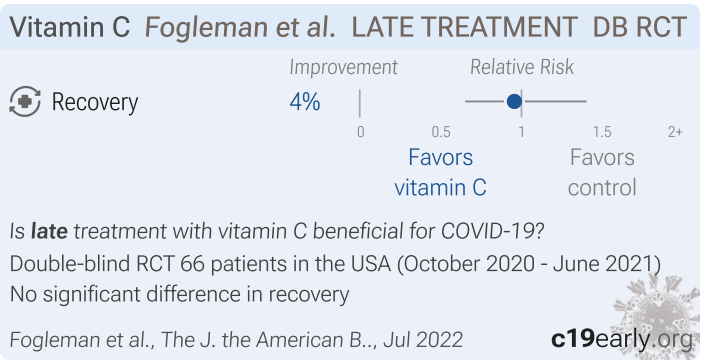
Prospective study of 144 hospitalized COVID-19 patients in the DRC and South Sudan, showing lower mortality with vitamin C treatment.

Elhadi



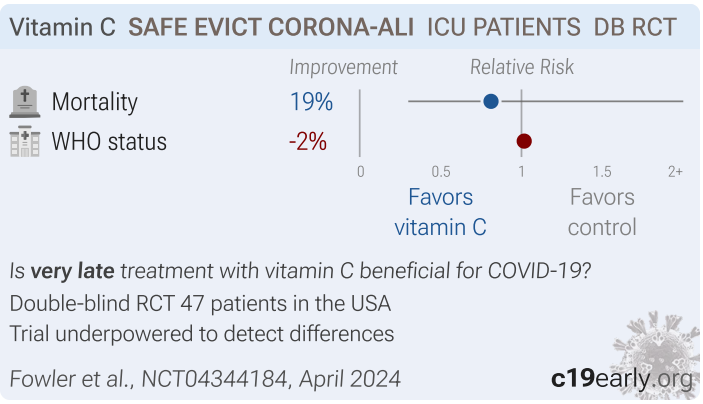
Prospective study of 465 COVID-19 ICU patients in Libya showing no significant differences with treatment.

Fogleman



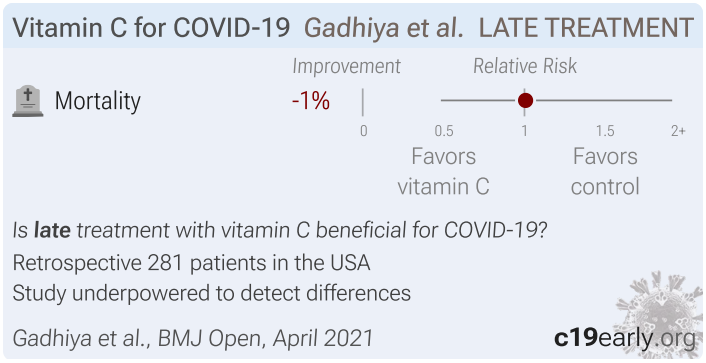
Early terminated low-risk patient RCT with 32 low-dose vitamin C, 32 melatonin, and 34 placebo patients, showing faster resolution of symptoms with melatonin in spline regression analysis, and no significant difference for vitamin C. All patients recovered with no serious outcomes reported. Baseline symptoms scores were higher in the melatonin and vitamin C arms (median 27 and 24 vs. 18 for placebo).

Fowler



RCT 47 ICU patients showing no significant differences with vitamin C treatment.

Gadhiya

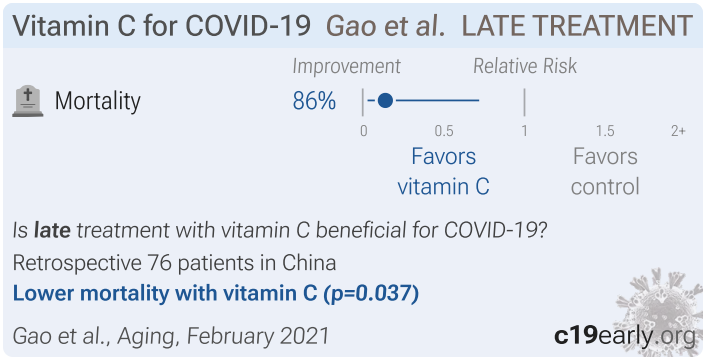


Retrospective 283 patients in the USA showing higher mortality with all treatments (not statistically significant). Confounding by indication is likely. In the supplementary appendix, authors note that the treatments were usually given for patients that required oxygen therapy. Oxygen therapy and ICU admission (possibly, the paper includes ICU admission for model 2 in some places but not others) were the only variables indicating severity used in adjustments.

Galindo

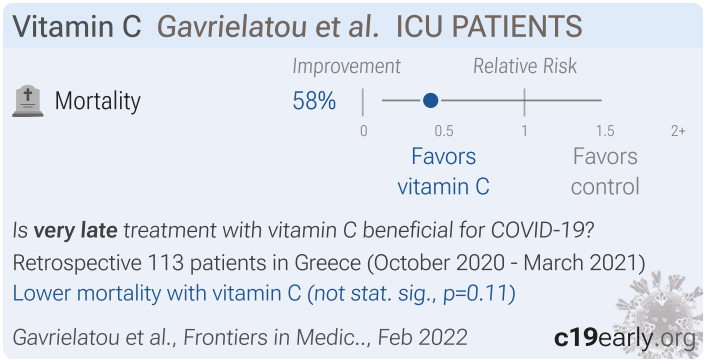
Estimated 160 patient vitamin C late treatment RCT with results not reported over 3 years after estimated completion.

Gao



Retrospective 76 COVID-19 patients, 46 treated with intravenous high-dose vitamin C, showing lower mortality and improved oxygen requirements with treatment. Dosage was 6g intravenous infusion per 12hr on the first day, and 6g once for the following 4 days.

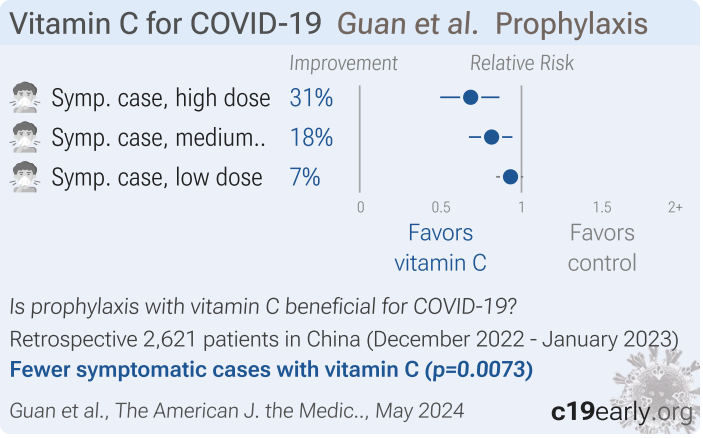
Gavrielatou



Retrospective 113 consecutive mechanically ventilated COVID+ ICU patients in Greece, 10 receiving high-dose IV vitamin C, showing lower mortality with treatment, without statistical significance (p=0.11).

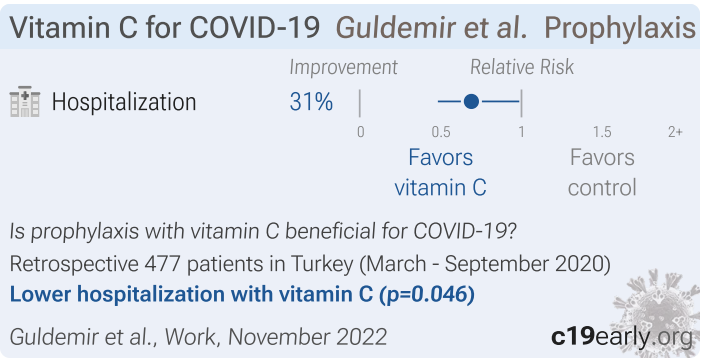
The associated meta analysis includes only 11 studies, while there are currently 75 studies, 46 with mortality results. Authors only include critical patients, however not all studies with critical patients are included, for example [90,94,125,130]. The meta analysis also uses unadjusted results, while PSM, Cox proportional hazards, or KM results are reported by [80,128,210,211]. For [80] authors use 28 day mortality, while the study reports longer term in-hospital mortality.

Guan



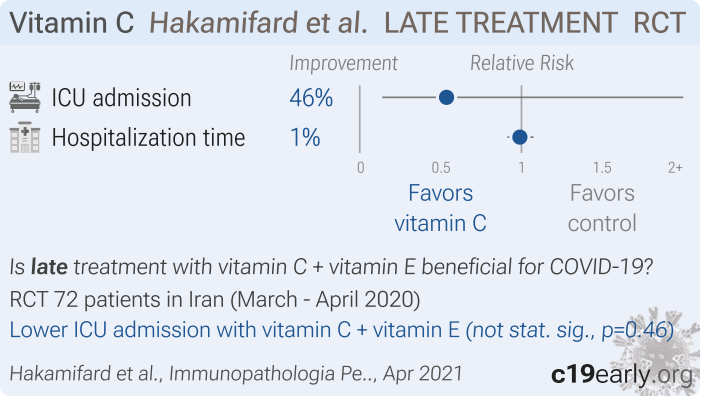
Retrospective 2,746 individuals in China showing significantly lower incidence of COVID-19 symptoms and fever with higher vitamin C intake, with a dose response relationship.

Guldemir



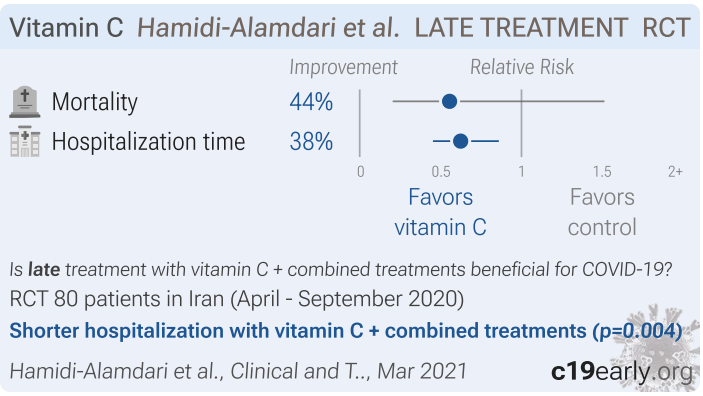
Retrospective 477 COVID+ public transportation workers in Turkey, showing lower risk of hospitalization with vitamin C use in unadjusted results.

Hakamifard



RCT with 38 patients treated with vitamin C and vitamin E, and 34 control patients, showing lower ICU admission with treatment, but not statistically significant.

Hamidi-Alamdari

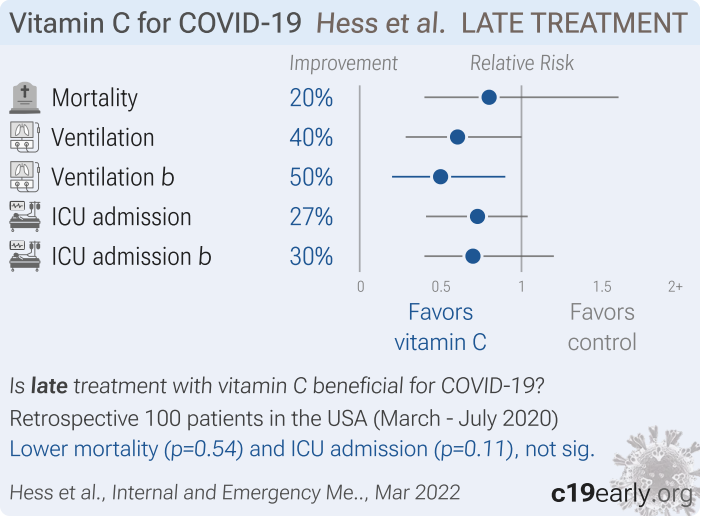


RCT 80 hospitalized patients with severe COVID-19, 40 treated with methylene blue + vitamin C + N-acetylcysteine, showing lower mortality, shorter hospitalization, and significantly improved SpO2 and respiratory distress with treatment.

He

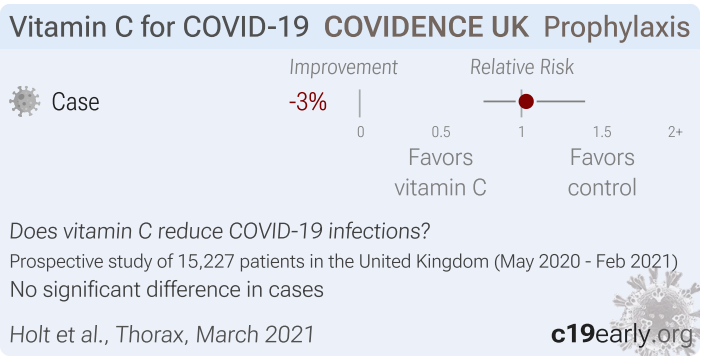
60 patient vitamin C late treatment RCT with results not reported over 4 years after completion.

Hess



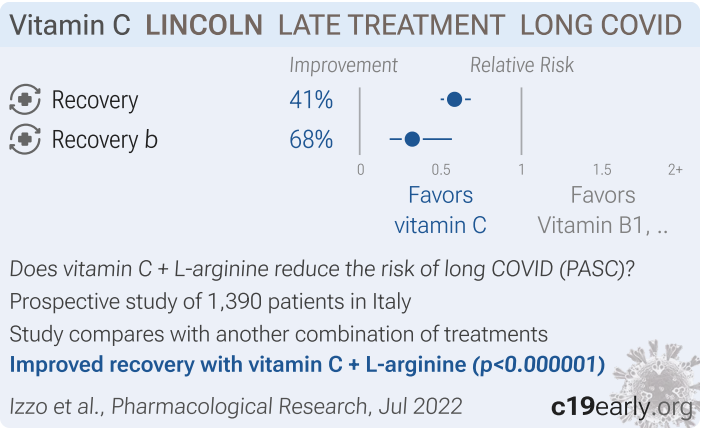
Retrospective 100 severe condition hospitalized patients in the USA, 25 treated with high-dose IV vitamin C, showing lower mechanical ventilation and cardiac arrest, and increased length of survival with treatment. 3g IV vitamin C every 6h for 7 days.

Holt



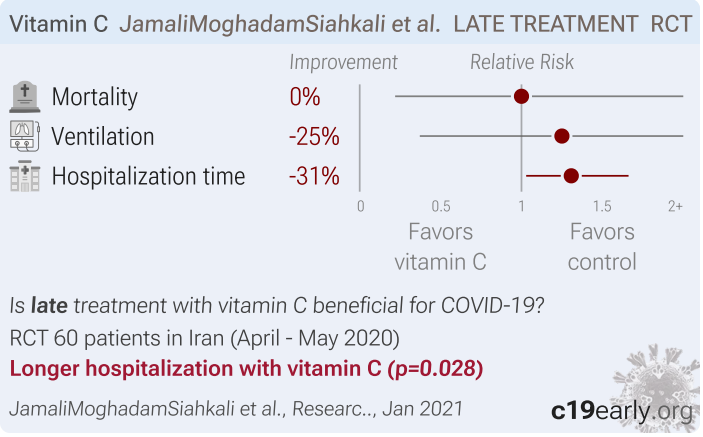
Prospective survey-based study with 15,227 people in the UK, showing lower risk of COVID-19 cases with vitamin A, vitamin D, zinc, selenium, probiotics, and inhaled corticosteroids; and higher risk with metformin and vitamin C. Statistical significance was not reached for any of these. Except for vitamin D, the results for treatments we follow were only adjusted for age, sex, duration of participation, and test frequency.

Izzo



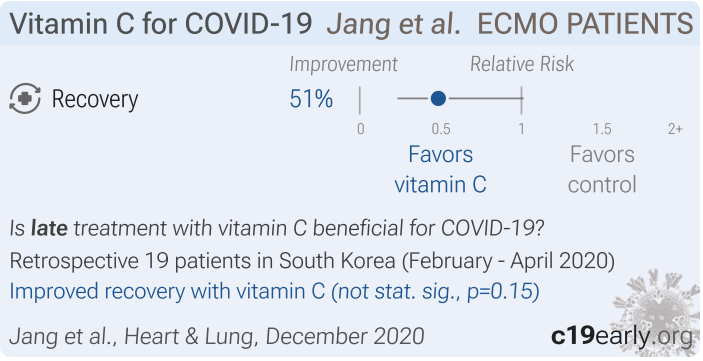
Long COVID trial comparing L-arginine + vitamin C with multivitamin treatment (vitamin B1, B2, B6, B12, nicotinamide, folic acid, pantothenic acid), showing significant improvement in symptoms with L-arginine + vitamin C treatment.

JamaliMoghadamSiahkali



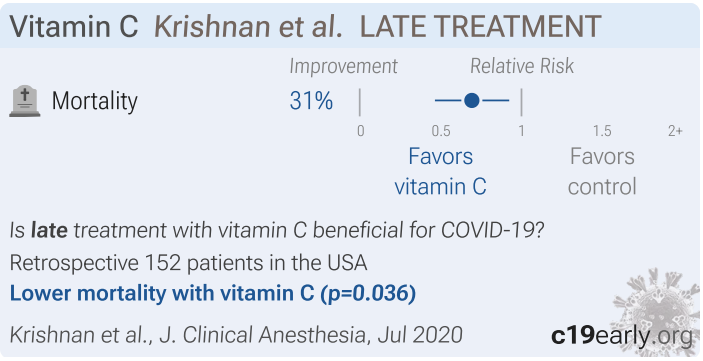
Small late stage RCT for the addition of vitamin C to HCQ and lopinavir/ritonavir, with 30 treatment and 30 control patients, finding a significant reduction in temperature and a significant improvement in oxygenation after 3 days in the vitamin C group. However, hospitalization time was longer and there was no significant difference in mortality.

Jang



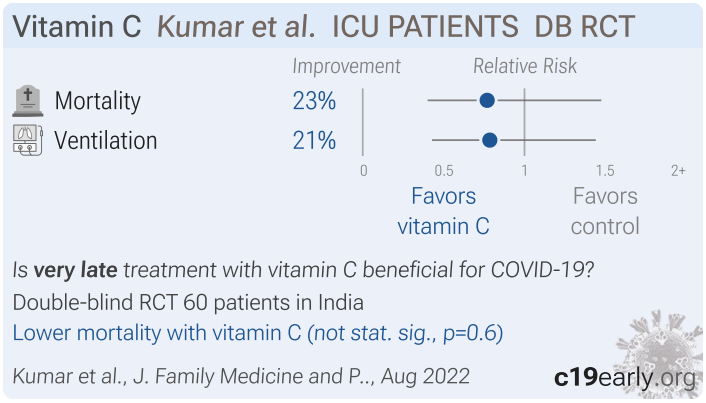
Retrospective 19 COVID-19 ECMO patients in South Korea, showing a higher rate of weaning from ECMO with vitamin C treatment, without statistical significance. Authors perform multivariate analysis but do not provide full results, only reporting p > 0.05.

Krishnan



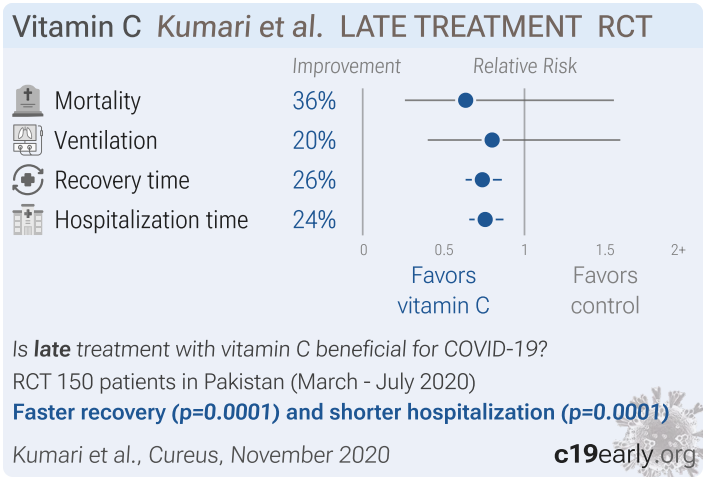
Retrospective 152 mechanically ventilated patients in the USA showing unadjusted lower mortality with vitamin C, vitamin D, HCQ, and zinc treatment, statistically significant only for vitamin C.

Kumar



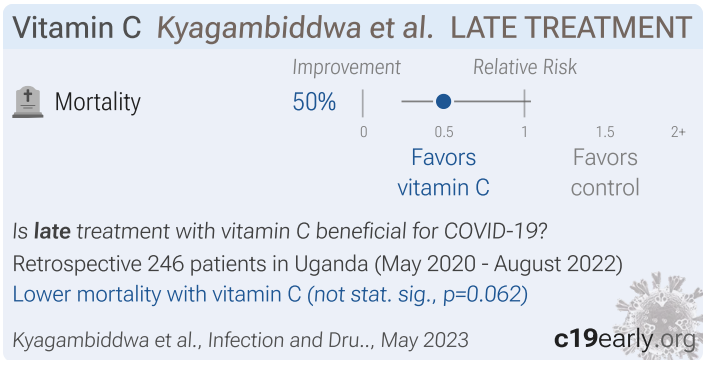
RCT 60 ICU patients in India, showing no significant difference in outcomes with vitamin C. Mortality was lower in the vitamin C arm despite having more severe cases at baseline (87% vs. 67%). 1 gram intravenous vitamin C 8 hourly for four days.

Kumari



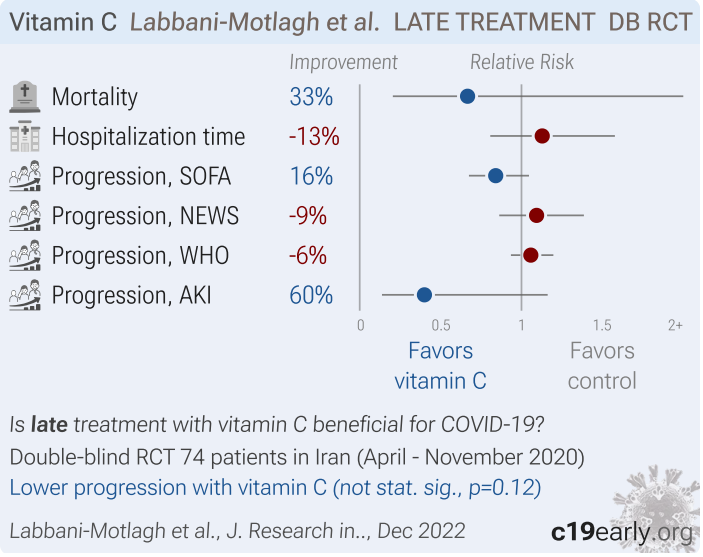
RCT 150 hospitalized patients in Pakistan showing 26% faster recovery, p < 0.0001. 36% lower mortality, not statistically significant due to the small number of events. Dosage was 50 mg/kg/day of intravenous vitamin C.

Kyagambiddwa



Retrospective 246 severe COVID-19 patients in Uganda, showing lower mortality with vitamin C treatment, without statistical significance (p = 0.06).

Labbani-Motlagh

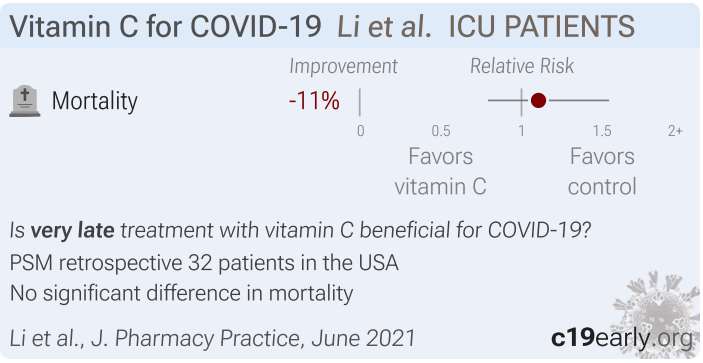


RCT 74 patients in Iran, showing no significant differences in outcomes with high-dose vitamin C treatment. Tables 1b and 2a show conflicting baseline SOFA scores. The percentages of patients receiving antiviral treatments and corticosteroids are switched between the text and Table 1b. Authors indicate ICU admission was an outcome, but the result is not provided. AKI was lower with treatment, though not reaching statistical significance.

Lamontagne

392 patient vitamin C late treatment RCT with results not reported over 2 years after completion. The companion non-COVID trial NCT03680274 has reported results.

Li

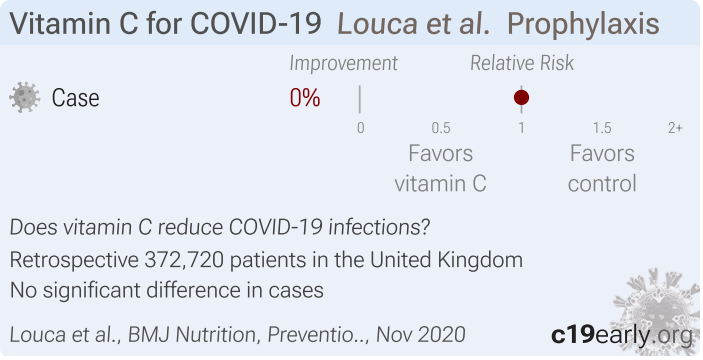


PSM retrospective 8 ICU patients treated with vitamin C and 24 matched controls, showing no significant difference. Authors note that "it is possible for the delayed timing of IV vitamin C to have blunted the beneficial effects as these patients may have already progressed to the late fibroproliferative phase or ARDS". IV vitamin C 1.5 grams every 6 hours.

Liu

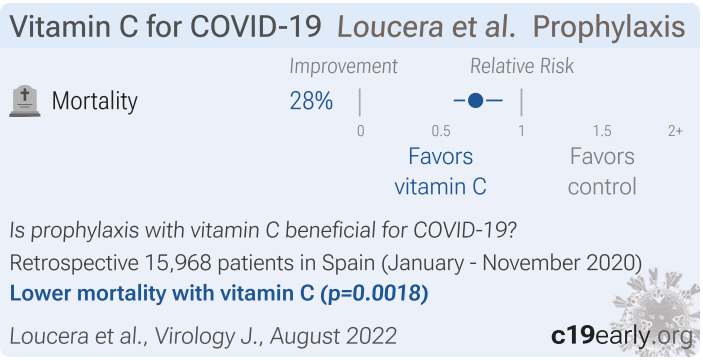
Estimated 608 patient vitamin C late treatment RCT with results not reported over 2 years after estimated completion.

Louca



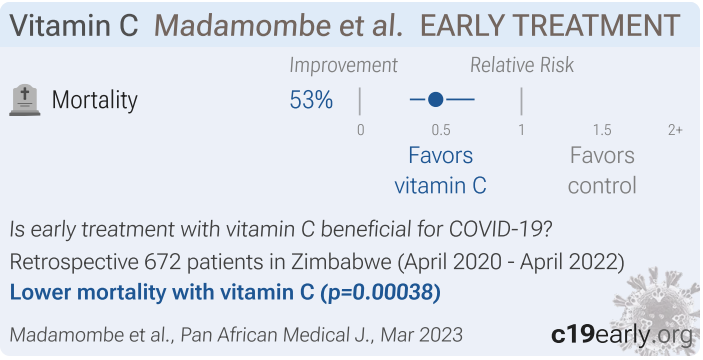
Survey analysis of dietary supplements showing no significant difference in PCR+ cases with vitamin C usage in the UK, however significant reductions were found in the US and Sweden. These results are for PCR+ cases only, they do not reflect potential benefits for reducing the severity of cases. A number of biases could affect the results, for example users of the app may not be representative of the general population, and people experiencing symptoms may be more likely to install and use the app.

Loucera



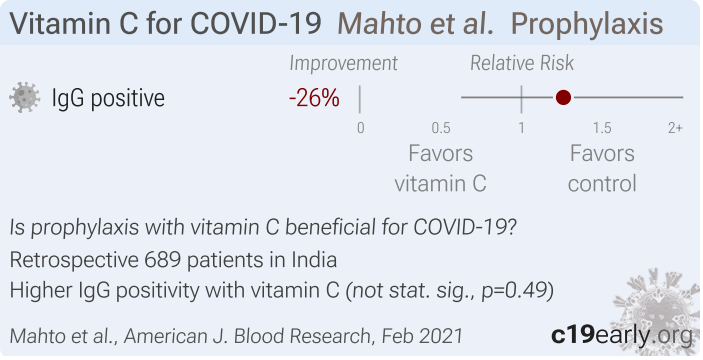
Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

Madamombe



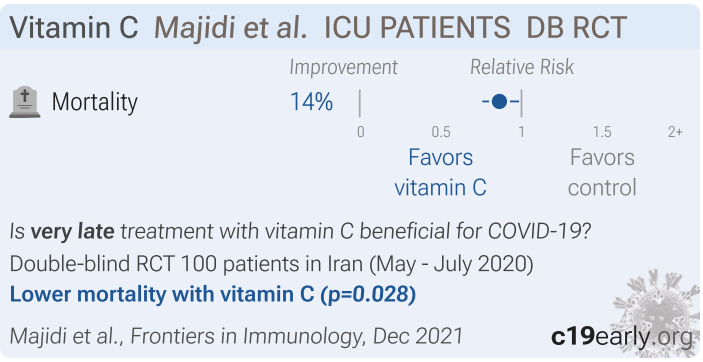
Retrospective 672 COVID-19 patients in Zimbabwe, showing lower mortality with vitamin C treatment.

Mahto



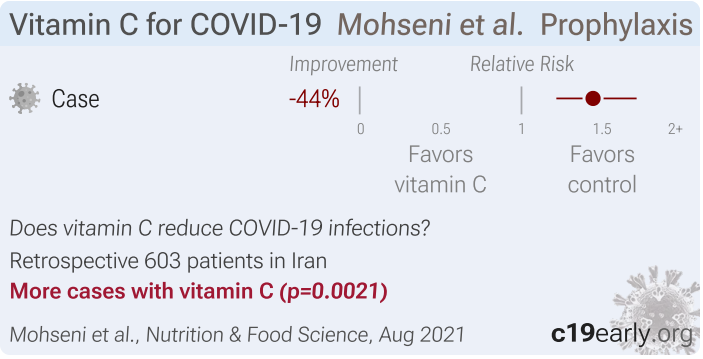
Retrospective 689 healthcare workers in India, showing no significant difference in IgG positivity with vitamin C prophylaxis.

Majidi



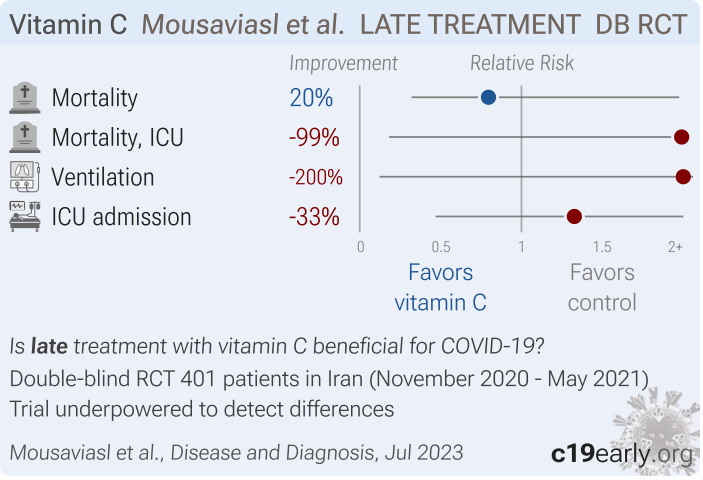
RCT 100 ICU patients in Iran, 31 treated with vitamin C, showing lower mortality with treatment.

Mohseni



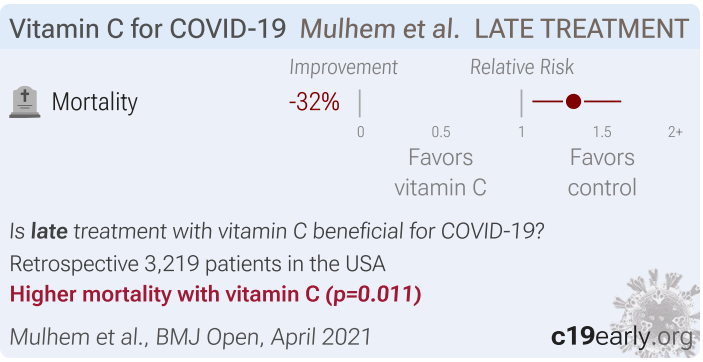
Retrospective 603 patients in Iran, 34 taking vitamin C supplements, showing increased risk of COVID-19 cases in unadjusted results. IR.SHOUSHTAR.REC.1399.015.

Mousaviasl



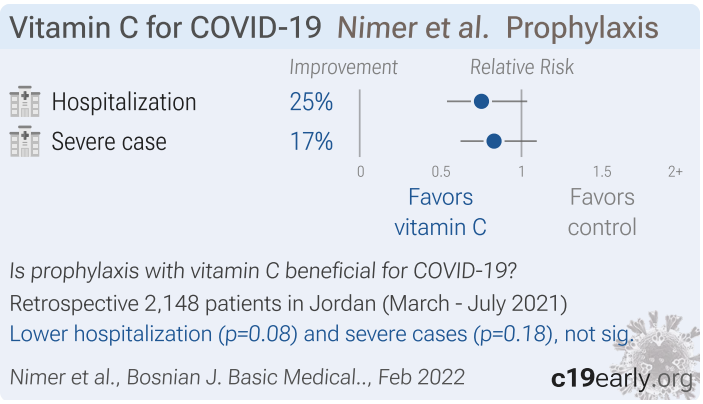
RCT 401 hospitalized COVID-19 patients showing no significant differences with low-dose oral vitamin C (1000mg daily for 5 days).

Mulhem



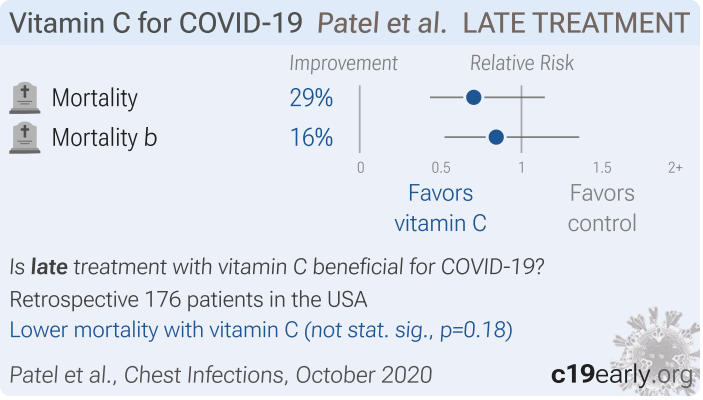
Retrospective database analysis of 3,219 hospitalized patients in the USA. Very different results in the time period analysis (Table S2), and results significantly different to other studies for the same medications (e.g., heparin OR 3.06 [2.44-3.83]) suggest significant confounding by indication and confounding by time.

Nimer



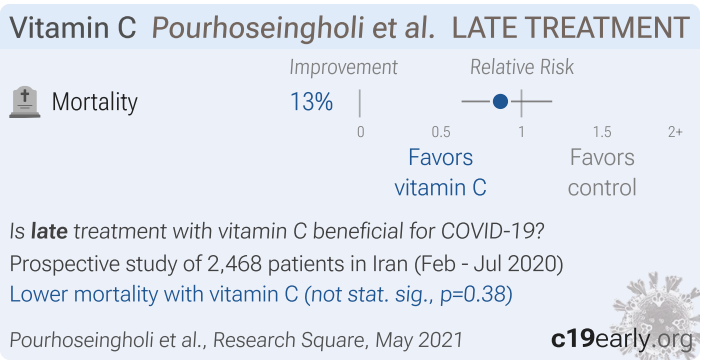
Retrospective 2,148 COVID-19 recovered patients in Jordan, showing lower risk of severity and hospitalization with vitamin C prophylaxis, without statistical significance.

Patel



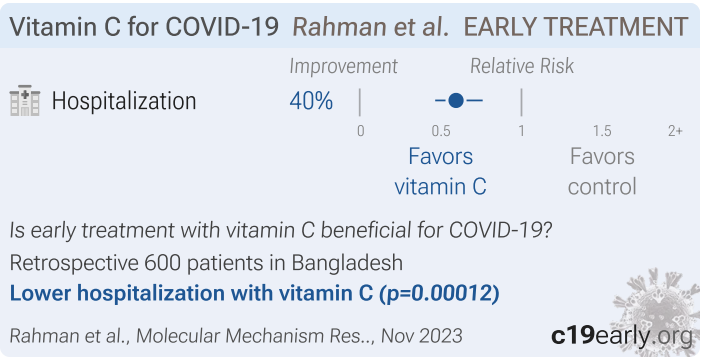
Retrospective 176 hospitalized patients, 96 treated with oral vitamin C (from 500mg to 1500mg daily), showing lower mortality with treatment.

Pourhoseingholi



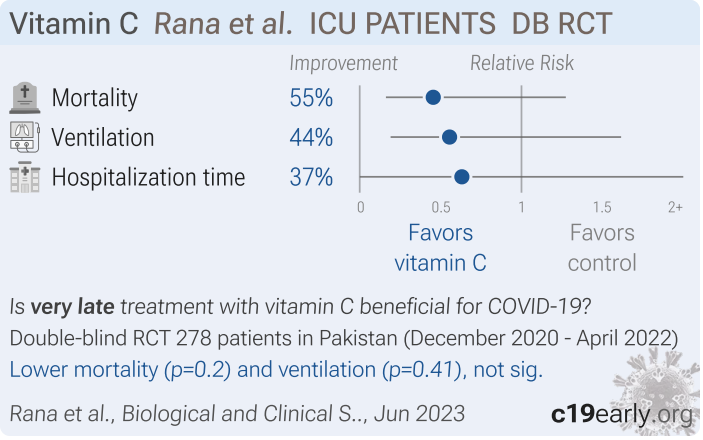
Prospective study of 2,468 hospitalized COVID-19 patients in Iran, showing no significant difference with vitamin C treatment. IR.MUQ.REC.1399.013.

Rahman



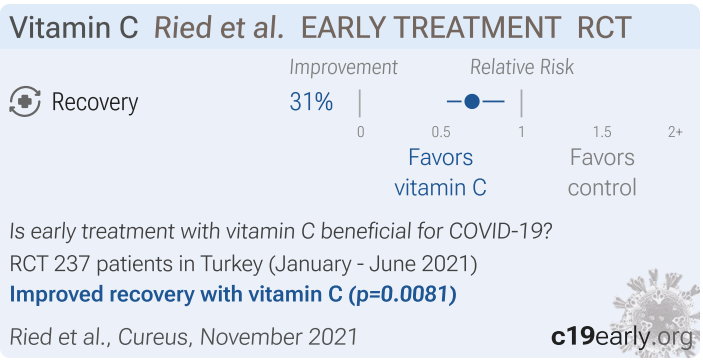
Retrospective 416 non-hospitalized and 184 hospitalized COVID-19 patients in Bangladesh, showing higher acetaminophen and lower vitamin C usage for hospitalized patients. Confounding may be significant and baseline details per treatment group are not provided, however fever and symptomatic patients were more common in the non-hospitalized group. Note there is an alignment mismatch in Table 1.

Rana



RCT 278 COVID-19 ICU patients in Pakistan, showing lower mortality and ventilation, and shorter length of stay with high-dose vitamin C treatment, without statistical significance. 30 grams IV vitamin C for four days.

Ried

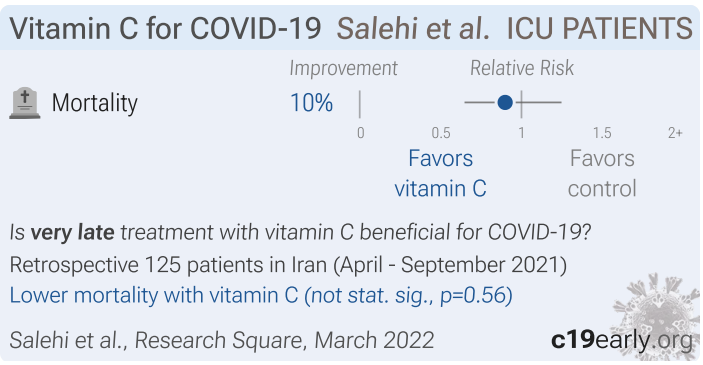


RCT 237 patients in Turkey, 162 treated with IV vitamin C in addition to HCQ/AZ/zinc/vitamin D used for all patients, showing significantly faster recovery with the addition of IV vitamin C.

97% of patients were vitamin D deficient, and lower vitamin D levels were associated with ICU admission and longer hospital stay.

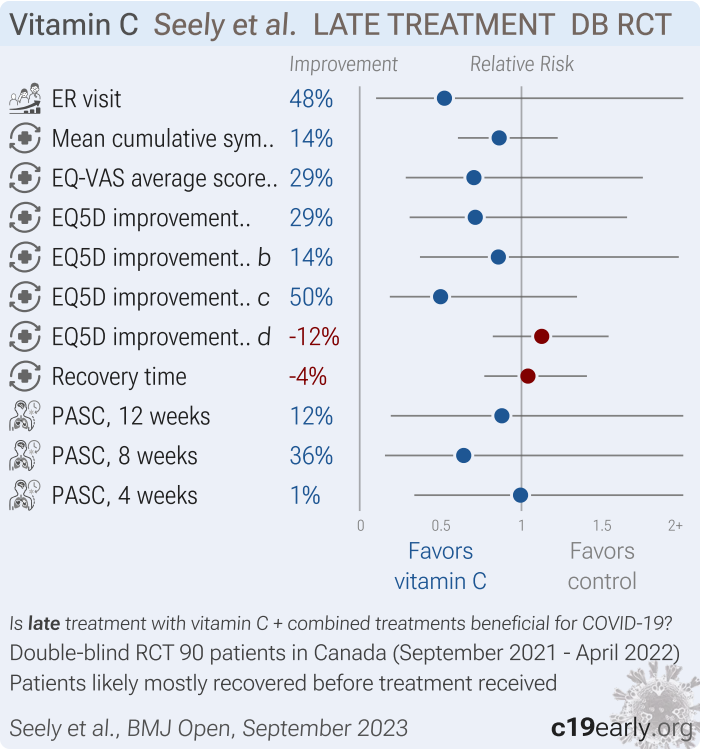
Only 1 of 237 hospitalized patients died (average age 63, range 22-99) - a 70-year-old patient with heart and lung disease and severely deficient vitamin D levels (6 nmol/L). IV vitamin C (sodium ascorbate) was given as 50 mg/kg every six hours on day 1, followed by 100 mg/kg every six hours (four times daily, 400 mg/kg/day) for seven days. NCT04395768.

Salehi



Retrospective 125 mechanically ventilated ICU patients in Iran, showing no significant difference with vitamin C treatment in unadjusted results.

Seely



Early terminated low-risk population (no hospitalization) very late treatment (mean 8 days) RCT with 44 patients treated with vitamin C, D, K, and zinc, and 46 control patients, showing no significant differences.

Authors acknowledge that the very late treatment is a major limitation, noting that in an ideal setting, *"patients would begin taking therapeutic interventions immediately after noticing symptoms"*. Authors note that patients already had a low symptom burden at baseline and that *"it is likely that the majority of the participants had almost fully recovered before starting treatment."*

Authors note that most participants were young, had few comorbidities and had excellent self-rated health at baseline, leaving less room for improvement.

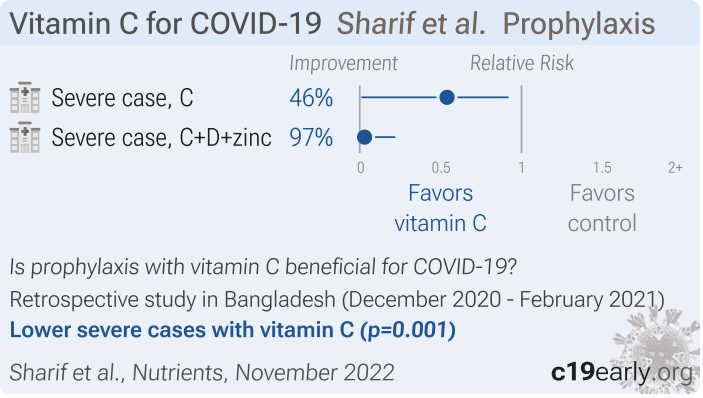
There was low compliance with completing surveys. Data from only 64% of patients was in the main analysis.

Authors claim "high internal validity", but the loss of data was statistically significantly different between arms, without analysis or mention. Since the study involves widely available treatments, one possibility is that patients in the control arm who feel sick may be more likely to independently take the treatments (via supplementation or food/sun exposure), believing that they are in the control arm or that additional dosing is safe, and they may then feel it's inappropriate to continue submitting the surveys.

Discussion is biased, stating that "evidence for the use of these products in people with COVID-19 is limited", however there were 219 controlled studies at the time, including 8, 27, and 16 RCTs for vitamin C, D, and zinc. Authors claim high similarity between arms however there was 60% vs. 41% male patients, and 88% vs. 68% of patients that received a third dose.

Authors claim that treatment "showed no beneficial effects for overall health or symptom burden". However 48% lower ER visits is beneficial, and most outcomes show a benefit. The only statistically significant effect was the loss of data, however significant clinical effects are not expected based on the small sample, very late treatment, event rates, and outcomes.

Sharif

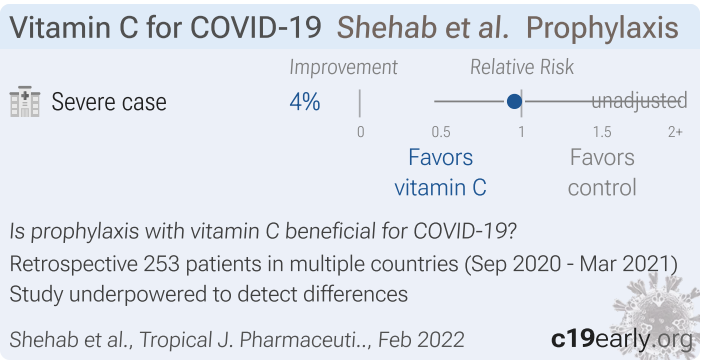


Retrospective 962 COVID-19 patients in Bangladesh, showing significantly lower severity with vitamin C, vitamin D, and zinc supplementation, and improved results from the combination of all three.

Sharmin

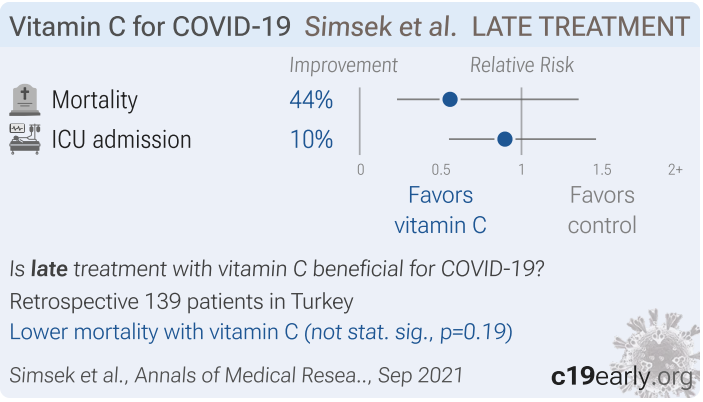
Estimated 50 patient vitamin C late treatment RCT with results not reported over 3 years after estimated completion.

Shehab



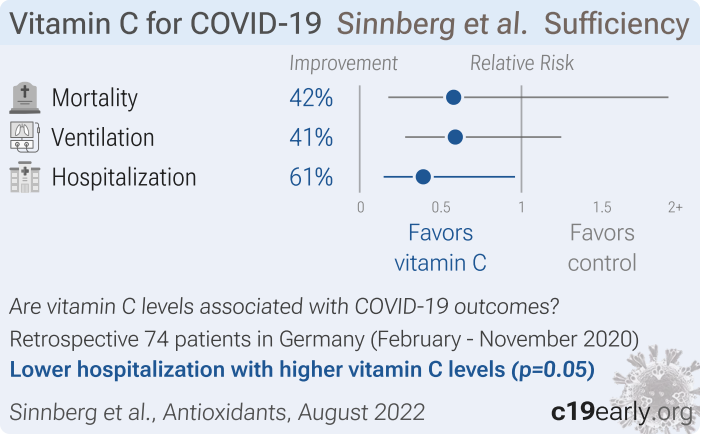
Retrospective survey-based analysis of 349 COVID-19 patients, showing no significant difference with vitamin C prophylaxis in unadjusted analysis. REC/UG/2020/03.

Simsek



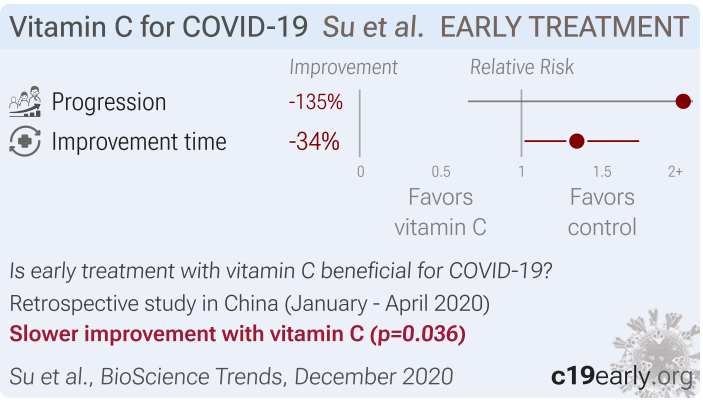
Retrospective 139 hospitalized patients in Turkey, 58 treated with high-dose vitamin C, showing improved kidney functioning with treatment. Mortality was lower with treatment, but not reaching statistical significance with the small sample size.

Sinnberg



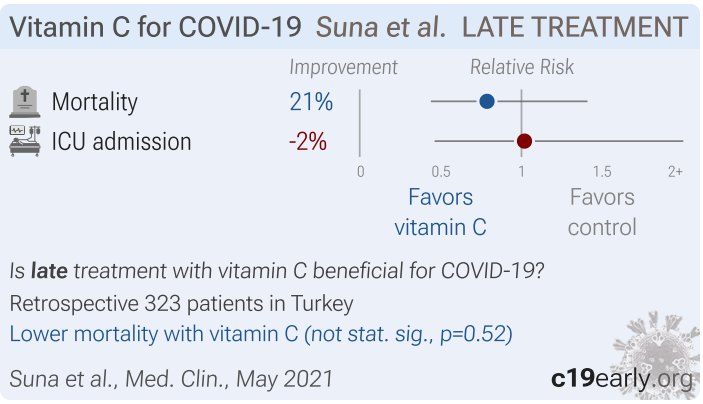
Analysis of 74 COVID-19 patients and 8 controls in Germany, showing low vitamin C levels associated with mortality. There was no significant difference for vitamin A, D, or E levels. Very few group details are provided, for example the age of patients in the control group and each severity group is not provided.

Su



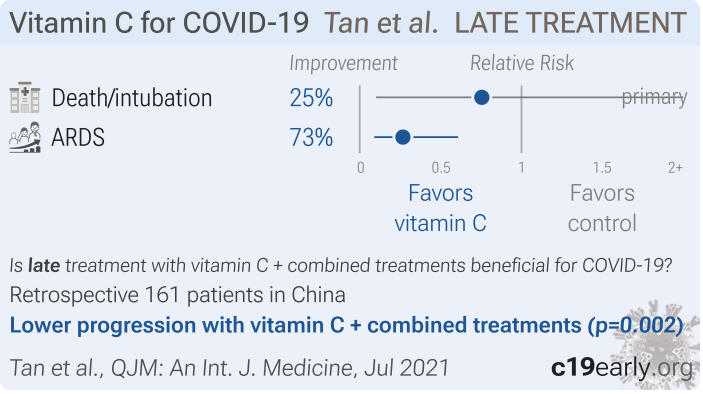
Retrospective 616 patients in China showing increased risk of disease progression with vitamin C treatment.

Suna



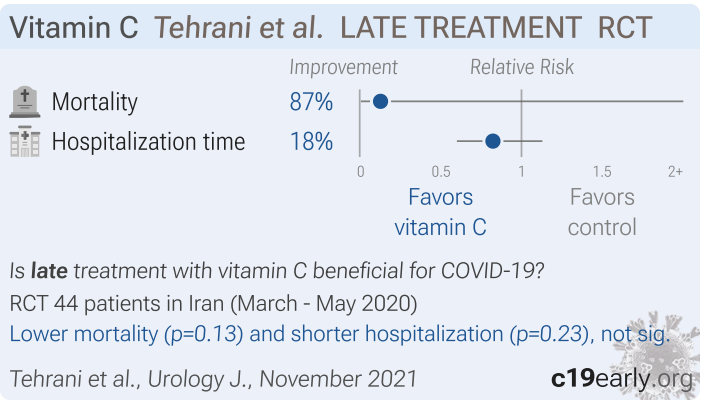
Retrospective 323 hospitalized patients, 153 treated with vitamin C, showing no significant differences. Patients in each group were in different time periods, with the vitamin C group first. Time based confounding is possible due to improvements in SOC.

Tan



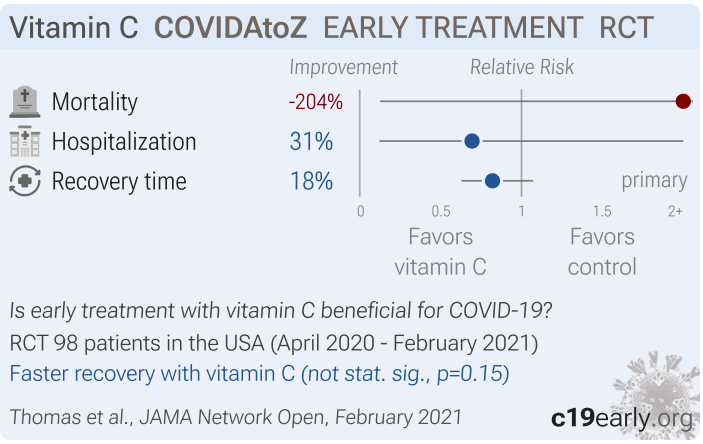
PSM retrospective 207 hospitalized patients in China, 46 treated with diammonium glycyrrhizinate and vitamin C, showing lower risk of ARDS with treatment.

Tehrani



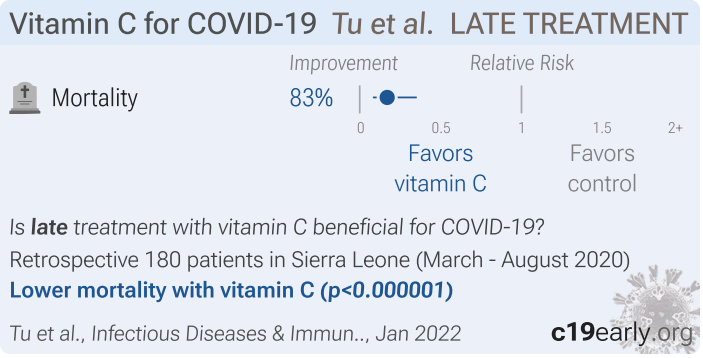
RCT 54 late stage patients, 18 treated with IV vitamin C (2g every 6h for 5 days), showing significant relative improvements in oxygen saturation and respiratory rate.

Thomas



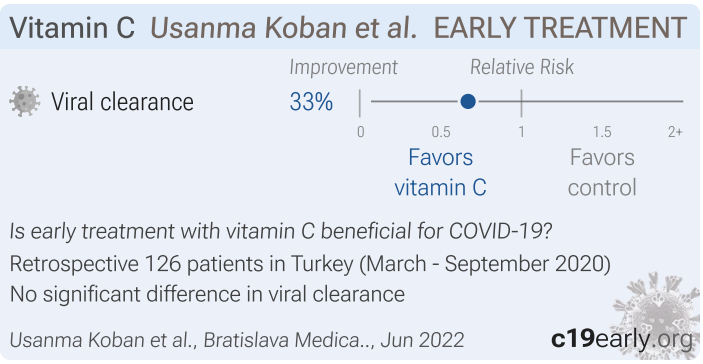
Small 214 low-risk outpatient RCT showing non-statistically significant faster recovery with zinc and with vitamin C. A secondary analysis concludes that vitamin C increases recovery rate by 71% (p = 0.036)[241]. See also[242].

Tu



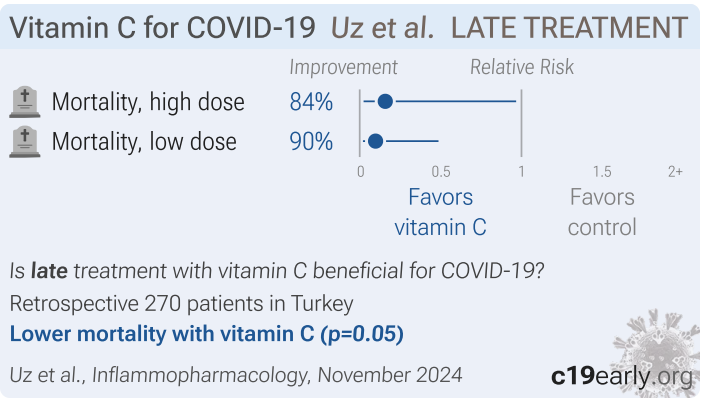
Retrospective 180 hospitalized COVID-19 patients in Sierra Leone, showing lower mortality with vitamin C treatment in unadjusted results.

Usanma Koban



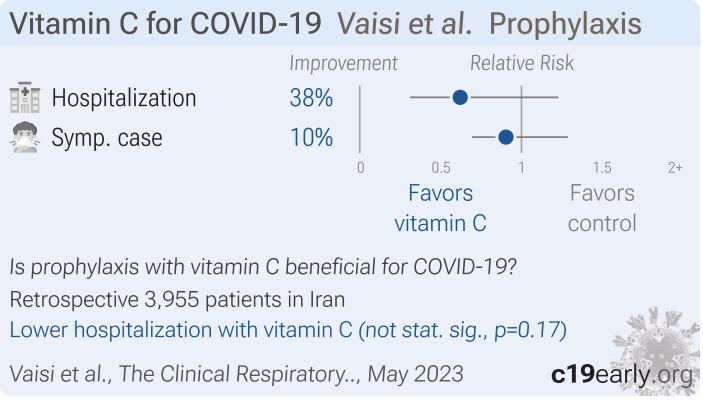
Retrospective 126 patients in Turkey, showing no significant difference in PCR+ at day 14 with vitamin C treatment.

Uz



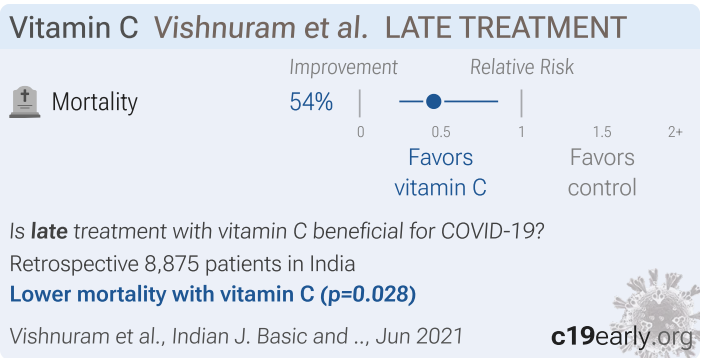
Retrospective 270 moderate/severe hospitalized COVID-19 patients, showing lower mortality with high (25 g/day) or low-dose (2 g/day) intraveneous vitamin C.

Vaisi



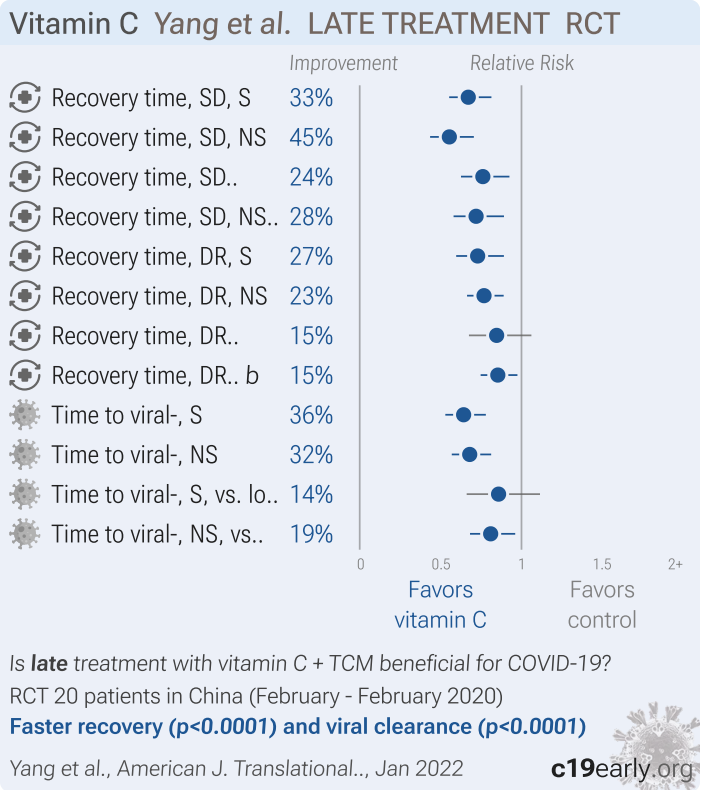
Analysis of nutrient intake and COVID-19 outcomes for 3,996 people in Iran, showing lower risk of COVID-19 hospitalization with sufficient vitamin A, vitamin C, and selenium intake, with statistical significance for vitamin A and selenium.

Vishnuram



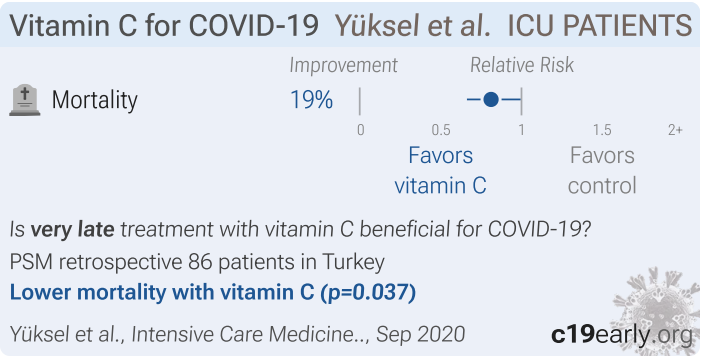
Retrospective 8,634 hospitalized patients in India, showing lower mortality with high-dose vitamin C in unadjusted results. No group details are provided, the text and table appear to show different results, and some numbers do not match.

Yang



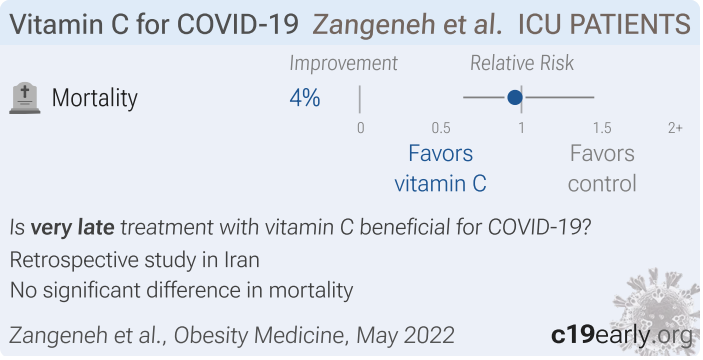
Prospective study of 60 patients in China with three arms: SOC, SOC+TCM, and SOC+TCM+high-dose vitamin C, showing successively faster recovery with the addition of TCM and the addition of high-dose vitamin C. TCM included inhaled vitamin C 10g, 3-7 times per day. IV vitamin C 10g/60kg twice a day, and oral vitamin C 3g three times a day. Group C vs. group A includes combined treatment with TCM, while group C vs. group B both include vitamin C (high vs. low dose).

Yüksel



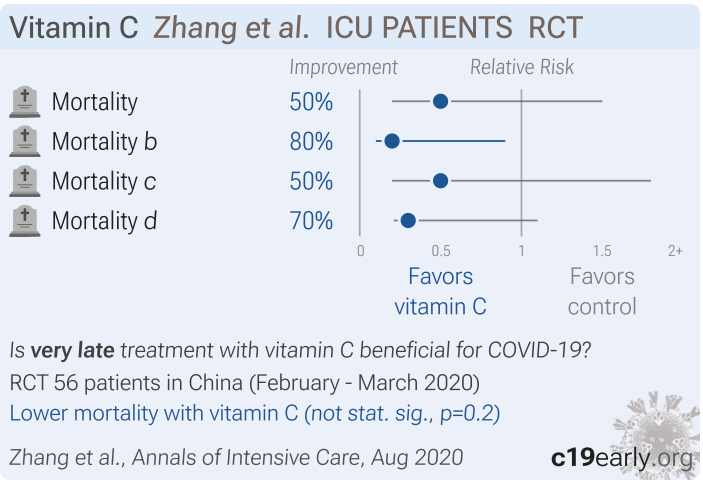
PSM retrospective 86 ICU patients on mechanical ventilation in Turkey, showing lower mortality with high-dose vitamin C treatment (≥200mg/kg for 4 days).

Zangeneh



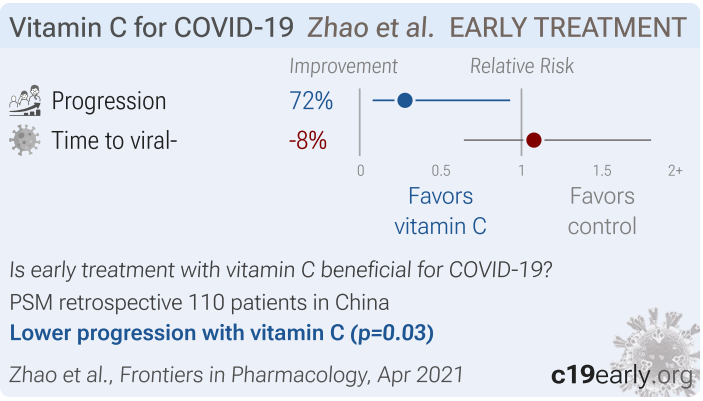
Retrospective 193 ICU patients in Iran, showing no significant difference with vitamin C treatment.

Zhang



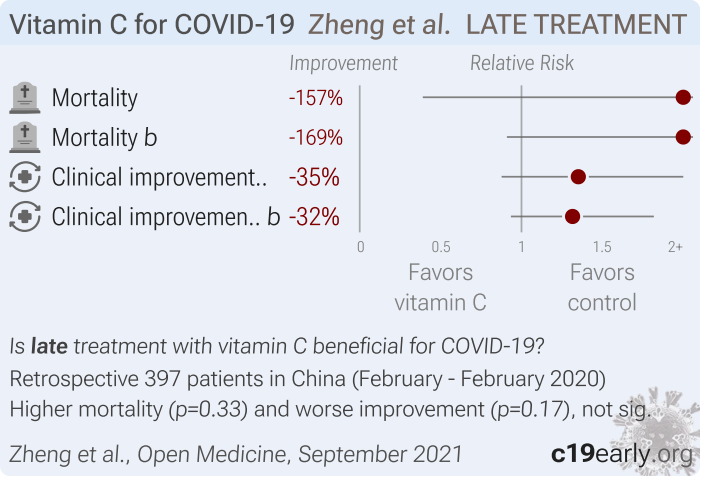
Small RCT for high-dose vitamin C for ICU patients showing reduced (but not statistically significant) mortality. Dosage was 12g of vitamin C/50ml every 12 hours for 7 days at a rate of 12ml/hour.

Zhao



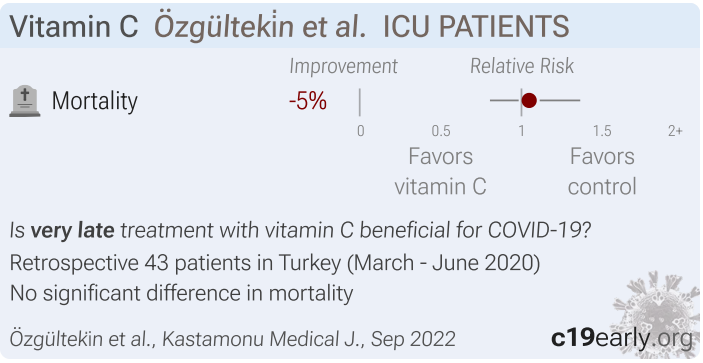
PSM retrospective 110 patients, 55 treated with high-dose IV vitamin C, showing lower progression to severe disease with treatment. Patients in each group were in different time periods, time based confounding is likely due to SOC improving over time. ChiCTR2000033050.

Zheng



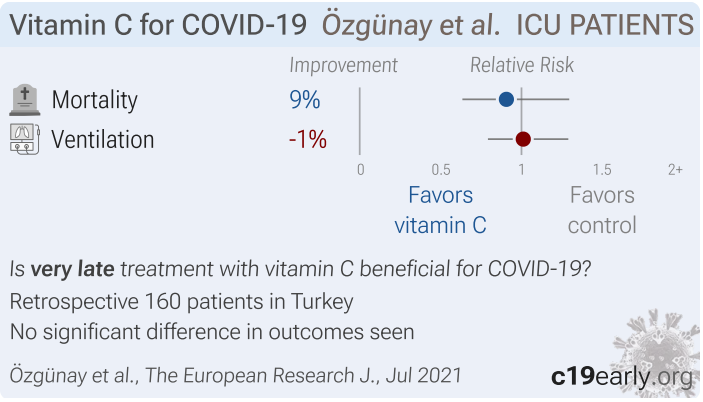
Retrospective 397 severe COVID-19 patients in China, showing worse outcomes with vitamin C treatment, without statistical significance. IV vitamin C 2-4g/day. Subject to confounding by indication and immortal time bias. Exclusion criteria were (a) the duration of hospitalization was less than 3 days; (b) vitamin C treatment started before admission; and (c) the length of vitamin C use was less than 3 days. Includes vitamin C use started at any time during hospitalization, for many patients this was >15 days later (Figure A2). Duration of treatment varied widely (Figure A1). Treatment was determined by clinicians according to the condition of each patient.

Özgültekin



Retrospective 43 ICU patients in Turkey, 21 treated with vitamin C, showing no significant difference in mortality and increased renal failure. Treatment included stage 1 AKI patients. Vitamin C 45-50 g/day for 5 days.

Özgünay



Retrospective 160 ICU patients, 32 with raised neutrophil/lymphocyte ratio treated with vitamin C, showing no significant differences.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are "vitamin C", "ascorbic acid" and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of vitamin C for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

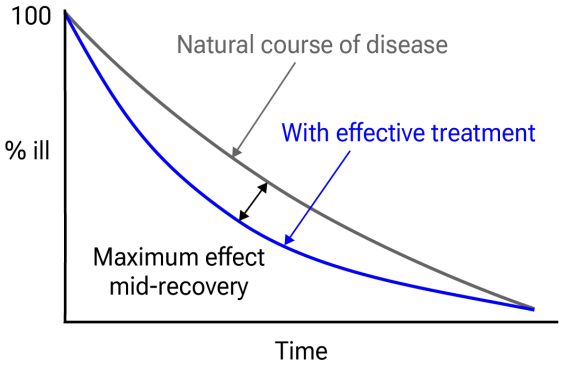


Figure 37. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral outcomes. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction [243]. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang (B) et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [247]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

Forest plots are computed using PythonMeta [248] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression

results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective [131,132].

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

A summary of study results is below. Please submit updates and corrections at https://c19early.org/cmeta.html.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Boukef, 2/28/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Tunisia, trial NCT05670444 (history).	150 patient RCT with results unknown and over 2 years late.
Madamombe, 3/21/2023, retrospective, Zimbabwe, peer-reviewed, 9 authors, study period April 2020 - April 2022, dosage not specified.	risk of death, 53.0% lower, OR 0.47, $p < 0.001$, adjusted per study, multivariable, RR approximated with OR.
Rahman, 11/8/2023, retrospective, Bangladesh, peer-reviewed, 5 authors, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details; significant unadjusted confounding possible.	risk of hospitalization, 40.5% lower, RR 0.60, $p < 0.001$, treatment 128 of 476 (26.9%), control 56 of 124 (45.2%), NNT 5.5.
Ried, 11/25/2021, Randomized Controlled Trial, Turkey, peer-reviewed, 3 authors, study period January 2021 - June 2021, average treatment delay 4.0 days, dosage 50mg/kg qid day 1, 100mg/kg qid days 2-7, trial ACTRN12620000557932.	risk of no recovery, 30.6% lower, RR 0.69, $p = 0.008$, treatment 69 of 162 (42.6%), control 46 of 75 (61.3%), NNT 5.3, mid-recovery, day 15.
Su, 12/23/2020, retrospective, China, peer-reviewed, 9 authors, study period 20 January, 2020 - 30 April, 2020, dosage 10000mg days 1-3, 5-15g per day for at least 3 days.	risk of progression, 135.3% higher, HR 2.35, $p = 0.18$, adjusted per study, binary logistic regression.
	improvement time, 34.2% worse, relative time 1.34, $p = 0.04$, adjusted per study, inverted to make RR<1 favor treatment, Cox proportional hazards.
Thomas (B), 2/12/2021, Randomized Controlled Trial, USA, peer-reviewed, 11 authors, study period 8 April, 2020 - 11 February, 2021, dosage 8000mg days 1-10, trial NCT04342728 (history) (COVIDAtoZ).	risk of death, 204.2% higher, RR 3.04, $p = 0.49$, treatment 1 of 48 (2.1%), control 0 of 50 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 30.6% lower, RR 0.69, $p = 1.00$, treatment 2 of 48 (4.2%), control 3 of 50 (6.0%), NNT 55.
	recovery time, 17.9% lower, relative time 0.82, $p = 0.15$, treatment mean 5.5 (±3.7) n=48, control mean 6.7 (±4.4) n=50, mean time to a 50% reduction in symptoms, primary outcome.

Usanma Koban, 6/7/2022, retrospective, Turkey, peer-reviewed, 3 authors, study period 1 March, 2020 - 30 September, 2020, dosage not specified.	risk of no viral clearance, 33.0% lower, OR 0.67, $p = 0.73$, treatment 31, control 95, adjusted per study, multivariable, day 14, RR approximated with OR.
Zhao, 4/22/2021, retrospective, propensity score matching, China, peer-reviewed, 15 authors, average treatment delay 4.0 days, dosage 100mg/kg days 1-7, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	risk of progression, 72.0% lower, RR 0.28, $p = 0.03$, treatment 4 of 55 (7.3%), control 12 of 55 (21.8%), NNT 6.9, adjusted per study, PSM.
	time to viral-, 7.7% higher, relative time 1.08, $p = 0.79$, treatment 55, control 55, PSM.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Adhikari (B), 10/25/2023, Double Blind Randomized Controlled Trial, multiple countries, peer-reviewed, 82 authors, dosage 50mg/kg qid days 1-4, trial NCT04401150 (history) (LOVIT-COVID).	risk of death, 27.8% lower, HR 0.72, $p = 0.19$, treatment 190, control 194, combined.
	risk of death, 27.5% lower, HR 0.72, $p = 0.34$, treatment 84, control 97, inverted to make HR<1 favor treatment, LOVIT-COVID critical.
	risk of death, 28.1% lower, HR 0.72, $p = 0.37$, treatment 106, control 97, inverted to make HR<1 favor treatment, LOVIT-COVID non-critical.
Adhikari, 10/25/2023, Randomized Controlled Trial, multiple countries, peer-reviewed, 82 authors, dosage 50mg/kg qid days 1-4, trial NCT04401150 (history) (REMAP-CAP).	risk of death, 19.5% higher, HR 1.19, $p = 0.08$, treatment 1,303, control 903, combined.
	risk of death, 16.3% higher, HR 1.16, $p = 0.22$, treatment 953, control 434, inverted to make HR<1 favor treatment, REMAP-CAP critical.
	risk of death, 26.6% higher, HR 1.27, $p = 0.19$, treatment 350, control 469, inverted to make HR<1 favor treatment, REMAP-CAP non-critical.
	risk of mechanical ventilation, 35.1% higher, HR 1.35, $p = 0.04$, treatment 1,032, control 528, inverted to make HR<1 favor treatment, combined trials, critical.
	risk of mechanical ventilation, 69.5% higher, HR 1.69, $p = 0.008$, treatment 454, control 563, inverted to make HR<1 favor treatment, combined trials, non-critical.
Al Sulaiman, 4/2/2021, retrospective, propensity score matching, Saudi Arabia, preprint, 12 authors, dosage 1000mg days 1-11.	risk of death, 14.9% lower, RR 0.85, $p = 0.27$, treatment 46 of 142 (32.4%), control 59 of 142 (41.5%), NNT 11, odds ratio converted to relative risk, PSM.
Baguma, 12/28/2021, retrospective, Uganda, preprint, 16 authors, study period March 2020 - October 2021, dosage not specified.	risk of death, 48.5% higher, RR 1.48, $p = 0.54$, treatment 385, control 96, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariable, control prevalance approximated with overall prevalence.
Bepouka, 5/14/2025, retrospective, DR Congo, peer-reviewed, 14 authors, study period 20 March, 2020 - 2 January, 2022.	risk of death, 76.0% lower, OR 0.24, $p = 0.01$, treatment 185, control 225, adjusted per study, multivariable, RR approximated with OR.

Coppock, 3/19/2022, Randomized Controlled Trial, USA, peer-reviewed, 14 authors, dosage 300mg/kg day 1, 600mg/kg day 2, 900mg/kg days 3-6.	**risk of progression, 5.0% lower, HR 0.95, $p = 0.64$**, treatment 4 of 44 (9.1%), control 2 of 22 (9.1%), adjusted per study, within 36 hours.
	risk of no improvement, 49.7% better, RR 0.50, $p = 0.16$, treatment 6 of 44 (13.6%), control 6 of 22 (27.3%), NNT 7.3, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, within 36 hours.
	risk of no hospital discharge, 22.5% lower, RR 0.78, $p = 0.07$, treatment 31 of 44 (70.5%), control 20 of 22 (90.9%), NNT 4.9, within 36 hours.
Corrao, 7/8/2024, prospective, Italy, peer-reviewed, 7 authors, trial NCT04323514 (history).	**risk of death, 39.4% lower, RR 0.61, $p = 0.37$**, treatment 9 of 104 (8.7%), control 6 of 42 (14.3%), NNT 18.
	risk of death/ICU, 19.0% lower, OR 0.81, $p = 0.24$, treatment 104, control 42, adjusted per study, multivariable, RR approximated with OR.
	risk of ICU admission, 101.9% higher, RR 2.02, $p = 0.51$, treatment 10 of 104 (9.6%), control 2 of 42 (4.8%).
	hospitalization time, 25.0% lower, relative time 0.75, $p = 0.16$, treatment 104, control 42.
Coskun, 3/21/2023, retrospective, Turkey, peer-reviewed, 1 author, study period March 2020 - June 2020, trial NCT04710329 (history), excluded in exclusion analyses: very late stage, ICU patients.	**risk of death, 25.4% lower, RR 0.75, $p = 0.26$**, treatment 17 of 38 (44.7%), control 24 of 40 (60.0%), NNT 6.6.
	risk of mechanical ventilation, 1.8% lower, RR 0.98, $p = 1.00$, treatment 28 of 38 (73.7%), control 30 of 40 (75.0%), NNT 76.
	relative SOFA score, 28.4% better, RR 0.72, $p = 0.005$, treatment 38, control 40, mean SOFA score, day 4.
Darban, 12/15/2020, Randomized Controlled Trial, Iran, peer-reviewed, 8 authors, study period 7 April, 2020 - 8 June, 2020, dosage 2000mg qid days 1-10, this trial uses multiple treatments in the treatment arm (combined with melatonin and zinc) - results of individual treatments may vary, trial IRCT20151228025732N52, excluded in exclusion analyses: very late stage, ICU patients.	**risk of progression, 33.3% lower, RR 0.67, $p = 1.00$**, treatment 2 of 10 (20.0%), control 3 of 10 (30.0%), NNT 10.
	ICU time, 6.0% lower, relative time 0.94, $p = 0.30$, treatment 10, control 10.
Dinoi, 2/20/2025, retrospective, Italy, peer-reviewed, 11 authors, study period 17 March, 2020 - 15 June, 2021, dosage not specified.	**risk of death, 31.5% higher, OR 1.32, $p = 0.30$**, treatment 38 of 247 (15.4%) cases, 30 of 247 (12.1%) controls, case control OR.
Doocy, 10/19/2022, prospective, multiple countries, peer-reviewed, 6 authors, study period December 2020 - June 2021, dosage not specified, trial NCT04568499 (history).	**risk of death, 62.8% lower, RR 0.37, $p = 0.22$**, treatment 2 of 64 (3.1%), control 22 of 80 (27.5%), NNT 4.1, adjusted per study, inverted to make RR<1 favor treatment, multivariable.
Elhadi, 4/30/2021, prospective, Libya, peer-reviewed, 21 authors, study period 29 May, 2020 - 30 December, 2020, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details; very late stage, ICU patients.	**risk of death, 12.0% higher, RR 1.12, $p = 0.15$**, treatment 175 of 277 (63.2%), control 106 of 188 (56.4%).
Fogleman, 7/27/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, mean age 52.0, 7 authors, study period 5	**relative recovery, 4.4% better, RR 0.96, $p = 0.83$**, treatment mean 17.59 (±13.1) n=32, control mean 16.82 (±15.7) n=34, mid-recovery, relative symptom improvement, day 9.

October, 2020 - 21 June, 2021, average treatment delay 6.0 days, dosage 1000mg days 1-14, trial NCT04530539 (history).	
Fowler, 4/4/2024, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 1 author, trial NCT04344184 (history) (SAFE EVICT CORONA-ALI), excluded in exclusion analyses: very late stage, ICU patients.	risk of death, 18.8% lower, RR 0.81, $p = 0.75$, treatment 5 of 22 (22.7%), control 7 of 25 (28.0%), NNT 19.
	relative WHO status, 1.7% worse, RR 1.02, $p = 0.28$, treatment mean 3.05 (±0.22) n=21, control mean 3.0 (±0.0) n=23, day 27.
Gadhiya, 4/8/2021, retrospective, USA, peer-reviewed, 4 authors, dosage not specified, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of death, 0.7% higher, RR 1.01, $p = 0.98$, treatment 19 of 55 (34.5%), control 36 of 226 (15.9%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression.
Galindo, 5/15/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Colombia, trial NCT05029037 (history).	Estimated 160 patient RCT with results unknown and over 3 years late.
Gao, 2/26/2021, retrospective, China, peer-reviewed, 14 authors, dosage 12000mg day 1, 6,000mg days 2-5.	risk of death, 86.0% lower, HR 0.14, $p = 0.04$, treatment 1 of 46 (2.2%), control 5 of 30 (16.7%), NNT 6.9, adjusted per study, KM.
Gavrielatou, 2/11/2022, retrospective, Greece, peer-reviewed, 10 authors, study period 21 October, 2020 - 8 March, 2021, average treatment delay 5.5 days, excluded in exclusion analyses: very late stage, ICU patients.	risk of death, 58.0% lower, RR 0.42, $p = 0.11$, treatment 2 of 10 (20.0%), control 49 of 103 (47.6%), NNT 3.6.
Hakamifard, 4/14/2021, Randomized Controlled Trial, Iran, peer-reviewed, 8 authors, study period March 2020 - April 2020, dosage 1000mg daily, this trial uses multiple treatments in the treatment arm (combined with vitamin E) - results of individual treatments may vary.	risk of ICU admission, 46.3% lower, RR 0.54, $p = 0.46$, treatment 3 of 38 (7.9%), control 5 of 34 (14.7%), NNT 15.
	hospitalization time, 1.0% lower, relative time 0.99, $p = 0.82$, treatment 38, control 34.
Hamidi-Alamdari, 3/8/2021, Randomized Controlled Trial, Iran, peer-reviewed, 23 authors, study period 19 April, 2020 - 21 September, 2020, this trial uses multiple treatments in the treatment arm (combined with methylene blue and N-acetyl cysteine) - results of individual treatments may vary, trial NCT04370288 (history).	risk of death, 44.4% lower, RR 0.56, $p = 0.38$, treatment 5 of 40 (12.5%), control 9 of 40 (22.5%), NNT 10.0.
	hospitalization time, 37.6% lower, relative time 0.62, $p = 0.004$, treatment 40, control 40.
He, 1/31/2021, Single Blind Randomized Controlled Trial, China, trial NCT04664010 (history).	60 patient RCT with results unknown and over 4 years late.
Hess, 3/29/2022, retrospective, USA, peer-reviewed, 9 authors, study period March 2020 - July 2020.	risk of death, 20.0% lower, HR 0.80, $p = 0.54$, treatment 10 of 25 (40.0%), control 37 of 75 (49.3%), NNT 11, time to event analysis, propensity score weighting.
	risk of mechanical ventilation, 39.5% lower, RR 0.60, $p = 0.05$, treatment 18 of 25 (72.0%), control 54 of 75 (72.0%), odds ratio converted to relative risk, propensity score weighting.
	risk of mechanical ventilation, 50.0% lower, HR 0.50, $p = 0.03$, treatment 18 of 25 (72.0%), control 54 of 75 (72.0%), time to event analysis, propensity score weighting.
	risk of ICU admission, 27.2% lower, RR 0.73, $p = 0.10$, treatment 22 of 25 (88.0%), control 63 of 75 (84.0%), odds ratio converted to relative risk, propensity score weighting.

	risk of ICU admission, 30.0% lower, HR 0.70, p = 0.19, treatment 22 of 25 (88.0%), control 63 of 75 (84.0%), time to event analysis, propensity score weighting.
Izzo, 7/19/2022, prospective, Italy, peer-reviewed, 21 authors, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with L-arginine) - results of individual treatments may vary, LINCOLN trial.	relative recovery, 41.4% better, RR 0.59, p < 0.001, treatment mean 8.15 (±1.3) n=869, control mean 13.9 (±2.3) n=521, relative symptom score.
	relative recovery, 67.5% better, RR 0.33, p < 0.001, treatment 869, control 521, relative Borg score.
JamaliMoghadamSiahkali, 1/9/2021, Randomized Controlled Trial, Iran, preprint, 17 authors, study period April 2020 - May 2020, dosage 1500mg qid days 1-5.	risk of death, no change, RR 1.00, p = 1.00, treatment 3 of 30 (10.0%), control 3 of 30 (10.0%).
	risk of mechanical ventilation, 25.0% higher, RR 1.25, p = 1.00, treatment 5 of 30 (16.7%), control 4 of 30 (13.3%).
	hospitalization time, 30.8% higher, relative time 1.31, p = 0.03, treatment 30, control 30.
Jang, 12/16/2020, retrospective, South Korea, peer-reviewed, median age 63.0, 10 authors, study period February 2020 - April 2020, dosage not specified, excluded in exclusion analyses: very late stage, ECMO patients.	risk of no recovery, 51.4% lower, RR 0.49, p = 0.15, treatment 5 of 12 (41.7%), control 6 of 7 (85.7%), NNT 2.3, weaning from ECMO.
Krishnan, 7/20/2020, retrospective, USA, peer-reviewed, 13 authors, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 30.7% lower, RR 0.69, p = 0.04, treatment 40 of 79 (50.6%), control 52 of 73 (71.2%), NNT 4.9, odds ratio converted to relative risk.
Kumar (B), 8/30/2022, Double Blind Randomized Controlled Trial, placebo-controlled, India, peer-reviewed, mean age 57.0, 11 authors, average treatment delay 7.5 days, dosage 1000mg tid days 1-4, trial CTRI/2020/11/029230, excluded in exclusion analyses: very late stage, ICU patients.	risk of death, 23.1% lower, RR 0.77, p = 0.60, treatment 10 of 30 (33.3%), control 13 of 30 (43.3%), NNT 10.0.
	risk of mechanical ventilation, 21.4% lower, RR 0.79, p = 0.60, treatment 11 of 30 (36.7%), control 14 of 30 (46.7%), NNT 10.0.
Kumari, 11/30/2020, Randomized Controlled Trial, Pakistan, peer-reviewed, 10 authors, study period March 2020 - July 2020, dosage 50mg/kg daily.	risk of death, 36.4% lower, RR 0.64, p = 0.45, treatment 7 of 75 (9.3%), control 11 of 75 (14.7%), NNT 19.
	risk of mechanical ventilation, 20.0% lower, RR 0.80, p = 0.67, treatment 12 of 75 (16.0%), control 15 of 75 (20.0%), NNT 25.
	recovery time, 26.0% lower, relative time 0.74, p < 0.001, treatment 75, control 75, days to symptom-free.
	hospitalization time, 24.3% lower, relative time 0.76, p < 0.001, treatment 75, control 75, days spent in hospital.
Kyagambiddwa, 5/11/2023, retrospective, Uganda, peer-reviewed, mean age 39.0, 15 authors, study period May 2020 - August 2022, dosage not specified.	risk of death, 50.0% lower, HR 0.50, p = 0.06, adjusted per study, multivariable, Cox proportional hazards.
Labbani-Motlagh, 12/14/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 12 authors, study period 5 April, 2020 - 19 November, 2020, dosage 12000mg days 1-4, trial IRCT20190917044805N2.	risk of death, 33.3% lower, RR 0.67, p = 0.74, treatment 4 of 37 (10.8%), control 6 of 37 (16.2%), NNT 18, day 28.
	hospitalization time, 12.8% higher, relative time 1.13, p = 0.49, treatment mean 9.24 (±7.5) n=37, control mean 8.19 (±5.34) n=37.

	risk of progression, 15.9% lower, RR 0.84, *p* = 0.12, treatment 37, control 37, SOFA, day 5.
	risk of progression, 9.3% higher, RR 1.09, *p* = 0.47, treatment 37, control 37, NEWS, day 5.
	risk of progression, 5.8% higher, RR 1.06, *p* = 0.38, treatment 37, control 37, WHO, day 5.
	risk of progression, 60.0% lower, RR 0.40, *p* = 0.14, treatment 4 of 37 (10.8%), control 10 of 37 (27.0%), NNT 6.2, AKI.
Lamontagne, 12/6/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Canada, trial NCT04401150 (history) (LOVIT-COVID).	392 patient RCT with results unknown and over 2 years late.
Li, 6/8/2021, retrospective, propensity score matching, USA, peer-reviewed, 6 authors, excluded in exclusion analyses: very late stage, ICU patients; very late stage, ICU patients.	**risk of death, 10.5% higher, RR 1.11, *p* = 1.00**, treatment 7 of 8 (87.5%), control 19 of 24 (79.2%), PSM.
Liu, 6/1/2023, Single Blind Randomized Controlled Trial, China, trial NCT05694975 (history) (CEMVISCC).	Estimated 608 patient RCT with results unknown and over 2 years late.
Majidi, 12/15/2021, Double Blind Randomized Controlled Trial, Iran, peer-reviewed, 16 authors, study period May 2020 - July 2020, dosage 500mg days 1-14, trial IRCT20151226025699N5, excluded in exclusion analyses: very late stage, ICU patients.	**risk of death, 13.6% lower, RR 0.86, *p* = 0.03**, treatment 26 of 31 (83.9%), control 67 of 69 (97.1%), NNT 7.6, day 28.
Mousaviasl, 7/22/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 13 authors, study period November 2020 - May 2021, dosage 500mg bid days 1-5.	**risk of death, 20.4% lower, RR 0.80, *p* = 0.64**, treatment 8 of 201 (4.0%), control 10 of 200 (5.0%), NNT 98, day 28.
	risk of death, 99.0% higher, RR 1.99, *p* = 1.00, treatment 2 of 201 (1.0%), control 1 of 200 (0.5%), ICU mortality.
	risk of mechanical ventilation, 199.5% higher, RR 3.00, *p* = 1.00, treatment 1 of 201 (0.5%), control 0 of 200 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of ICU admission, 32.7% higher, RR 1.33, *p* = 0.79, treatment 8 of 201 (4.0%), control 6 of 200 (3.0%).
Mulhem, 4/7/2021, retrospective, database analysis, USA, peer-reviewed, 3 authors, dosage not specified, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 32.2% higher, RR 1.32, *p* = 0.01**, treatment 157 of 794 (19.8%), control 359 of 2,425 (14.8%), adjusted per study, odds ratio converted to relative risk, logistic regression.
Patel, 10/1/2020, retrospective, USA, peer-reviewed, 8 authors, dosage 1000mg days 1-4, 500mg to 1500mg daily.	**risk of death, 29.5% lower, RR 0.71, *p* = 0.18**, treatment 22 of 96 (22.9%), control 26 of 80 (32.5%), NNT 10.
	risk of death, 15.6% lower, RR 0.84, *p* = 0.60, treatment 15 of 30 (50.0%), control 16 of 27 (59.3%), NNT 11, ICU patients.
Pourhoseingholi, 5/26/2021, prospective, Iran, preprint, mean age 57.9, 11 authors, study period 2 February, 2020 - 20 July, 2020, average treatment	**risk of death, 13.0% lower, HR 0.87, *p* = 0.38**, treatment 54 of 199 (27.1%), control 285 of 2,269 (12.6%), adjusted per study, multivariable, Cox proportional hazards.

delay 7.4 days, dosage not specified.	
Rana, 6/28/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Pakistan, peer-reviewed, 10 authors, study period 28 December, 2020 - 10 April, 2022, dosage 30000mg days 1-4, trial NCT04682574 (history), excluded in exclusion analyses: very late stage, ICU patients.	risk of death, 54.5% lower, RR 0.45, $p = 0.20$, treatment 5 of 139 (3.6%), control 11 of 139 (7.9%), NNT 23.
	risk of mechanical ventilation, 44.4% lower, RR 0.56, $p = 0.41$, treatment 5 of 139 (3.6%), control 9 of 139 (6.5%), NNT 35.
	hospitalization time, 36.8% lower, relative time 0.63, $p = 0.91$, treatment 139, control 139.
Salehi, 3/11/2022, retrospective, Iran, preprint, mean age 62.0, 11 authors, study period April 2021 - September 2021, excluded in exclusion analyses: unadjusted results with no group details; very late stage, ICU patients.	risk of death, 10.1% lower, RR 0.90, $p = 0.56$, treatment 22 of 40 (55.0%), control 52 of 85 (61.2%), NNT 16.
Seely, 9/22/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Canada, peer-reviewed, mean age 39.9, 10 authors, study period September 2021 - April 2022, this trial uses multiple treatments in the treatment arm (combined with vitamin C, D, K2, and zinc) - results of individual treatments may vary, trial NCT04780061 (history).	ER visit, 47.6% lower, RR 0.52, $p = 0.68$, treatment 2 of 42 (4.8%), control 4 of 44 (9.1%), NNT 23.
	relative mean cumulative symptom score, 13.8% better, RR 0.86, $p = 0.41$, treatment mean 166.3 (±92.3) n=34, control mean 192.9 (±153.6) n=24.
	EQ-VAS average score <80, 29.4% lower, RR 0.71, $p = 0.54$, treatment 7 of 34 (20.6%), control 7 of 24 (29.2%), NNT 12, average daily EQ-VAS score <80.
	relative EQ5D improvement, 28.6% better, RR 0.71, $p = 0.44$, treatment 32, control 31, relative improvement in EQ5D, week 1.
	relative EQ5D improvement, 14.3% better, RR 0.86, $p = 0.73$, treatment 33, control 30, relative improvement in EQ5D, week 2.
	relative EQ5D improvement, 50.0% better, RR 0.50, $p = 0.17$, treatment 32, control 33, relative improvement in EQ5D, week 3.
	relative EQ5D improvement, 12.5% worse, RR 1.12, $p = 0.47$, treatment 30, control 25, relative improvement in EQ5D, week 4.
	recovery time, 4.0% higher, relative time 1.04, $p = 0.81$, treatment 34, control 24.
	risk of PASC, 12.1% lower, RR 0.88, $p = 1.00$, treatment 3 of 33 (9.1%), control 3 of 29 (10.3%), NNT 80, 12 weeks.
	risk of PASC, 35.7% lower, RR 0.64, $p = 0.69$, treatment 3 of 35 (8.6%), control 4 of 30 (13.3%), NNT 21, 8 weeks.
	risk of PASC, 0.6% lower, RR 0.99, $p = 1.00$, treatment 6 of 35 (17.1%), control 5 of 29 (17.2%), NNT 1015, 4 weeks.
Sharmin, 9/1/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Bangladesh, trial NCT04558424 (history).	Estimated 50 patient RCT with results unknown and over 3 years late.
Simsek, 9/27/2021, retrospective, Turkey, peer-reviewed, 16 authors, dosage 25000mg days 1-7.	risk of death, 44.1% lower, RR 0.56, $p = 0.18$, treatment 6 of 58 (10.3%), control 15 of 81 (18.5%), NNT 12.
	risk of ICU admission, 10.2% lower, RR 0.90, $p = 0.66$, treatment 18 of 58 (31.0%), control 28 of 81 (34.6%), NNT 28.

Suna, 5/11/2021, retrospective, Turkey, peer-reviewed, 5 authors, dosage 2000mg daily, excluded in exclusion analyses: substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	risk of death, 21.3% lower, RR 0.79, $p = 0.52$, treatment 17 of 153 (11.1%), control 24 of 170 (14.1%), NNT 33.
	risk of ICU admission, 1.9% higher, RR 1.02, $p = 1.00$, treatment 11 of 153 (7.2%), control 12 of 170 (7.1%).
Tan, 7/26/2021, retrospective, China, peer-reviewed, 7 authors, dosage 500mg tid days 1-7, this trial uses multiple treatments in the treatment arm (combined with diammonium glycyrrhizinate) - results of individual treatments may vary.	risk of death/intubation, 24.5% lower, RR 0.75, $p = 0.74$, treatment 1 of 46 (2.2%), control 14 of 115 (12.2%), NNT 10.0, odds ratio converted to relative risk, primary outcome.
	risk of ARDS, 73.3% lower, RR 0.27, $p = 0.002$, treatment 7 of 46 (15.2%), control 41 of 115 (35.7%), NNT 4.9, odds ratio converted to relative risk.
Tehrani, 11/8/2021, Randomized Controlled Trial, Iran, peer-reviewed, 10 authors, study period March 2020 - May 2020, average treatment delay 9.0 days, dosage 2000mg qid days 1-5.	risk of death, 87.1% lower, RR 0.13, $p = 0.13$, treatment 0 of 18 (0.0%), control 4 of 26 (15.4%), NNT 6.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	hospitalization time, 17.6% lower, relative time 0.82, $p = 0.23$, treatment 18, control 26.
Tu, 1/13/2022, retrospective, Sierra Leone, peer-reviewed, 11 authors, study period 31 March, 2020 - 11 August, 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 83.0% lower, RR 0.17, $p < 0.001$, treatment 8 of 116 (6.9%), control 26 of 64 (40.6%), NNT 3.0.
Uz, 11/13/2024, retrospective, Turkey, peer-reviewed, 6 authors.	risk of death, 84.2% lower, OR 0.16, $p = 0.04998$, treatment 41, control 46, adjusted per study, high dose, multivariable, RR approximated with OR.
	risk of death, 90.2% lower, OR 0.10, $p = 0.004$, treatment 183, control 46, adjusted per study, low dose, multivariable, RR approximated with OR.
Vishnuram, 6/30/2021, retrospective, India, peer-reviewed, 5 authors, dosage 4000mg days 1-10, excluded in exclusion analyses: unadjusted results with no group details; minimal details of groups provided.	risk of death, 54.2% lower, RR 0.46, $p = 0.03$, treatment 164 of 8,634 (1.9%), control 10 of 241 (4.1%), NNT 44.
Yang (B), 1/15/2022, Randomized Controlled Trial, China, peer-reviewed, 11 authors, study period 1 February, 2020 - 29 February, 2020, this trial uses multiple treatments in the treatment arm (combined with TCM) - results of individual treatments may vary, trial ChiCTR2000032717, excluded in exclusion analyses: combined treatments may contribute significantly to the effect seen.	recovery time, 32.9% lower, relative time 0.67, $p < 0.001$, treatment mean 10.2 (±1.75) n=10, control mean 15.2 (±2.49) n=10, symptom disappearance, severe patients, group C vs. group A.
	recovery time, 44.6% lower, relative time 0.55, $p < 0.001$, treatment mean 4.1 (±0.88) n=10, control mean 7.4 (±1.26) n=10, symptom disappearance, non-severe patients, group C vs. group A.
	recovery time, 23.9% lower, relative time 0.76, $p = 0.006$, treatment mean 10.2 (±1.75) n=10, control mean 13.4 (±2.76) n=10, symptom disappearance, severe patients, group C vs. group B (high vs. low dose).
	recovery time, 28.1% lower, relative time 0.72, $p = 0.003$, treatment mean 4.1 (±0.88) n=10, control mean 5.7 (±1.16) n=10, symptom disappearance, non-severe patients, group C vs. group B (high vs. low dose).

	recovery time, 27.1% lower, relative time 0.73, $p = 0.002$, treatment mean 13.45 (±3.11) n=10, control mean 18.45 (±3.12) n=10, disease recovery, severe patients, group C vs. group A.
	recovery time, 23.2% lower, relative time 0.77, $p < 0.001$, treatment mean 7.0 (±0.94) n=10, control mean 9.11 (±1.25) n=10, disease recovery, non-severe patients, group C vs. group A.
	recovery time, 15.4% lower, relative time 0.85, $p = 0.15$, treatment mean 13.45 (±3.11) n=10, control mean 15.89 (±4.06) n=10, disease recovery, severe patients, group C vs. group B (high vs. low dose).
	recovery time, 14.6% lower, relative time 0.85, $p = 0.02$, treatment mean 7.0 (±0.94) n=10, control mean 8.2 (±1.14) n=10, disease recovery, non-severe patients, group C vs. group B (high vs. low dose).
Yüksel, 9/20/2020, retrospective, Turkey, preprint, 13 authors, dosage 200mg/kg days 1-4, excluded in exclusion analyses: very late stage, ICU patients.	**risk of death, 18.8% lower, RR 0.81, $p = 0.04$**, treatment 31 of 42 (73.8%), control 40 of 44 (90.9%), NNT 5.8, propensity score matching.
Zangeneh, 5/13/2022, retrospective, Iran, peer-reviewed, 3 authors, dosage not specified, excluded in exclusion analyses: very late stage, ICU patients.	**risk of death, 4.0% lower, HR 0.96, $p = 0.86$**, Cox proportional hazards.
Zhang, 8/10/2020, Randomized Controlled Trial, China, peer-reviewed, 11 authors, study period 14 February, 2020 - 29 March, 2020, dosage 12000mg bid days 1-7, excluded in exclusion analyses: very late stage, ICU patients.	**risk of death, 50.0% lower, RR 0.50, $p = 0.20$**, treatment 6 of 27 (22.2%), control 11 of 29 (37.9%), NNT 6.4, adjusted per study, ICU mortality.
	risk of death, 80.0% lower, RR 0.20, $p = 0.04$, treatment 5 of 27 (18.5%), control 11 of 29 (37.9%), NNT 5.2, adjusted per study, ICU mortality for SOFA>=3.
	risk of death, 50.0% lower, RR 0.50, $p = 0.31$, treatment 6 of 27 (22.2%), control 10 of 29 (34.5%), NNT 8.2, adjusted per study, 28 day mortality.
	risk of death, 70.0% lower, RR 0.30, $p = 0.07$, treatment 5 of 27 (18.5%), control 10 of 29 (34.5%), NNT 6.3, adjusted per study, 28 day mortality for SOFA>=3.
Zheng, 9/22/2021, retrospective, China, peer-reviewed, 10 authors, study period 13 February, 2020 - 29 February, 2020, dosage 3000mg days 1-5, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; immortal time bias may significantly affect results; treatment start times unknown, treatment may not have started at baseline.	**risk of death, 157.0% higher, HR 2.57, $p = 0.33$**, treatment 12 of 70 (17.1%), control 7 of 327 (2.1%), adjusted per study, propensity score matching.
	risk of death, 169.0% higher, HR 2.69, $p = 0.07$, treatment 12 of 70 (17.1%), control 7 of 327 (2.1%), adjusted per study, IPTW.
	clinical improvement ≥ 2 points, 35.1% worse, HR 1.35, $p = 0.17$, treatment 18 of 70 (25.7%), control 16 of 327 (4.9%), adjusted per study, inverted to make HR<1 favor treatment, propensity score matching.
	clinical improvement ≥ 2 points, 31.6% worse, HR 1.32, $p = 0.11$, treatment 18 of 70 (25.7%), control 16 of 327 (4.9%), adjusted per study, inverted to make HR<1 favor treatment, IPTW.
Özgültekin, 9/22/2022, retrospective, Turkey, peer-reviewed, 4 authors, study period March 2020 - June 2020, excluded in exclusion analyses: very late	**risk of death, 4.8% higher, RR 1.05, $p = 1.00$**, treatment 18 of 21 (85.7%), control 18 of 22 (81.8%).

stage, ICU patients.	
Özgünay, 7/4/2021, retrospective, Turkey, peer-reviewed, 7 authors, dosage 2000mg tid days 1-10, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; very late stage, ICU patients.	risk of death, 9.3% lower, RR 0.91, $p = 0.69$, treatment 17 of 32 (53.1%), control 75 of 128 (58.6%), NNT 18.
	risk of mechanical ventilation, 1.1% higher, RR 1.01, $p = 1.00$, treatment 23 of 32 (71.9%), control 91 of 128 (71.1%).

Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Abdulateef, 4/8/2021, retrospective, Iraq, peer-reviewed, 7 authors, study period July 2020 - August 2020, dosage varies, excluded in exclusion analyses: unadjusted results with no group details.	risk of hospitalization, 18.7% lower, RR 0.81, $p = 0.69$, treatment 8 of 132 (6.1%), control 22 of 295 (7.5%), NNT 72, unadjusted.
Akbar, 11/7/2023, retrospective, Qatar, peer-reviewed, mean age 40.3, 9 authors, study period March 2020 - September 2020, dosage not specified.	risk of case, 14.0% lower, OR 0.86, $p = 0.29$, treatment 665, control 9,335, adjusted per study, multivariable, model 2, RR approximated with OR.
Aldwihi, 5/11/2021, retrospective, Saudi Arabia, peer-reviewed, survey, mean age 36.5, 8 authors, study period August 2020 - October 2020, dosage not specified.	risk of hospitalization, 36.3% lower, RR 0.64, $p = 0.006$, treatment 142 of 505 (28.1%), control 95 of 233 (40.8%), NNT 7.9, adjusted per study, odds ratio converted to relative risk, multivariable.
Asoudeh, 3/21/2023, retrospective, Iran, peer-reviewed, 10 authors, study period June 2021 - September 2021.	risk of severe case, 69.0% lower, OR 0.31, $p = 0.003$, adjusted per study, T3 vs. T1, multivariable, model 3, RR approximated with OR.
Behera, 11/3/2020, retrospective, India, peer-reviewed, 13 authors.	risk of case, 18.0% lower, OR 0.82, $p = 0.58$, treatment 29 of 67 (43.3%) cases, 38 of 148 (25.7%) controls, adjusted per study, case control OR, model 2 conditional logistic regression.
	risk of case, 29.0% lower, OR 0.71, $p = 0.24$, treatment 29 of 67 (43.3%) cases, 38 of 148 (25.7%) controls, adjusted per study, case control OR, matched pair analysis.
Bejan, 2/28/2021, retrospective, USA, peer-reviewed, mean age 42.0, 6 authors.	risk of death, 34.0% lower, OR 0.66, $p = 0.33$, treatment 569, control 8,637, adjusted per study, RR approximated with OR.
	risk of mechanical ventilation, 25.0% lower, OR 0.75, $p = 0.47$, treatment 572, control 8,657, adjusted per study, RR approximated with OR.
	risk of ICU admission, 15.0% lower, OR 0.85, $p = 0.65$, treatment 577, control 8,690, adjusted per study, RR approximated with OR.
	risk of hospitalization, no change, OR 1.00, $p = 1.00$, treatment 626, control 9,122, adjusted per study, RR approximated with OR.
Guan, 5/22/2024, retrospective, China, peer-reviewed, 5 authors, study period December 2022 - January 2023.	risk of symptomatic case, 31.4% lower, RR 0.69, $p = 0.007$, treatment 28 of 46 (60.9%), control 2,017 of 2,454 (82.2%), NNT 4.7, adjusted per study, odds ratio converted to relative risk, high dose, multivariable.

	risk of symptomatic case, 18.5% lower, RR 0.82, p = 0.02, treatment 55 of 79 (69.6%), control 2,017 of 2,454 (82.2%), NNT 8.0, adjusted per study, odds ratio converted to relative risk, medium dose, multivariable.
	risk of symptomatic case, 6.8% lower, RR 0.93, p = 0.13, treatment 129 of 167 (77.2%), control 2,017 of 2,454 (82.2%), NNT 20, adjusted per study, odds ratio converted to relative risk, low dose, multivariable.
Guldemir, 11/16/2022, retrospective, Turkey, peer-reviewed, 3 authors, study period 30 March, 2020 - 23 September, 2020, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details.	**risk of hospitalization, 31.0% lower, RR 0.69, p = 0.046** (Fisher's exact test), treatment 33 of 173 (19.1%), control 84 of 304 (27.6%), NNT 12.
Holt, 3/30/2021, prospective, United Kingdom, peer-reviewed, 34 authors, study period 1 May, 2020 - 5 February, 2021, trial NCT04330599 (history) (COVIDENCE UK), excluded in exclusion analyses: significant unadjusted confounding possible.	**risk of case, 2.9% higher, RR 1.03, p = 0.86**, treatment 49 of 1,580 (3.1%), control 397 of 13,647 (2.9%), adjusted per study, odds ratio converted to relative risk, minimally adjusted, group sizes approximated.
Louca, 11/30/2020, retrospective, United Kingdom, peer-reviewed, 26 authors, dosage not specified.	**risk of case, no change, RR 1.00, p = 1.00**, odds ratio converted to relative risk, United Kingdom, all adjustment model.
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	**risk of death, 28.3% lower, HR 0.72, p = 0.002**, treatment 840, control 15,128, Cox proportional hazards, day 30.
Mahto, 2/15/2021, retrospective, India, peer-reviewed, 6 authors.	**risk of IgG positive, 25.9% higher, RR 1.26, p = 0.49**, treatment 34 of 140 (24.3%), control 59 of 549 (10.7%), adjusted per study, odds ratio converted to relative risk, multivariable.
Mohseni, 8/4/2021, retrospective, Iran, peer-reviewed, 4 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of case, 44.2% higher, RR 1.44, p = 0.002**, treatment 34 of 43 (79.1%), control 307 of 560 (54.8%).
Nimer, 2/28/2022, retrospective, Jordan, peer-reviewed, survey, 4 authors, study period March 2021 - July 2021, dosage not specified.	**risk of hospitalization, 24.7% lower, RR 0.75, p = 0.08**, treatment 52 of 651 (8.0%), control 167 of 1,497 (11.2%), NNT 32, adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of severe case, 17.0% lower, RR 0.83, p = 0.18, treatment 66 of 651 (10.1%), control 194 of 1,497 (13.0%), NNT 35, adjusted per study, odds ratio converted to relative risk, multivariable.
Sharif, 11/26/2022, retrospective, Bangladesh, peer-reviewed, 14 authors, study period 13 December, 2020 - 4 February, 2021.	**risk of severe case, 46.0% lower, OR 0.54, p = 0.001**, adjusted per study, multivariable, RR approximated with OR.
	risk of severe case, 97.0% lower, OR 0.03, p = 0.005, adjusted per study, combined use of vitamin C, vitamin D, and zinc, multivariable, RR approximated with OR.
Shehab, 2/28/2022, retrospective, multiple countries, peer-reviewed, survey, 7 authors, study period September 2020 - March 2021, excluded in exclusion analyses: unadjusted results with no group details.	**risk of severe case, 4.3% lower, RR 0.96, p = 1.00**, treatment 14 of 139 (10.1%), control 12 of 114 (10.5%), NNT 220, unadjusted, severe vs. mild cases.
Vaisi, 5/11/2023, retrospective, Iran, peer-reviewed, 5 authors.	**risk of hospitalization, 37.9% lower, HR 0.62, p = 0.17**, treatment 2,818, control 1,137, adjusted per study, inverted to make HR<1 favor treatment, sufficient vs. insufficient intake,

	multivariable, Cox proportional hazards.
	risk of symptomatic case, 9.6% lower, HR 0.90, p = 0.71, treatment 2,818, control 1,137, adjusted per study, inverted to make HR<1 favor treatment, sufficient vs. insufficient intake, multivariable, Cox proportional hazards.

Supplementary Data

Supplementary Data

Footnotes

a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

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