Zinc for COVID-19: real-time meta analysis of 62 studies (45 treatment studies and 17 sufficiency studies)

@CovidAnalysis, July 2024, Version 63
https://c19early.org/zmeta.html

Abstract

Statistically significant lower risk is seen for mortality, ventilation, hospitalization, progression, recovery, and viral clearance. 18 studies from 18 independent teams in 9 countries show significant improvements.

Meta analysis using the most serious outcome reported shows 28% [18-36%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, peer-reviewed studies, and after excluding studies using combined treatment.

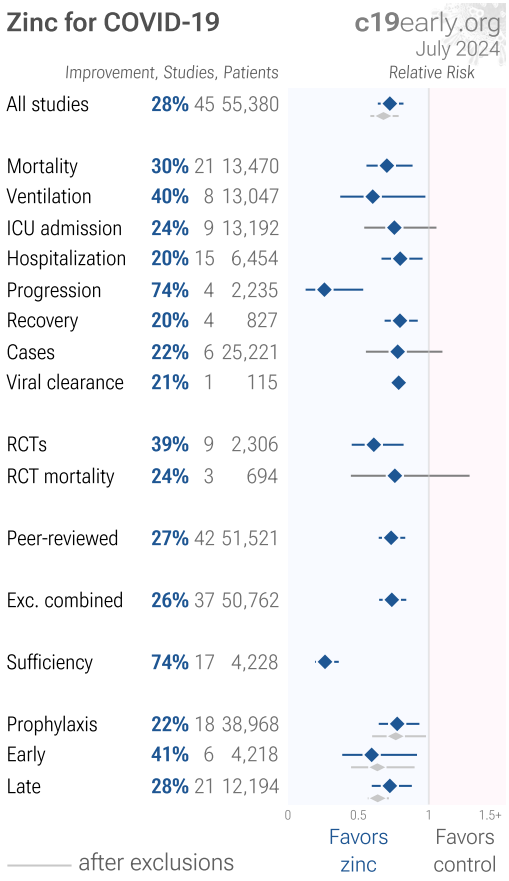
17 sufficiency studies analyze outcomes based on serum levels, showing 74% [64-81%] lower risk for patients with higher zinc levels.

Results are robust — in exclusion sensitivity analysis 20 of 45 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

8 studies use combined treatments. After exclusion the risk reduction is 26% [16-35%] compared to 28% [18-36%].

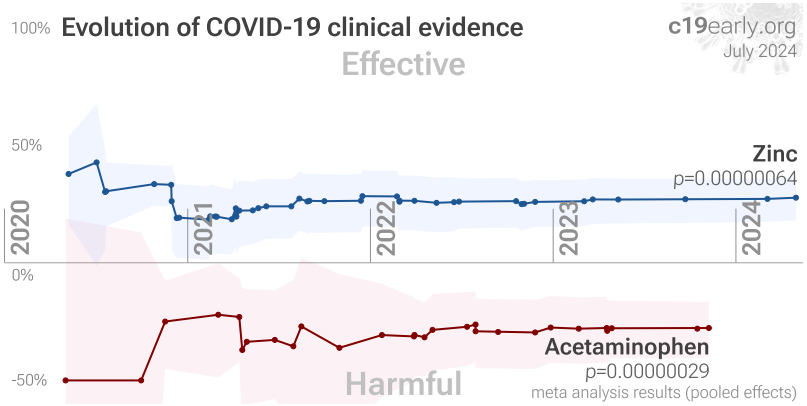
5 RCTs with 1,040 patients have not reported results (up to 3 years late).

The European Food Safety Authority has found evidence for a causal relationship between the intake of zinc and optimal immune system function [1,2]. Over-supplementation may be detrimental [3]. Bioaccessibility of supplements varies widely [4].



No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments are more effective. The quality of non-prescription supplements can vary widely [5,6].

All data to reproduce this paper and sources are in the appendix. 6 other meta analyses show significant improvements with zinc for mortality [7-11], severity [12], and cases [12].



ZINC FOR COVID-19 — HIGHLIGHTS

Zinc reduces risk with very high confidence for mortality, progression, recovery, and in pooled analysis, high confidence for ventilation and hospitalization, low confidence for ICU admission and viral clearance, and very low confidence for cases. Over-supplementation may be detrimental.

2nd treatment shown effective with ≥3 clinical studies in July 2020, now with $p = 0.00000064$ from 45 studies, and recognized in 17 countries.

Outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 78 treatments.

45 zinc COVID-19 studies (+5 unreported RCTs)

c19early.org
July 2024

	Improvement	RR [CI]		Treatment	Control	
Derwand	79%	0.21 [0.03-1.47]	death	1/141	13/377	CT[2]
Thomas (RCT)	-44%	1.44 [0.36-5.71]	hosp.	5/58	3/50	COVIDAtoZ
Aldwihi	24%	0.76 [0.51-1.08]	hosp.	53/199	184/539	
Asimi	97%	0.03 [0.00-0.44]	ventilation	0/270	9/86	CT[2]
Mayberry	53%	0.47 [0.33-0.65]	death	938 (n)	1,090 (n)	
Abdallah (DB RCT)	30%	0.70 [0.36-1.31]	death	15/231	22/239	VIZIR
Boukef (DB RCT)	unknown, >1 year late			150 (total)		
Early treatment	**41%**	**0.59 [0.39-0.92]**		74/1,837	231/2,381	**41% lower risk**

Tau^2 = 0.13, I^2 = 60.6%, p = 0.018

	Improvement	RR [CI]		Treatment	Control	
Carlucci	38%	0.62 [0.46-0.84]	death/HPC	54/411	119/521	
Krishnan	18%	0.82 [0.62-1.09]	death	31/58	61/94	
Yao	34%	0.66 [0.41-1.07]	death	73/196	21/46	
Frontera (PSM)	37%	0.63 [0.44-0.91]	death	121/1,006	424/2,467	CT[2]
Abd-Elsalam (RCT)	1%	0.99 [0.30-3.31]	death	5/96	5/95	data issues, see notes
Rosenthal	-16%	1.16 [1.05-1.28]	death	n/a	n/a	
Darban (RCT)	33%	0.67 [0.14-3.17]	progression	2/10	3/10	ICU patients CT[2]
Patel (DB RCT)	20%	0.80 [0.15-4.18]	death	2/15	3/18	
Mulhem	46%	0.54 [0.43-0.68]	death	256/1,596	260/1,623	
Gadhiya	-41%	1.41 [0.69-2.57]	death	21/54	34/229	
Al Sulaiman (ICU)	36%	0.64 [0.37-1.10]	death	23/82	32/82	ICU patients
Elavarasi	65%	0.35 [0.24-0.56]	death	486 (n)	1,201 (n)	
Assiri (ICU)	-81%	1.81 [0.41-6.97]	death	10/60	4/58	ICU patients
Kaplan (RCT)	-14%	1.14 [0.08-16.6]	ventilation	1/14	1/16	Reszinate CT[2]
Zangeneh (ICU)	-21%	1.21 [0.51-2.90]	death	n/a	n/a	ICU patients
Alahmari	30%	0.70 [0.63-0.78]	hosp. time	130 (n)	847 (n)	
Doocy	41%	0.59 [0.19-1.85]	death	3/28	21/116	
Ibrahim Alhajjaji	88%	0.12 [0.01-2.24]	death	0/44	4/57	
Kyagambiddwa	25%	0.75 [0.44-1.25]	death	20/89	22/73	
Seely (DB RCT)	48%	0.52 [0.10-2.71]	progression	2/42	4/44	CT[2]
Milan	56%	0.44 [0.18-1.09]	death	9/129	8/51	
Sharmin (DB RCT)	unknown, >2 years late			50 (est. total)		
Correa (DB RCT)	unknown, >2 years late			105 (total)		
Güerri-Fern.. (RCT)	unknown, >2 years late			75 (total)		MARZINC
Late treatment	**28%**	**0.72 [0.60-0.88]**		633/4,546	1,026/7,648	**28% lower risk**

Tau^2 = 0.11, I^2 = 83.8%, p = 0.0012

	Improvement	RR [CI]		Treatment	Control	
Louca	1%	0.99 [0.93-1.06]	cases	population-based cohort		
Mahto	37%	0.63 [0.22-1.49]	IgG+	10/38	83/651	
Bejan	18%	0.82 [0.22-3.13]	ventilation	155 (n)	9,074 (n)	
Holt	7%	0.93 [0.59-1.44]	cases	21/750	425/14,477	COVIDENCE UK
Abdulateef	13%	0.87 [0.38-1.97]	hosp.	7/111	23/317	
Seet (CLUS. RCT)	50%	0.50 [0.34-0.75]	symp. case	33/634	64/619	OT[1]
Israel	100%	0.00 [0.00-0.89]	hosp.	case control		CT[2]
Bagheri	60%	0.40 [0.04-3.53]	severe case	33 (n)	477 (n)	
Gordon	68%	0.32 [0.01-7.87]	death	0/104	1/96	
Kumar	20%	0.80 [0.21-2.99]	death	6/75	3/30	
Nimer	-25%	1.25 [0.87-1.77]	hosp.	41/326	178/1,822	
Shehab	47%	0.53 [0.19-1.47]	severe case	4/65	22/188	
Citu	18%	0.82 [0.12-5.68]	severe case	2/74	2/61	CT[2]
Stambouli (DB RCT)	68%	0.32 [0.03-2.95]	symp. case	1/59	3/56	
Adrean	-12%	1.12 [0.74-1.70]	cases	30/2,111	80/6,315	
Sharif	40%	0.60 [0.46-0.77]	severe case	n/a	n/a	
Asoudeh	57%	0.43 [0.21-0.90]	severe case	250 (all patients)		
Seifi	31%	0.69 [0.52-0.94]	hosp.	n/a	n/a	per unit change
Ajili (DB RCT)	unknown, >3 years late			660 (est. total)		COVID-Milit
Prophylaxis	**22%**	**0.78 [0.64-0.93]**		155/4,535	884/34,183	**22% lower risk**

Tau^2 = 0.06, I^2 = 57.7%, p = 0.0071

All studies	**28%**	**0.72 [0.64-0.82]**		862/10,918	2,141/44,212	**28% lower risk**

0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+

Favors zinc — Favors control

[1] OT: comparison with other treatment
[2] CT: study uses combined treatment

Tau^2 = 0.08, I^2 = 77.9%, p < 0.0001

Effect extraction pre-specified
(most serious outcome, see appendix)

A

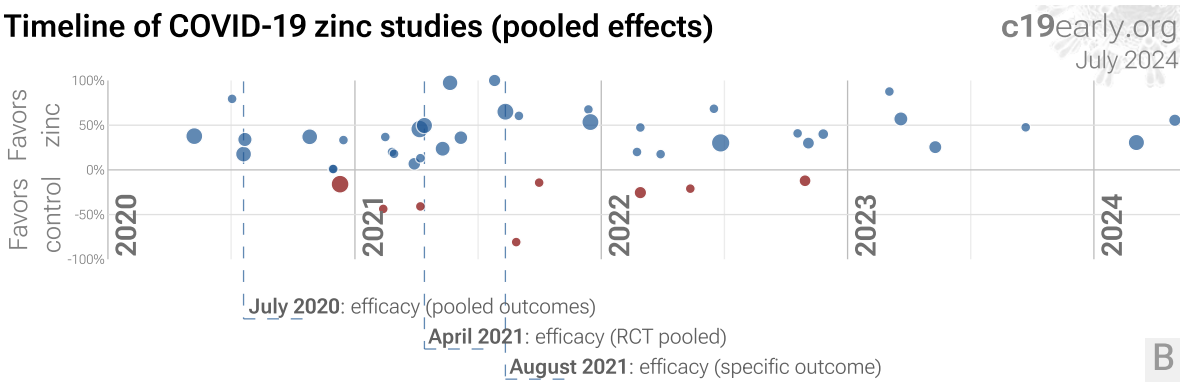


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in zinc 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 8.8 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 12.7 months, compared to using pooled outcomes.

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[13-20] and cognitive deficits[15,20], cardiovascular complications[21], organ failure, and death. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors[A,22-26], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk[27], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Other infections. Studies have shown efficacy with zinc for acute respiratory tract infections[28] and the common cold[29].

Analysis. We analyze all significant controlled studies of zinc 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 2 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.

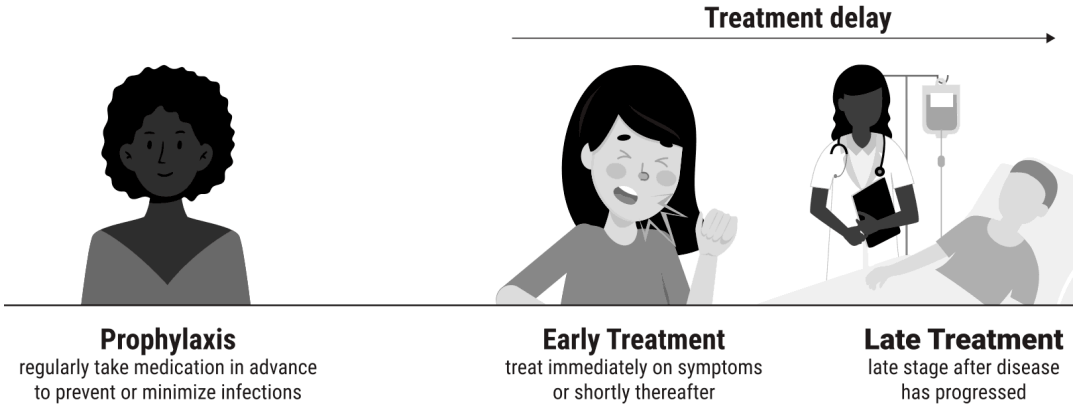


Figure 2. Treatment stages.

Preclinical Research

5 *In Silico* studies support the efficacy of zinc[30-34].

4 *In Vitro* studies support the efficacy of zinc[32,35-37].

An *In Vivo* animal study supports the efficacy of zinc[32].

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, with different exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 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, sufficiency studies, peer reviewed studies, and all studies excluding combined treatment studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	28% [18-36%] ****	45	55,380	470
After exclusions	32% [21-41%] ****	29	34,641	319
Peer-reviewed studies	27% [17-36%] ****	42	51,521	441
Excluding combined treatment	26% [16-35%] ****	37	50,762	396
Randomized Controlled Trials	39% [18-55%] **	9	2,306	124
Mortality	30% [12-44%] **	21	13,470	210
Ventilation	40% [2-63%] *	8	13,047	64
ICU admission	24% [-5-46%]	9	13,192	94
Hospitalization	20% [4-34%] *	15	6,454	132
Recovery	20% [8-31%] **	4	827	55
Cases	22% [-10-45%]	6	25,221	105
RCT mortality	24% [-29-55%]	3	694	46
RCT hospitalization	4% [-8-14%]	4	514	57

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, with different exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	41% [8-61%] *	28% [12-40%] **	22% [7-36%] **
After exclusions	37% [10-55%] *	36% [28-43%] ****	23% [2-40%] *
Peer-reviewed studies	37% [10-55%] *	27% [10-41%] **	22% [7-36%] **
Excluding combined treatment	34% [7-54%] *	26% [9-41%] **	23% [6-36%] **
Randomized Controlled Trials	21% [-41-55%]	21% [-60-61%]	50% [26-67%] ***
Mortality	50% [33-63%] ****	26% [5-42%] *	30% [-137-79%]
Ventilation	86% [-66-99%]	18% [-13-41%]	18% [-213-78%]
ICU admission	59% [48-68%] ****	6% [-4-15%]	30% [-154-81%]
Hospitalization	66% [-4-89%]	15% [-5-31%]	13% [-26-40%]
Recovery	23% [4-37%] *	11% [-19-34%]	
Cases			22% [-10-45%]
RCT mortality	30% [-31-64%]	8% [-144-65%]	
RCT hospitalization	16% [-254-80%]	4% [-8-14%]	

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

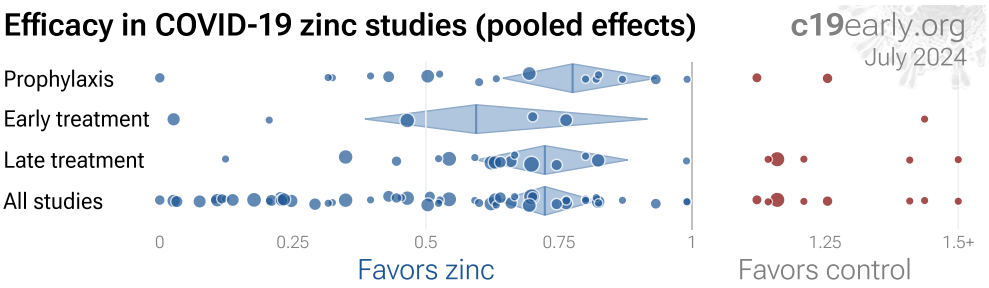


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

45 zinc COVID-19 studies (+5 unreported RCTs)

c19early.org
July 2024

	Improvement	RR [CI]		Treatment	Control	
Derwand	79%	0.21 [0.03-1.47]	death	1/141	13/377	CT[2]
Thomas (RCT)	-44%	1.44 [0.36-5.71]	hosp.	5/58	3/50	COVIDAtoZ
Aldwihi	24%	0.76 [0.51-1.08]	hosp.	53/199	184/539	
Asimi	97%	0.03 [0.00-0.44]	ventilation	0/270	9/86	CT[2]
Mayberry	53%	0.47 [0.33-0.65]	death	938 (n)	1,090 (n)	
Abdallah (DB RCT)	30%	0.70 [0.36-1.31]	death	15/231	22/239	VIZIR
Boukef (DB RCT)	unknown, >1 year late			150 (total)		
Early treatment	**41%**	**0.59 [0.39-0.92]**		74/1,837	231/2,381	**41% lower risk**

Tau^2 = 0.13, I^2 = 60.6%, p = 0.018

	Improvement	RR [CI]		Treatment	Control	
Carlucci	38%	0.62 [0.46-0.84]	death/HPC	54/411	119/521	
Krishnan	18%	0.82 [0.62-1.09]	death	31/58	61/94	
Yao	34%	0.66 [0.41-1.07]	death	73/196	21/46	
Frontera (PSM)	37%	0.63 [0.44-0.91]	death	121/1,006	424/2,467	CT[2]
Abd-Elsalam (RCT)	1%	0.99 [0.30-3.31]	death	5/96	5/95	data issues, see notes
Rosenthal	-16%	1.16 [1.05-1.28]	death	n/a	n/a	
Darban (RCT)	33%	0.67 [0.14-3.17]	progression	2/10	3/10	ICU patients CT[2]
Patel (DB RCT)	20%	0.80 [0.15-4.18]	death	2/15	3/18	
Mulhem	46%	0.54 [0.43-0.68]	death	256/1,596	260/1,623	
Gadhiya	-41%	1.41 [0.69-2.57]	death	21/54	34/229	
Al Sulaiman (ICU)	36%	0.64 [0.37-1.10]	death	23/82	32/82	ICU patients
Elavarasi	65%	0.35 [0.24-0.56]	death	486 (n)	1,201 (n)	
Assiri (ICU)	-81%	1.81 [0.41-6.97]	death	10/60	4/58	ICU patients
Kaplan (RCT)	-14%	1.14 [0.08-16.6]	ventilation	1/14	1/16	Reszinate CT[2]
Zangeneh (ICU)	-21%	1.21 [0.51-2.90]	death	n/a	n/a	ICU patients
Alahmari	30%	0.70 [0.63-0.78]	hosp. time	130 (n)	847 (n)	
Doocy	41%	0.59 [0.19-1.85]	death	3/28	21/116	
Ibrahim Alhajjaji	88%	0.12 [0.01-2.24]	death	0/44	4/57	
Kyagambiddwa	25%	0.75 [0.44-1.25]	death	20/89	22/73	
Seely (DB RCT)	48%	0.52 [0.10-2.71]	progression	2/42	4/44	CT[2]
Milan	56%	0.44 [0.18-1.09]	death	9/129	8/51	
Sharmin (DB RCT)	unknown, >2 years late			50 (est. total)		
Correa (DB RCT)	unknown, >2 years late			105 (total)		
Güerri-Fern.. (RCT)	unknown, >2 years late			75 (total)		MARZINC
Late treatment	**28%**	**0.72 [0.60-0.88]**		633/4,546	1,026/7,648	**28% lower risk**

Tau^2 = 0.11, I^2 = 83.8%, p = 0.0012

	Improvement	RR [CI]		Treatment	Control	
Louca	1%	0.99 [0.93-1.06]	cases	population-based cohort		
Mahto	37%	0.63 [0.22-1.49]	IgG+	10/38	83/651	
Bejan	18%	0.82 [0.22-3.13]	ventilation	155 (n)	9,074 (n)	
Holt	7%	0.93 [0.59-1.44]	cases	21/750	425/14,477	COVIDENCE UK
Abdulateef	13%	0.87 [0.38-1.97]	hosp.	7/111	23/317	
Seet (CLUS. RCT)	50%	0.50 [0.34-0.75]	symp. case	33/634	64/619	OT[1]
Israel	100%	0.00 [0.00-0.89]	hosp.	case control		CT[2]
Bagheri	60%	0.40 [0.04-3.53]	severe case	33 (n)	477 (n)	
Gordon	68%	0.32 [0.01-7.87]	death	0/104	1/96	
Kumar	20%	0.80 [0.21-2.99]	death	6/75	3/30	
Nimer	-25%	1.25 [0.87-1.77]	hosp.	41/326	178/1,822	
Shehab	47%	0.53 [0.19-1.47]	severe case	4/65	22/188	
Citu	18%	0.82 [0.12-5.68]	severe case	2/74	2/61	CT[2]
Stambouli (DB RCT)	68%	0.32 [0.03-2.95]	symp. case	1/59	3/56	
Adrean	-12%	1.12 [0.74-1.70]	cases	30/2,111	80/6,315	
Sharif	40%	0.60 [0.46-0.77]	severe case	n/a	n/a	
Asoudeh	57%	0.43 [0.21-0.90]	severe case	250 (all patients)		
Seifi	31%	0.69 [0.52-0.94]	hosp.	n/a	n/a	per unit change
Ajili (DB RCT)	unknown, >3 years late			660 (est. total)		COVID-Milit
Prophylaxis	**22%**	**0.78 [0.64-0.93]**		155/4,535	884/34,183	**22% lower risk**

Tau^2 = 0.06, I^2 = 57.7%, p = 0.0071

All studies	**28%**	**0.72 [0.64-0.82]**		862/10,918	2,141/44,212	**28% lower risk**

0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+

Favors zinc — Favors control

[1] OT: comparison with other treatment
[2] CT: study uses combined treatment

Tau^2 = 0.08, I^2 = 77.9%, p < 0.0001

Effect extraction pre-specified
(most serious outcome, see appendix)

Figure 4. **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.

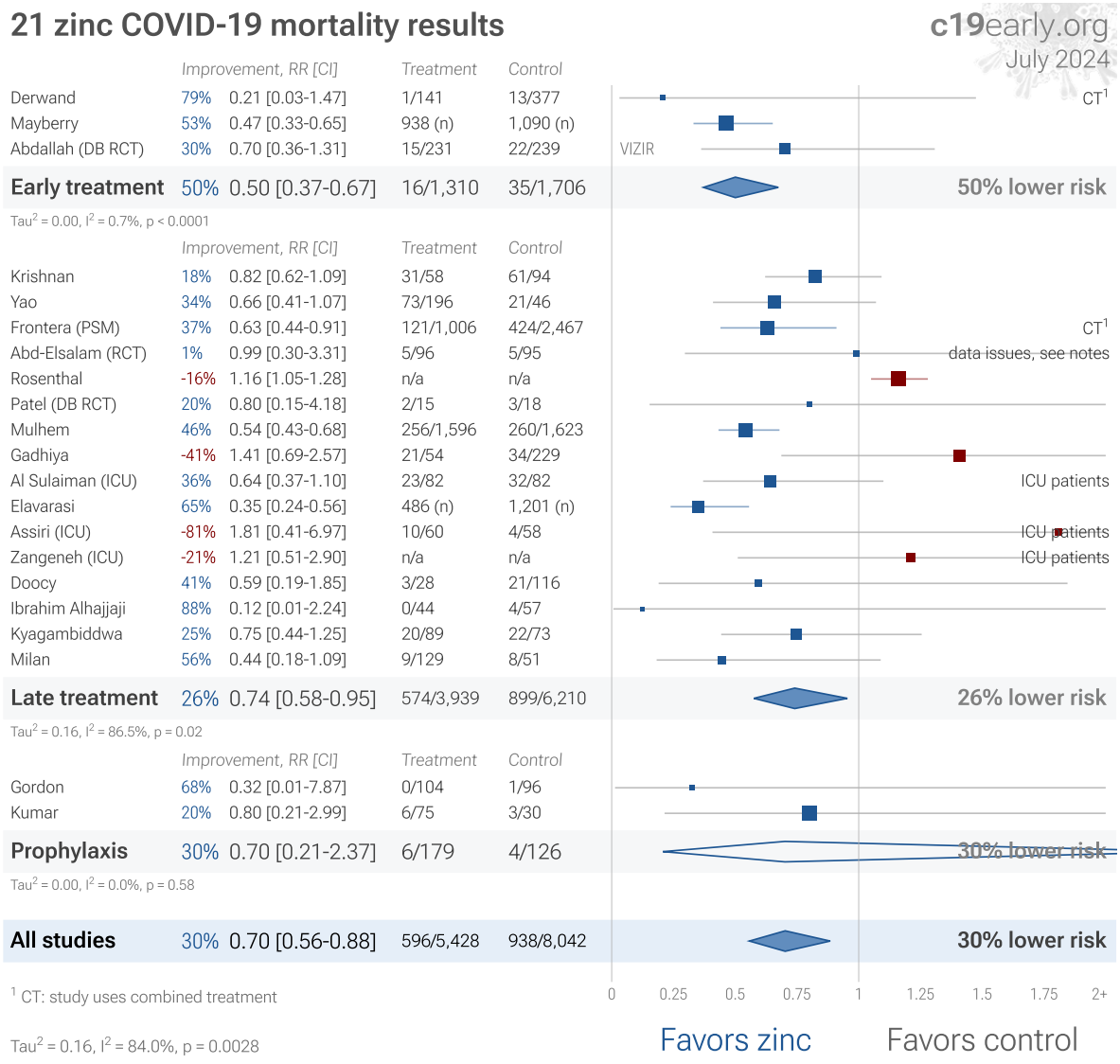


Figure 5. **Random effects meta-analysis for mortality results.**

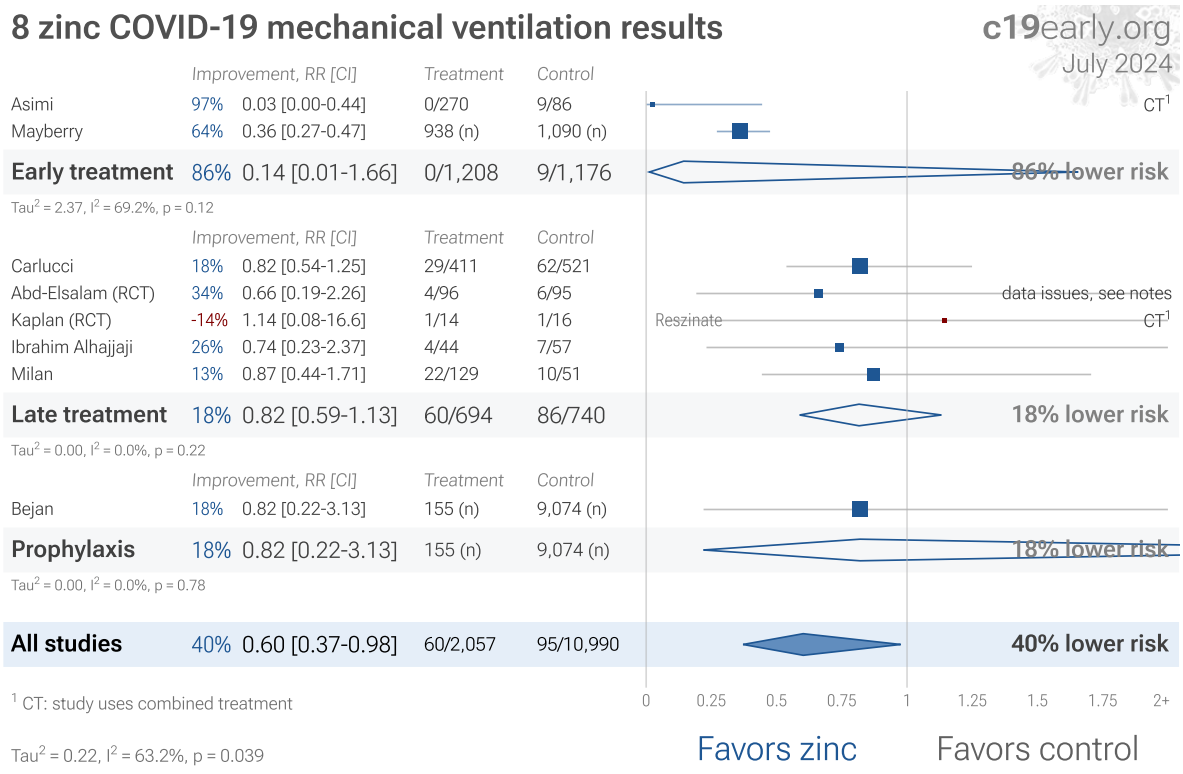


Figure 6. Random effects meta-analysis for ventilation.

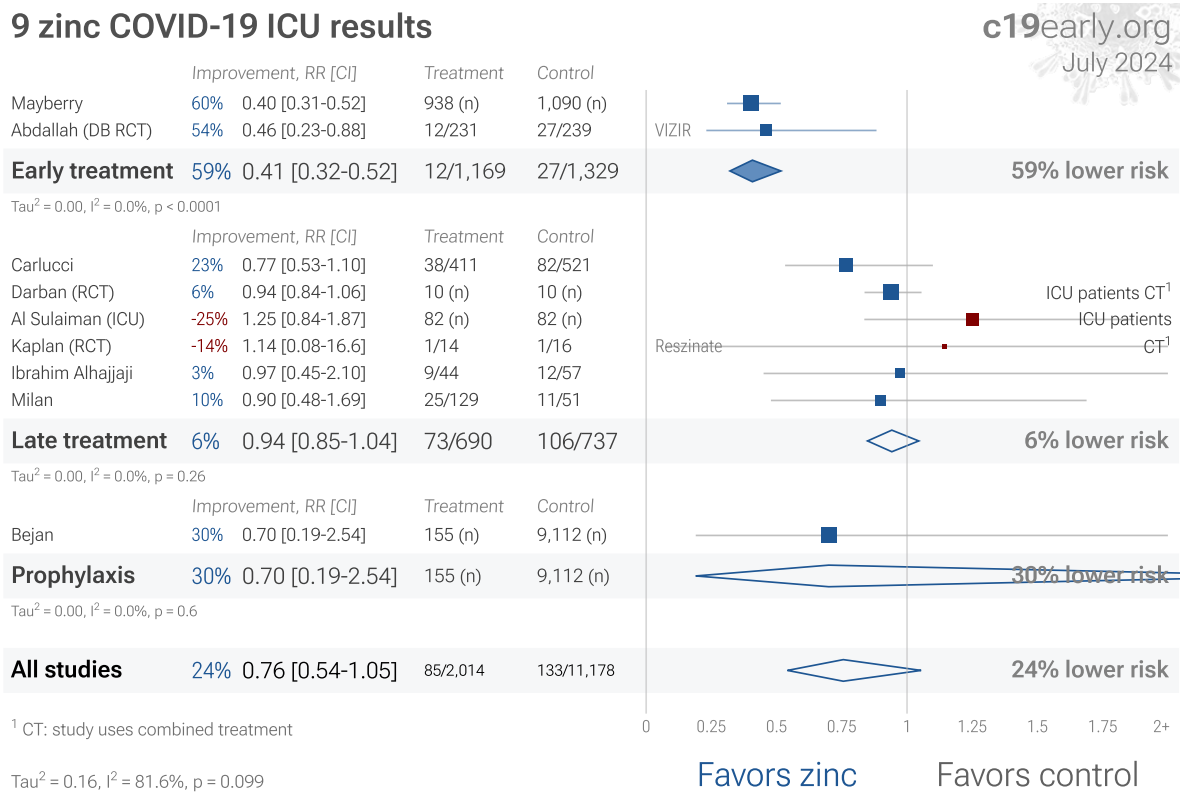


Figure 7. Random effects meta-analysis for ICU admission.

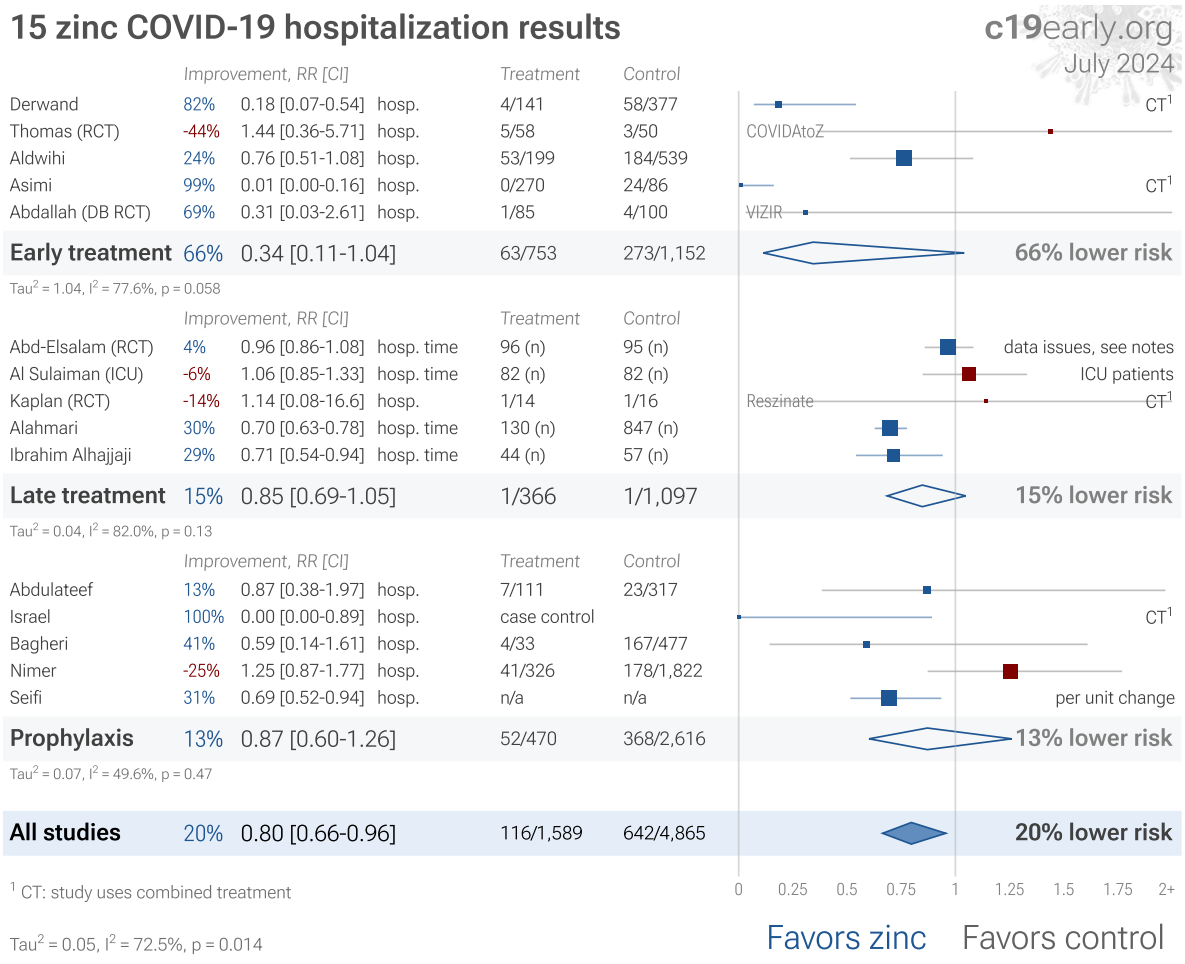


Figure 8. Random effects meta-analysis for hospitalization.

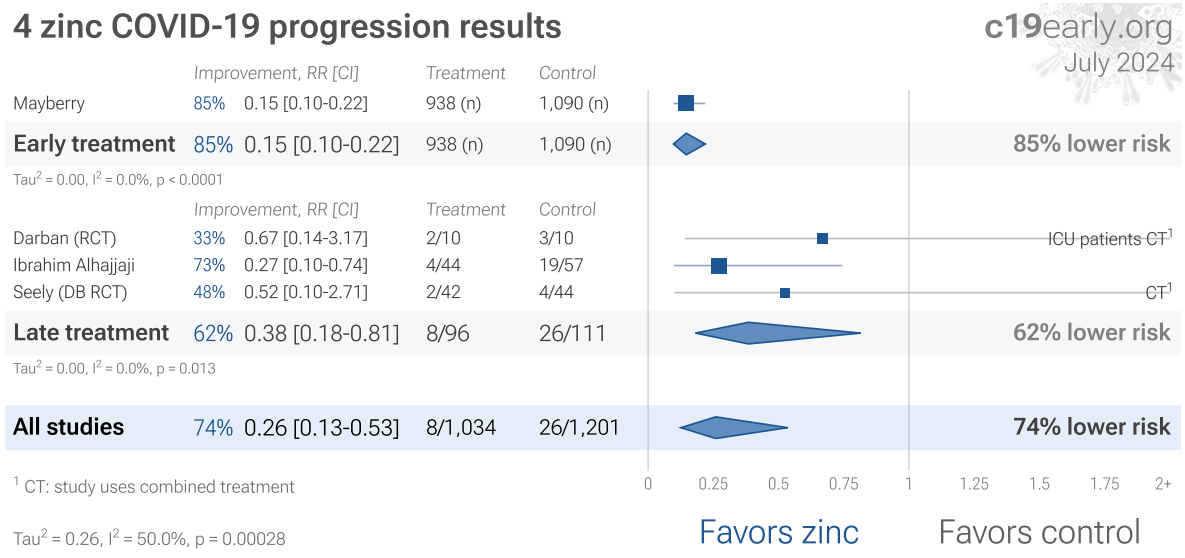


Figure 9. Random effects meta-analysis for progression.

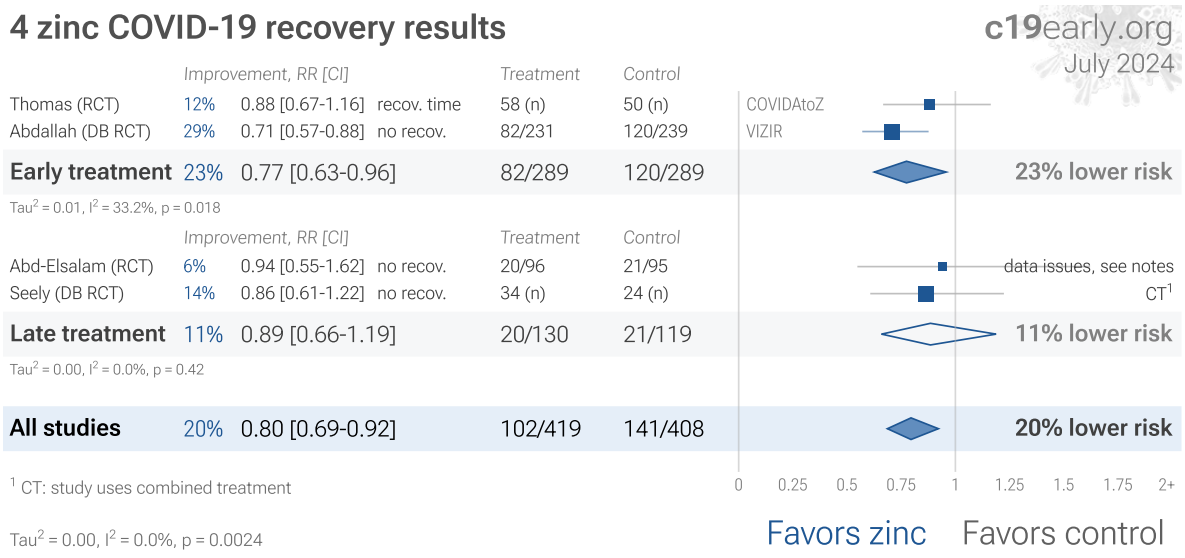


Figure 10. Random effects meta-analysis for recovery.

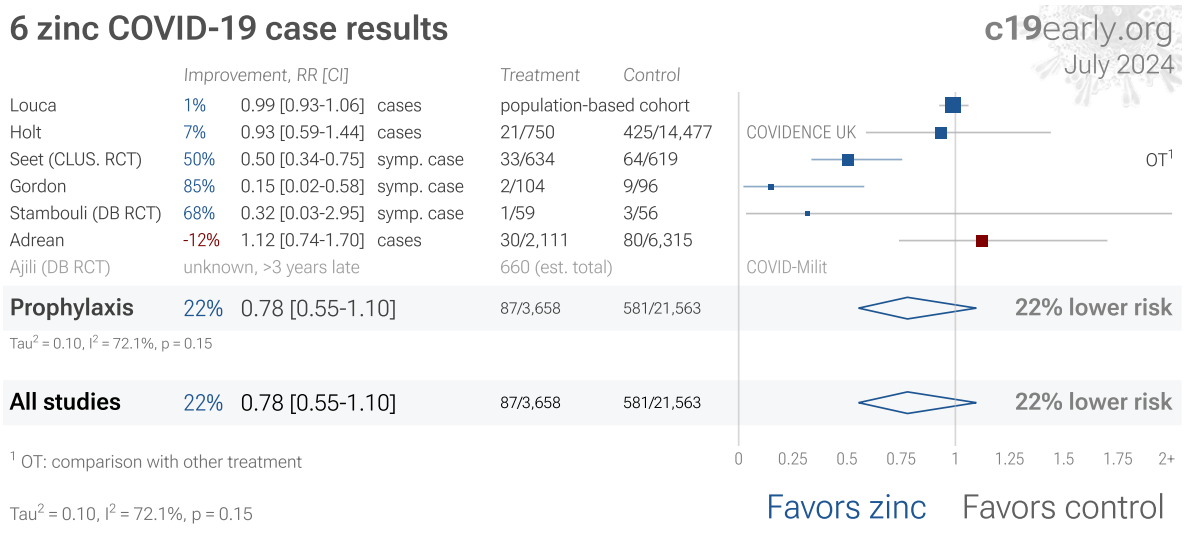


Figure 11. Random effects meta-analysis for cases.

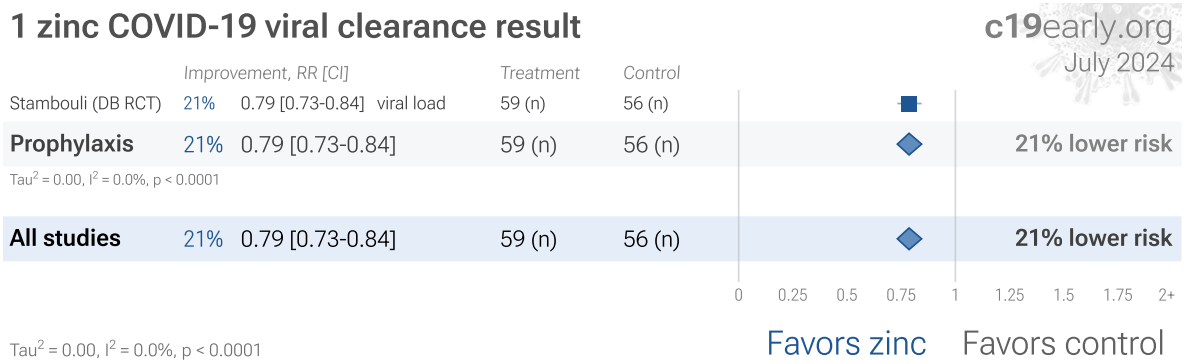


Figure 12. Random effects meta-analysis for viral clearance.

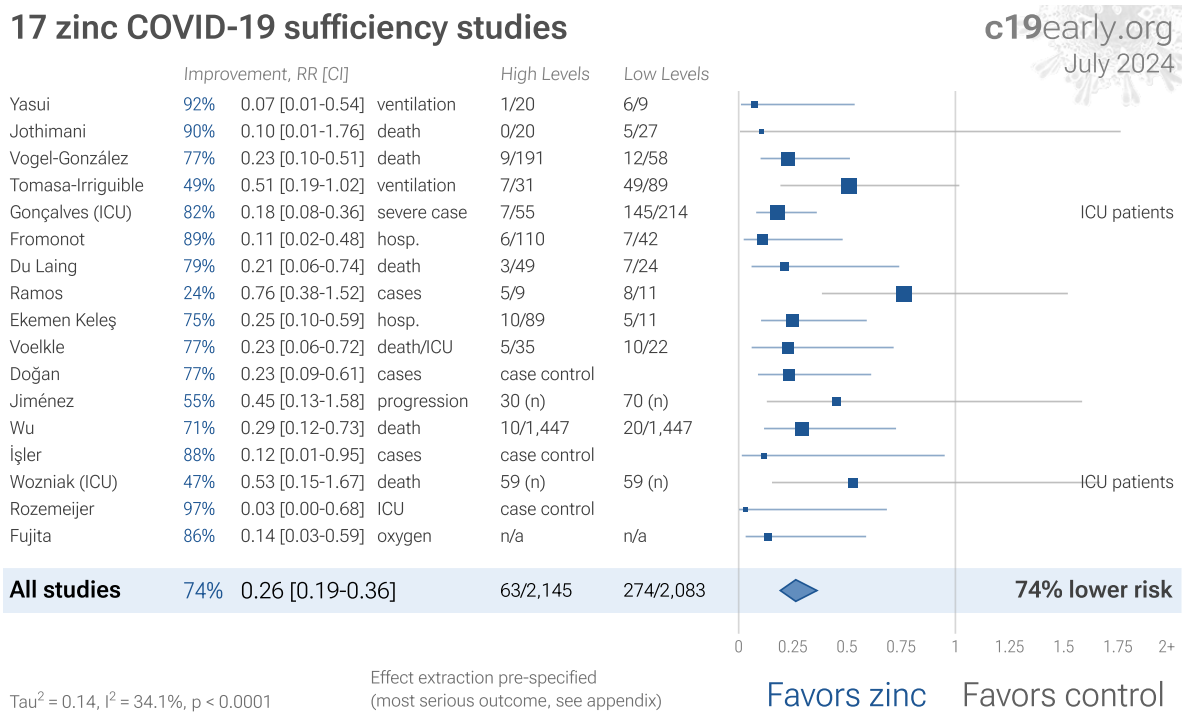


Figure 13. **Random effects meta-analysis for sufficiency studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

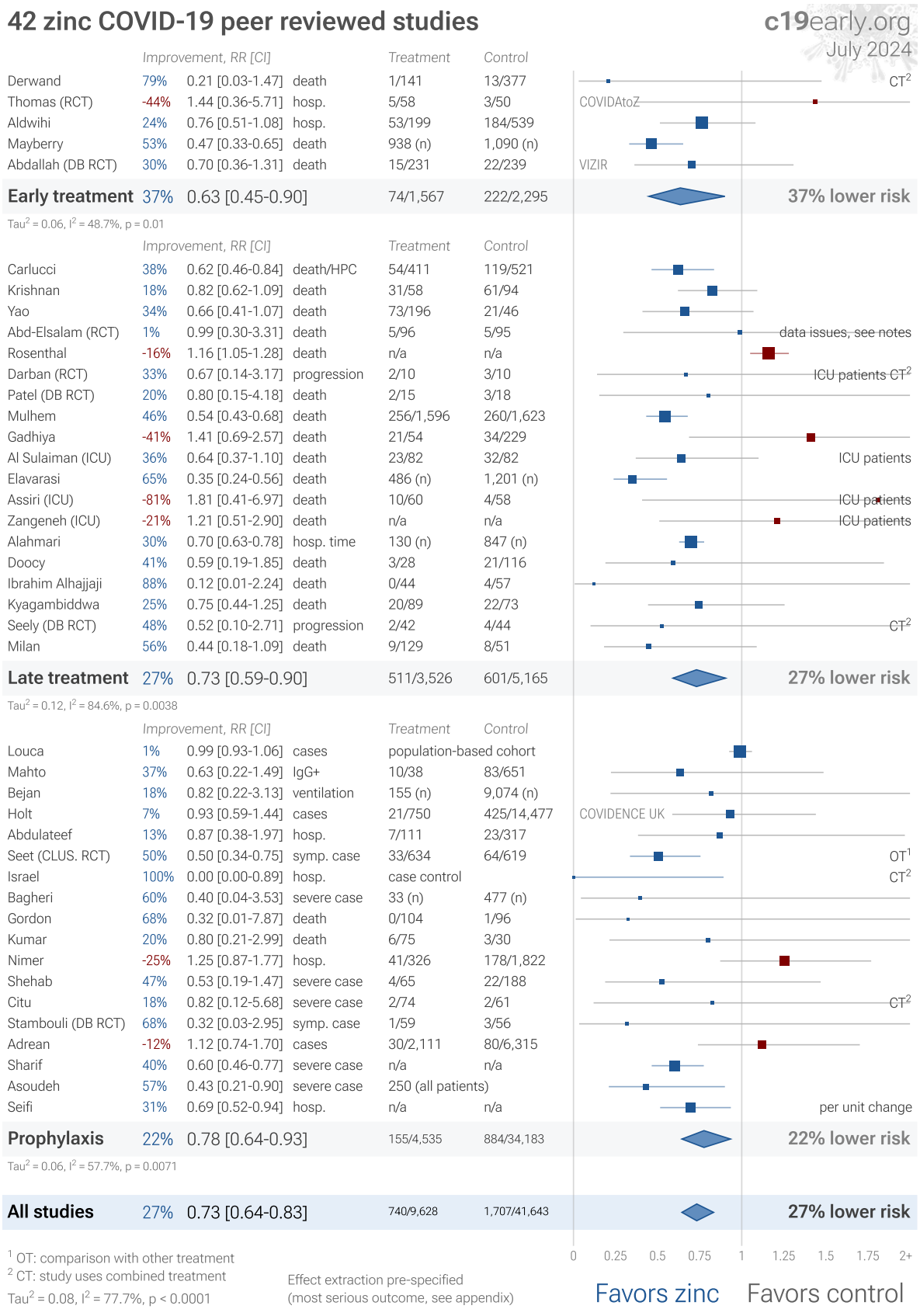


Figure 14. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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.

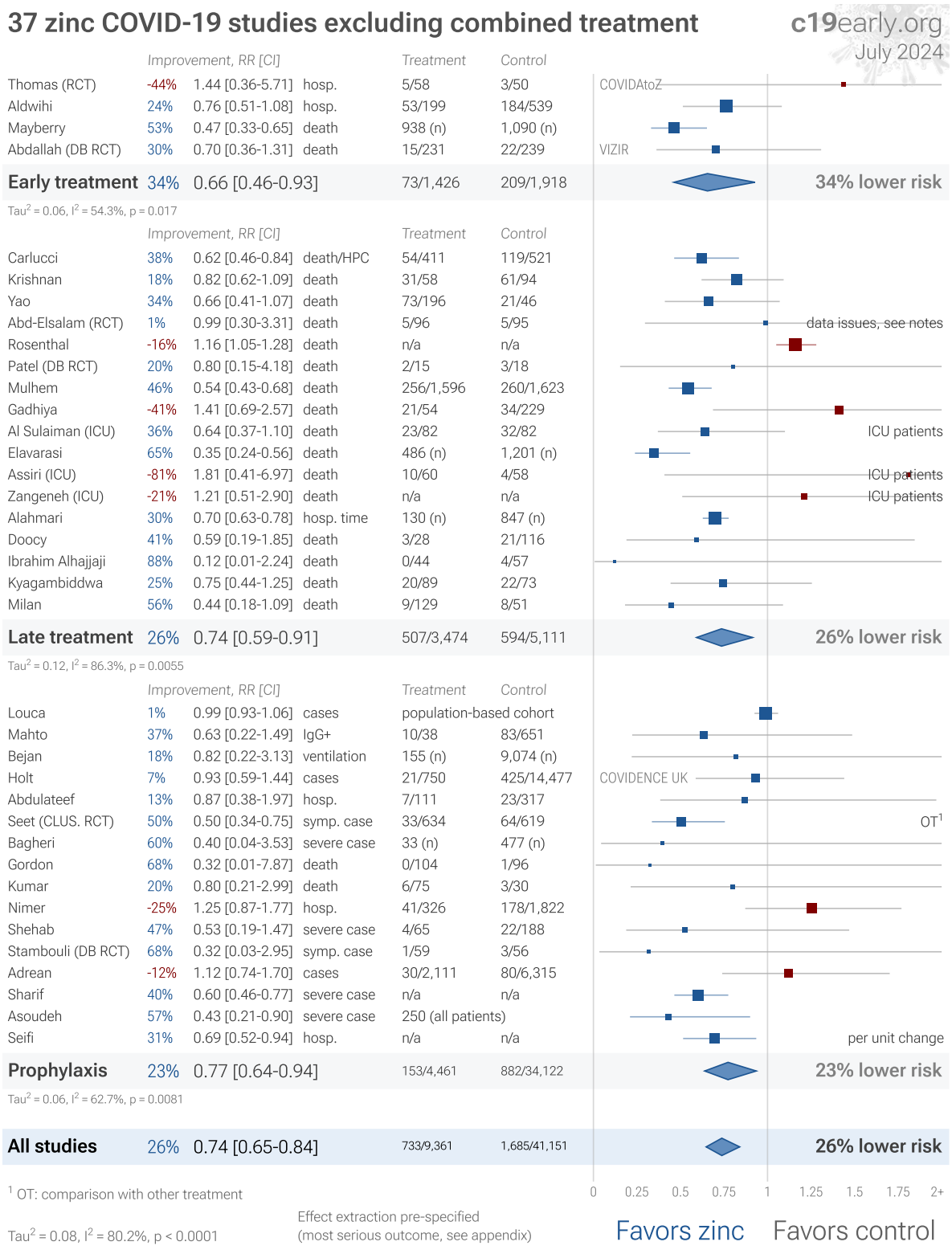


Figure 15. **Random effects meta-analysis for all studies excluding combined treatment studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Figure 16 shows a comparison of results for RCTs and non-RCT studies. Random effects meta analysis of RCTs shows 39% improvement, compared to 27% for other studies. Figure 17, 18, and 19 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.

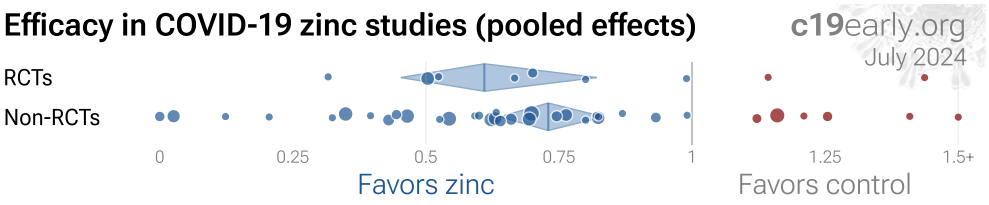


Figure 16. **Results for RCTs and non-RCT studies.**

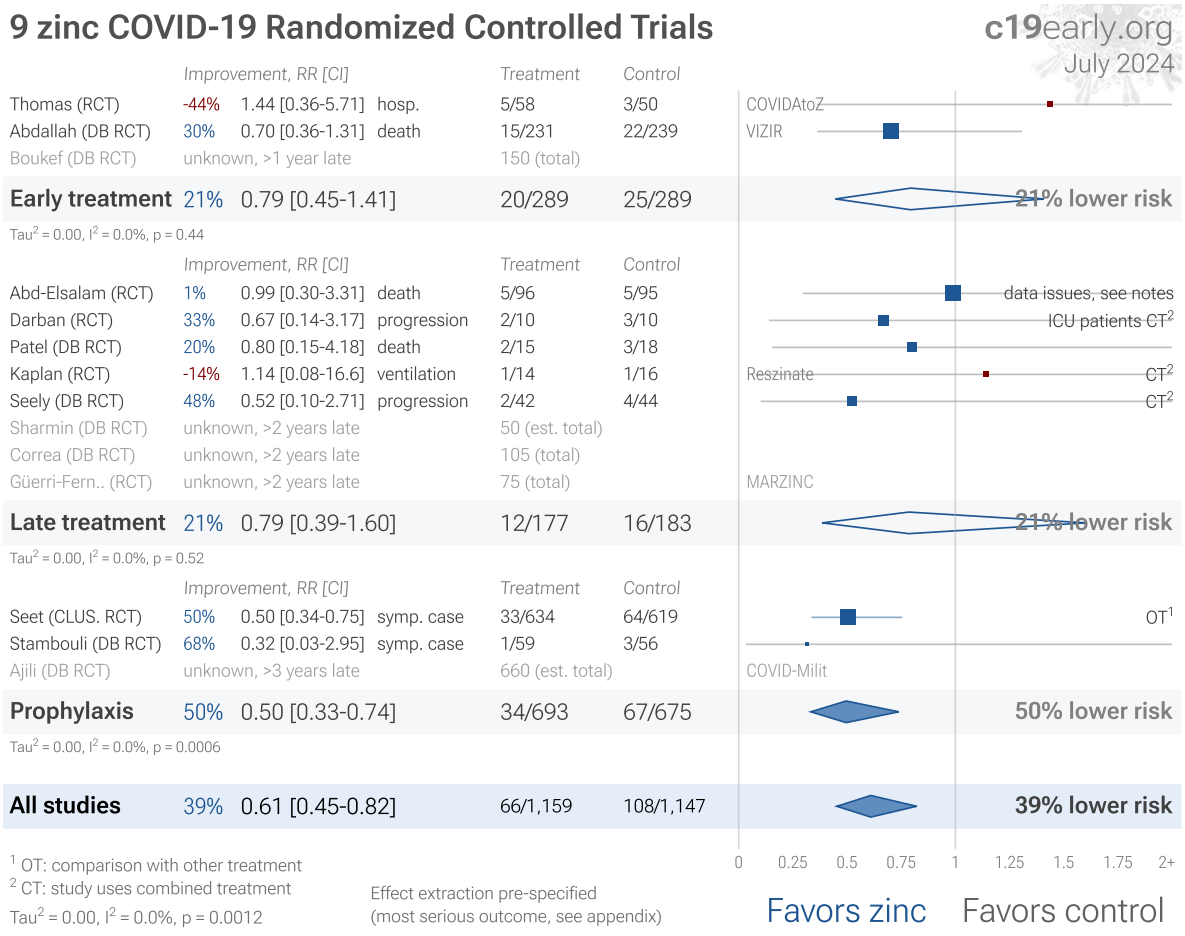


Figure 17. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

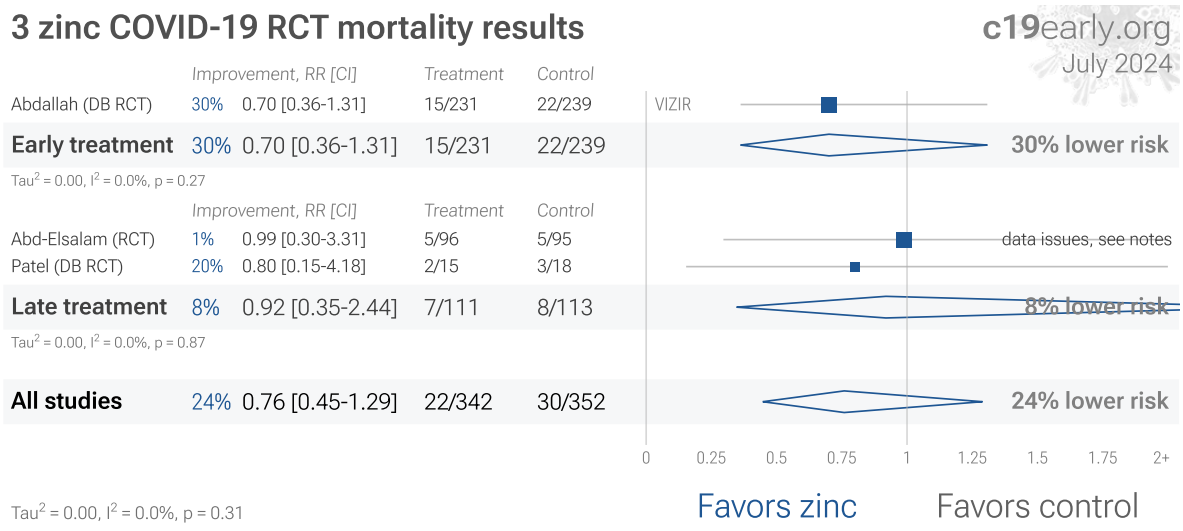


Figure 18. Random effects meta-analysis for RCT mortality results.

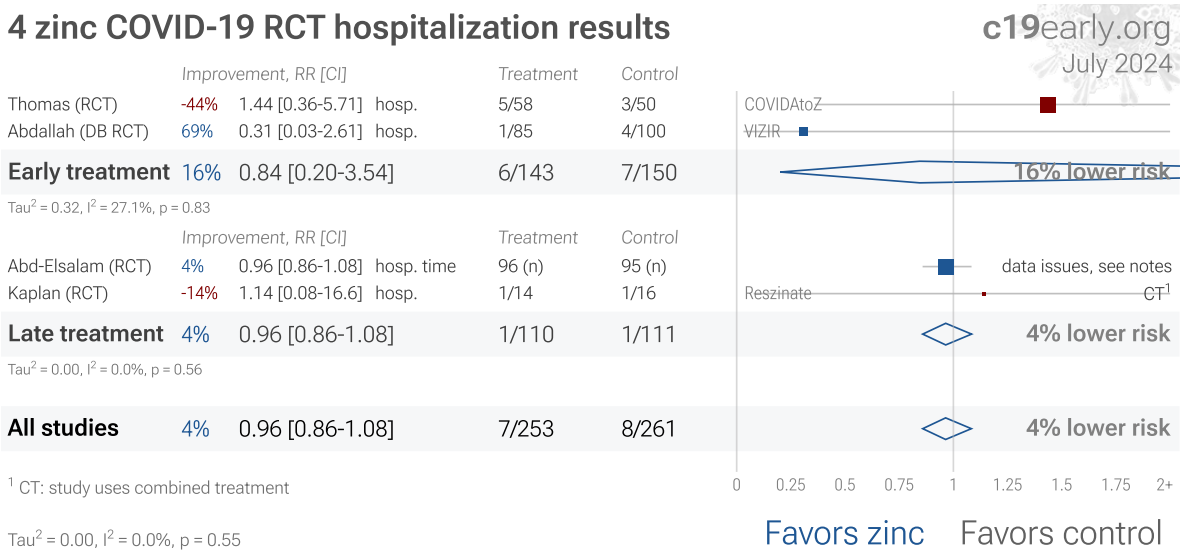


Figure 19. Random effects meta-analysis for RCT hospitalization results.

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[40], and analysis of double-blind RCTs has identified extreme levels of bias[41]. 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 78 treatments we have analyzed, 64% 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.

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT 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.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *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. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet 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 [46,47].

Using all studies identifies efficacy 7+ months faster (8+ months for low-cost treatments). Currently, 46 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, 30 have been confirmed in RCTs, with a mean delay of 7.0 months. When considering only low cost treatments, 25 have been confirmed with a delay of 8.4 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

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.

Unreported RCTs

5 zinc RCTs have not reported results [48-52]. The trials report a total of 1,040 patients, with 3 trials having actual enrollment of 330, and the remainder estimated. The results are delayed from 1 year to over 3 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 20 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Abd-Elsalam, multiple potential data reliability issues.

Abdulateef, unadjusted results with no group details.

Asimi, excessive unadjusted differences between groups.

Assiri, unadjusted results with no group details.

Doocy, unadjusted results with no group details.

Gadhiya, substantial unadjusted confounding by indication likely.

Holt, significant unadjusted confounding possible.

Ibrahim Alhajjaji, excessive unadjusted differences between groups.

Israel, treatment or control group size extremely small.

Krishnan, unadjusted results with no group details.

Kumar, unadjusted results with no group details.

Kyagambiddwa, 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.

Rosenthal, confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

Seifi, the hospitalization result is only provided with respect to continuous values and the confidence interval is not reported for the case result.

Shehab, unadjusted results with no group details.

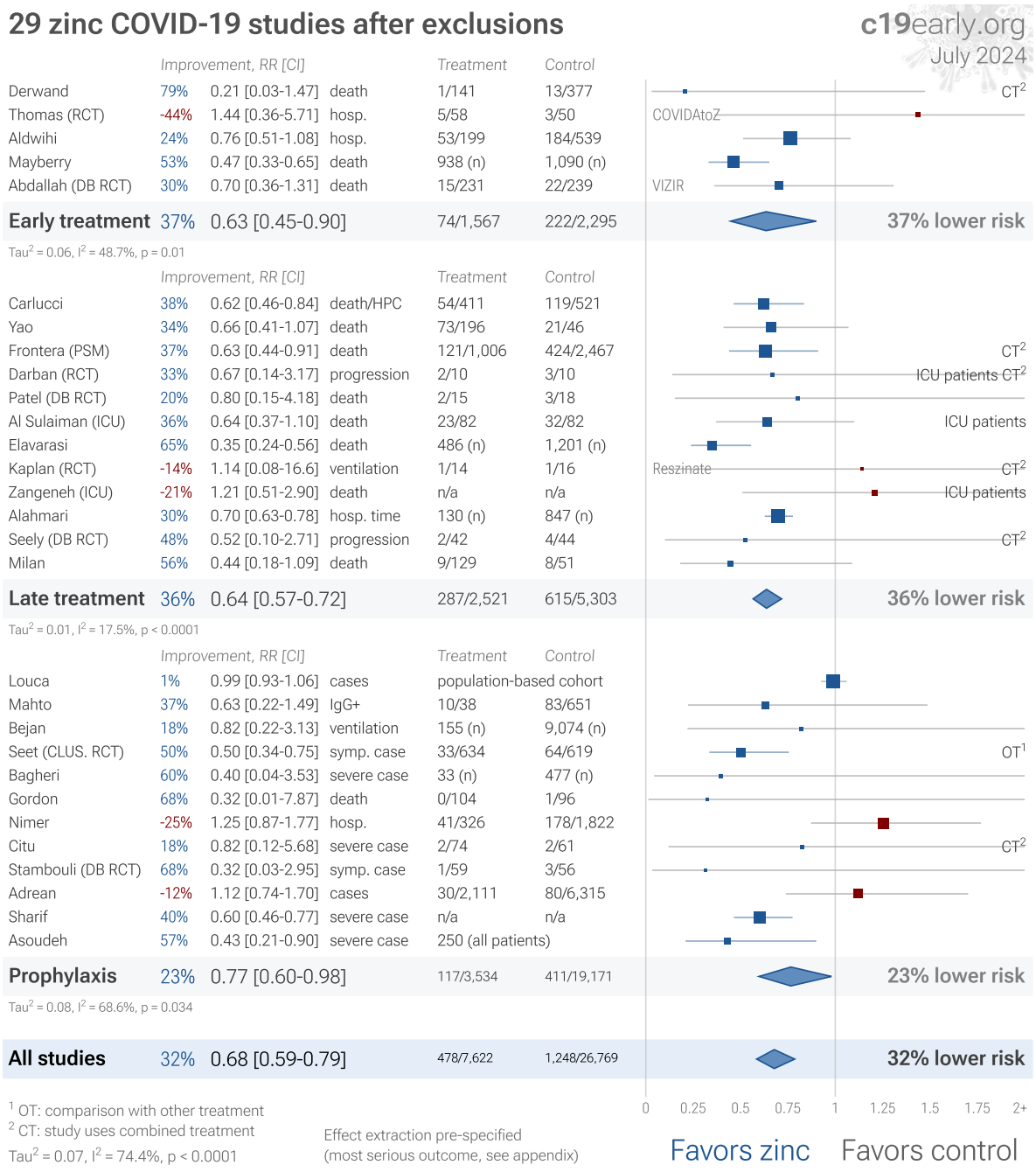


Figure 20. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome 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[69,70]. Baloxavir 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 (B) et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases [71]
<24 hours	-33 hours symptoms [72]
24-48 hours	-13 hours symptoms [72]
Inpatients	-2.5 hours to improvement [73]

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

Figure 21 shows a mixed-effects meta-regression of efficacy as a function of treatment delay in COVID-19 zinc studies, with group estimates for different stages when a specific value is not provided. For comparison, Figure 22 shows a meta-regression for all studies providing specific values across 78 treatments. Efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

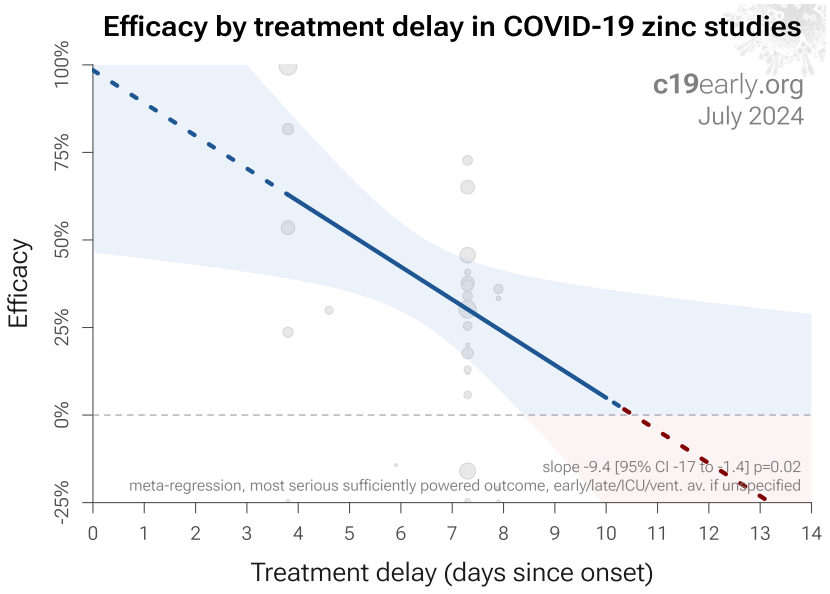


Figure 22. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 zinc studies.

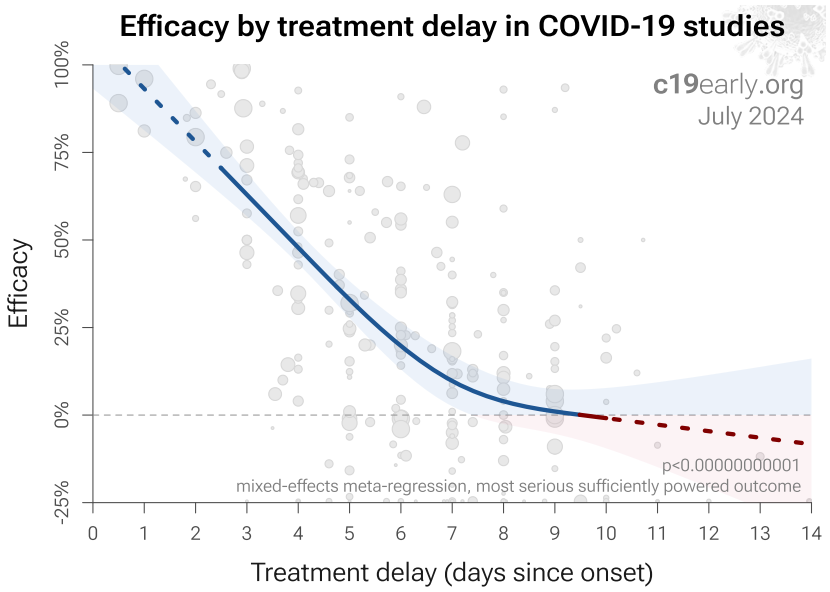


***Figure 22.* Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 78 treatments.

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.*

Variants. Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants[75], for example the Gamma variant shows significantly different characteristics[76-79]. 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[80,81].

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen.

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[82-92], therefore efficacy may depend strongly on combined treatments.

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 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[5,6].

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 August 2021. This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however note that pooled effects are no longer required for zinc as of August 2021. Efficacy is now known based on specific outcomes. Efficacy based on specific outcomes was delayed by 12.7 months, compared to using pooled 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.

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.

Using more information. Another way to view pooled analysis is that we are using more of the available information. Logically we should, and do, use additional information. For example dose-response and treatment delay-response relationships provide significant additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

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 collection of evidence.

Improvement across outcomes. 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.

Validating pooled outcome analysis for COVID-19. Analysis of the the association between different outcomes across studies from all 78 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 23 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 24 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 25 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 $p = 0.0000011$ to $p = 0.0000000036$.

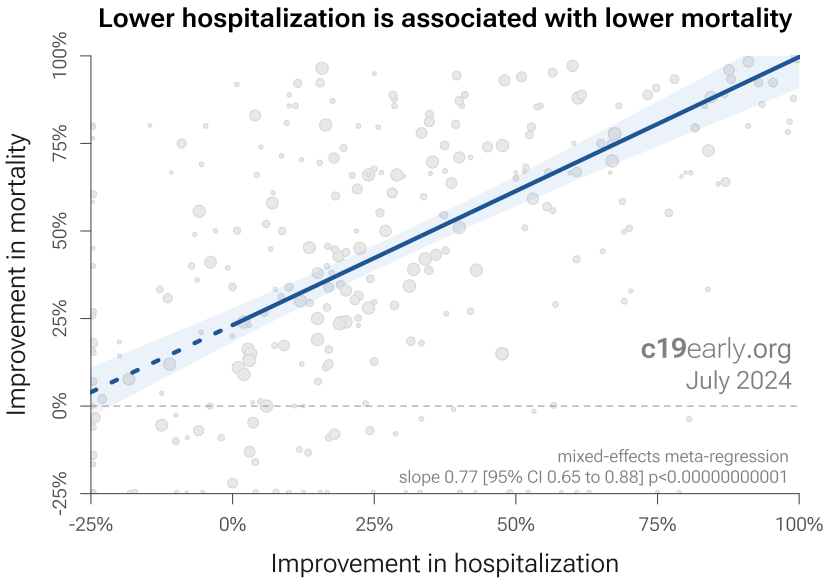


Figure 23. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

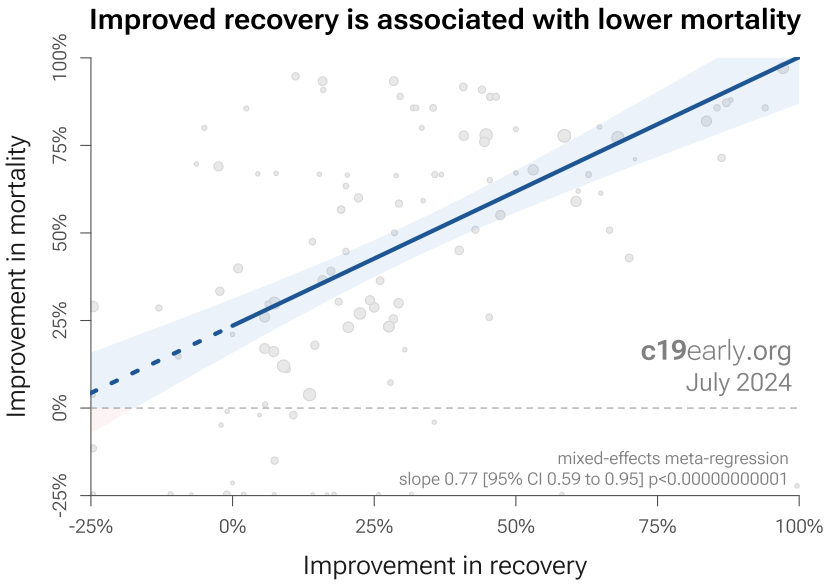


Figure 24. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

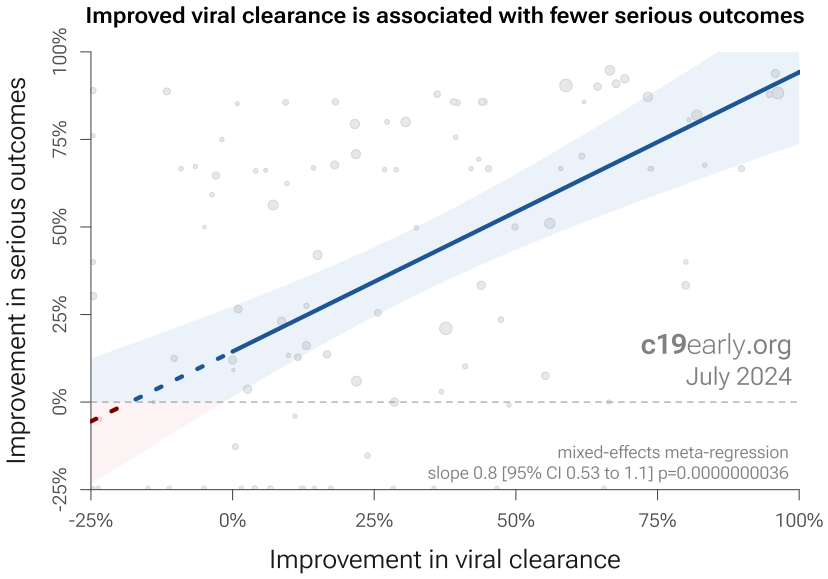


Figure 23. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (6 months for RCTs). Currently, 46 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 91% of these have been confirmed with one or more specific outcomes, with a mean delay of 5.0 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.4 months. Figure 26 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

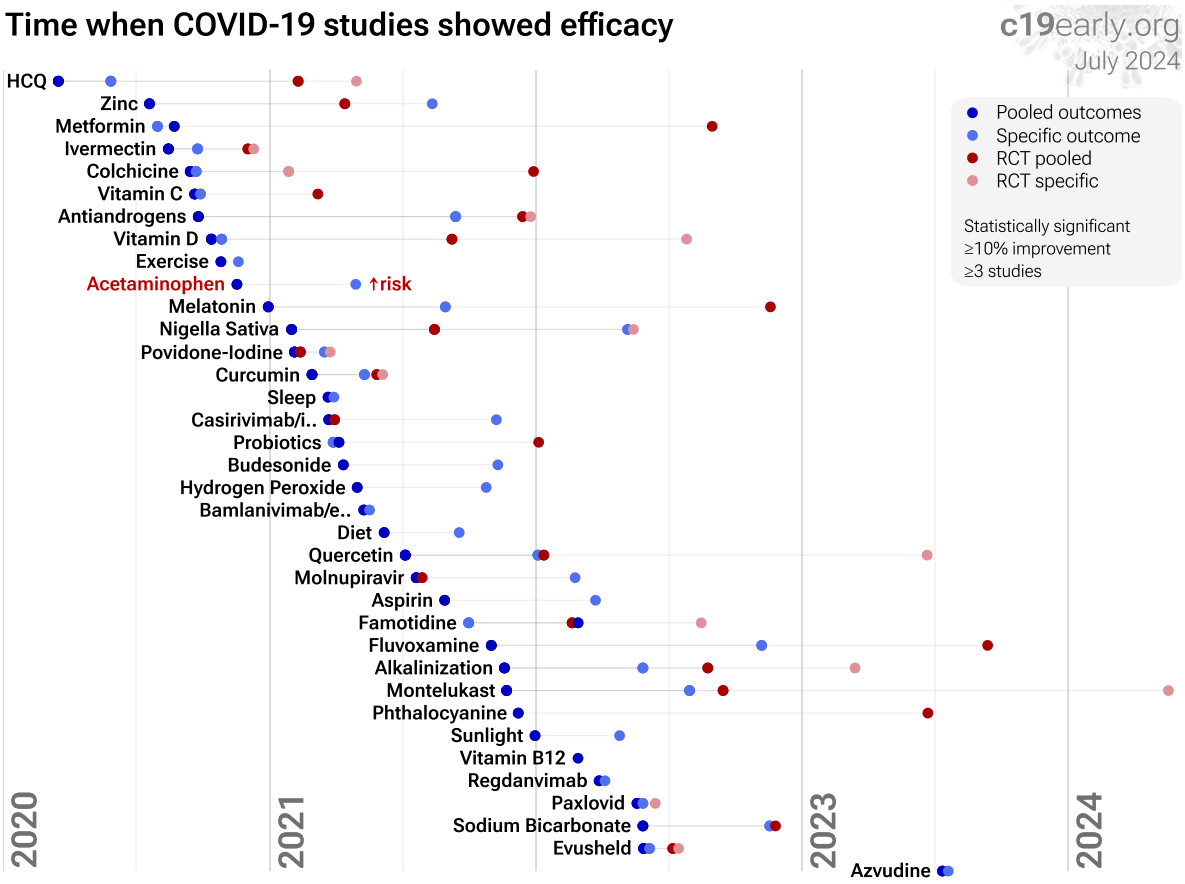


Figure 26. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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.

Discussion

Results for other viruses. Studies have also shown efficacy with zinc for acute respiratory tract infections[28] and the common cold[29].

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[96-99].

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 27 shows a scatter plot of results for prospective and retrospective treatment studies. Prospective studies show 31% [12-46%] improvement in meta analysis, compared to 27% [17-37%] for retrospective studies, showing no significant difference, with results to date favoring a possible negative publication bias.

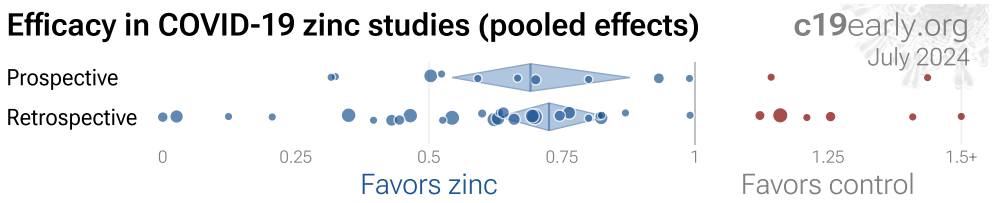


Figure 27. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Late treatment bias. Studies for zinc were primarily late treatment studies, in contrast with typical patented treatments that were tested with early treatment as recommended.

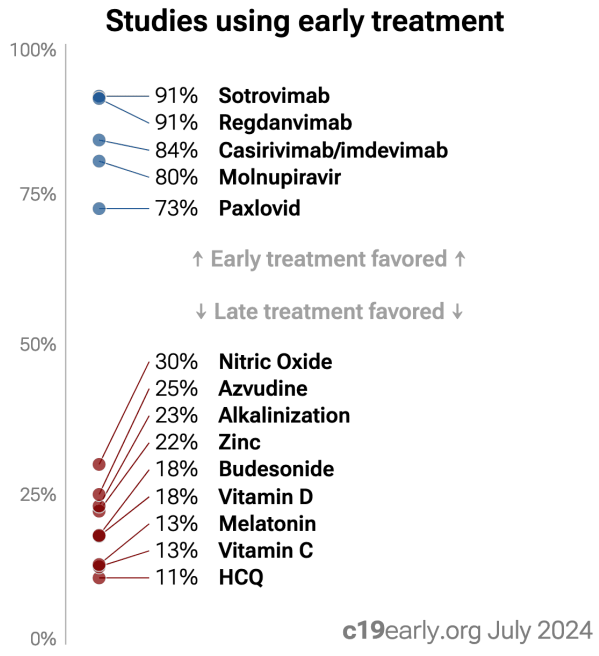


Figure 28. **Patented treatments received mostly early treatment studies, while low cost treatments were typically tested for late treatment.**

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 29 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 $p < 0.05$[100-107]. 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.

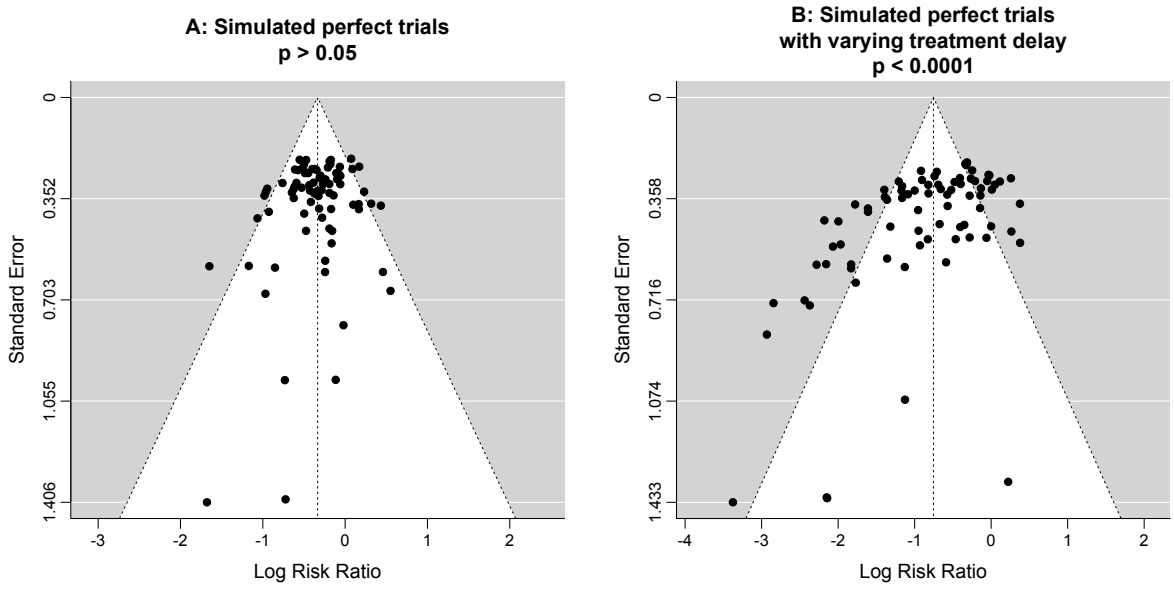


Figure 29. **Example funnel plot analysis for simulated perfect trials.**

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. Zinc for COVID-19 lacks this because it is an inexpensive and widely available supplement. In contrast, most COVID-19 zinc 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 zinc trials represent the optimal conditions for efficacy.

Physician case series results. Table 4 shows the reported results of physicians that use early treatments for COVID-19, compared to the results for a non-treating physician. The treatments used vary. Physicians typically use a combination of treatments, with almost all reporting use of ivermectin and/or HCQ, and most using additional treatments, including zinc. These results are subject to selection and ascertainment bias and more accurate analysis requires details of the patient populations and followup, however results are consistently better across many teams, and consistent with the extensive controlled trial evidence that shows a significant reduction in risk with many early treatments, and improved results with the use of multiple treatments in combination.

LATE TREATMENT						
Physician / Team	*Location*	*Patients*	*Hospitalization*		*Mortality*	
Dr. David Uip (*)	Brazil	2,200	38.6% (850)	Ref.	2.5% (54)	Ref.
EARLY TREATMENT - 40 physicians/teams						
Physician / Team	*Location*	*Patients*	*Hospitalization*	*Improvement*	*Mortality*	*Improvement*
Dr. Roberto Alfonso Accinelli 0/360 deaths for treatment within 3 days	Peru	1,265			0.6% (7)	77.5%
Dr. Mohammed Tarek Alam patients up to 84 years old	Bangladesh	100			0.0% (0)	100.0%
Dr. Oluwagbenga Alonge	Nigeria	310			0.0% (0)	100.0%
Dr. Raja Bhattacharya up to 88yo, 81% comorbidities	India	148			1.4% (2)	44.9%
Dr. Flavio Cadegiani	Brazil	3,450	0.1% (4)	99.7%	0.0% (0)	100.0%
Dr. Alessandro Capucci	Italy	350	4.6% (16)	88.2%		
Dr. Shankara Chetty	South Africa	8,000			0.0% (0)	100.0%
Dr. Deborah Chisholm	USA	100			0.0% (0)	100.0%
Dr. Ryan Cole	USA	400	0.0% (0)	100.0%	0.0% (0)	100.0%
Dr. Marco Cosentino vs. 3-3.8% mortality during period; earlier treatment better	Italy	392	6.4% (25)	83.5%	0.3% (1)	89.6%
Dr. Jeff Davis	USA	6,000			0.0% (0)	100.0%
Dr. Dhanajay	India	500			0.0% (0)	100.0%
Dr. Bryan Tyson & Dr. George Fareed	USA	20,000	0.0% (6)	99.9%	0.0% (4)	99.2%
Dr. Raphael Furtado	Brazil	170	0.6% (1)	98.5%	0.0% (0)	100.0%
Rabbi Yehoshua Gerzi	Israel	860	0.1% (1)	99.7%	0.0% (0)	100.0%
Dr. Heather Gessling	USA	1,500			0.1% (1)	97.3%
Dr. Ellen Guimarães	Brazil	500	1.6% (8)	95.9%	0.4% (2)	83.7%
Dr. Syed Haider	USA	4,000	0.1% (5)	99.7%	0.0% (0)	100.0%
Dr. Mark Hancock	USA	24			0.0% (0)	100.0%
Dr. Sabine Hazan	USA	1,000			0.0% (0)	100.0%
Dr. Mollie James	USA	3,500	1.1% (40)	97.0%	0.0% (1)	98.8%
Dr. Roberta Lacerda	Brazil	550	1.5% (8)	96.2%	0.4% (2)	85.2%
Dr. Katarina Lindley	USA	100	5.0% (5)	87.1%	0.0% (0)	100.0%
Dr. Ben Marble	USA	150,000			0.0% (4)	99.9%
Dr. Edimilson Migowski	Brazil	2,000	0.3% (7)	99.1%	0.1% (2)	95.9%
Dr. Abdulrahman Mohana	Saudi Arabia	2,733			0.0% (0)	100.0%
Dr. Carlos Nigro	Brazil	5,000	0.9% (45)	97.7%	0.5% (23)	81.3%
Dr. Benoit Ochs	Luxembourg	800			0.0% (0)	100.0%
Dr. Ortore	Italy	240	1.2% (3)	96.8%	0.0% (0)	100.0%
Dr. Valerio Pascua one death for a patient presenting on the 5th day in need of supplemental oxygen	Honduras	415	6.3% (26)	83.8%	0.2% (1)	90.2%
Dr. Sebastian Pop	Romania	300			0.0% (0)	100.0%

Dr. Brian Proctor	USA	869	2.3% (20)	94.0%	0.2% (2)	90.6%
Dr. Anastacio Queiroz	Brazil	700			0.0% (0)	100.0%
Dr. Didier Raoult	France	8,315	2.6% (214)	93.3%	0.1% (5)	97.6%
Dr. Karin Ried up to 99yo, 73% comorbidities, av. age 63	Turkey	237			0.4% (1)	82.8%
Dr. Roman Rozencwaig patients up to 86 years old	Canada	80			0.0% (0)	100.0%
Dr. Vipul Shah	India	8,000			0.1% (5)	97.5%
Dr. Silvestre Sobrinho	Brazil	116	8.6% (10)	77.7%	0.0% (0)	100.0%
Dr. Unknown	Brazil	957	1.7% (16)	95.7%	0.2% (2)	91.5%
Dr. Vladimir Zelenko	USA	2,200	0.5% (12)	98.6%	0.1% (2)	96.3%
Mean improvement with early treatment protocols		238,381	Hospitalization	94.4%	Mortality	94.9%

Table 4. **Physician results with early treatment protocols compared to no early treatment.** (*) Dr. Uip reportedly prescribed early treatment for himself, but not for patients [108].

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 [82-92]. 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 45 studies compare against other treatments, which may reduce the effect seen. 8 of 45 studies combine treatments. The results of zinc alone may differ. 3 of 9 RCTs use combined treatment. 6 other meta analyses show significant improvements with zinc for mortality[7-11], severity[12], and cases[12].

Reviews. Many reviews cover zinc for COVID-19, presenting additional background on mechanisms and related results, including[109-118].

NIH

NIH provides an analysis of zinc for COVID-19[119], concluding that there is insufficient evidence to recommend for or against use. However, they appear not to have looked at the majority of the evidence. For example, considering RCTs providing clinical results for COVID-19 and zinc, they reference only[53,120,121], and appear not to know about 6 other RCTs[122-127] as shown in Figure 30. Notably, the NIH selection is not based on quality, for example including *Abd-Elsalam et al.*, with data reliability issues, and not including *Seet et al.*, a much larger and higher quality trial.

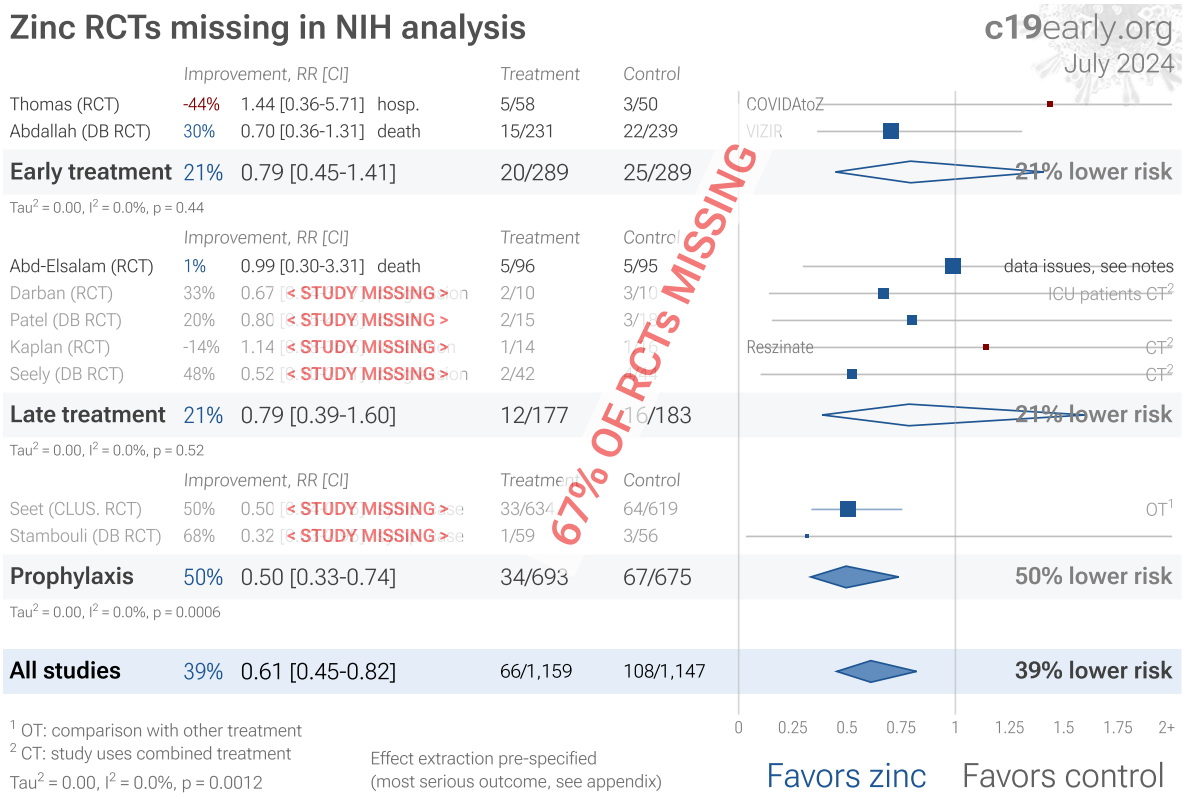


Figure 30. **Analysis by NIH is missing 6 RCTs.**

Perspective

Results compared with other treatments. SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors[22-26], providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk[27], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 31 shows an overview of the results for zinc in the context of multiple COVID-19 treatments, and Figure 32 shows a plot of efficacy vs. cost for COVID-19 treatments.

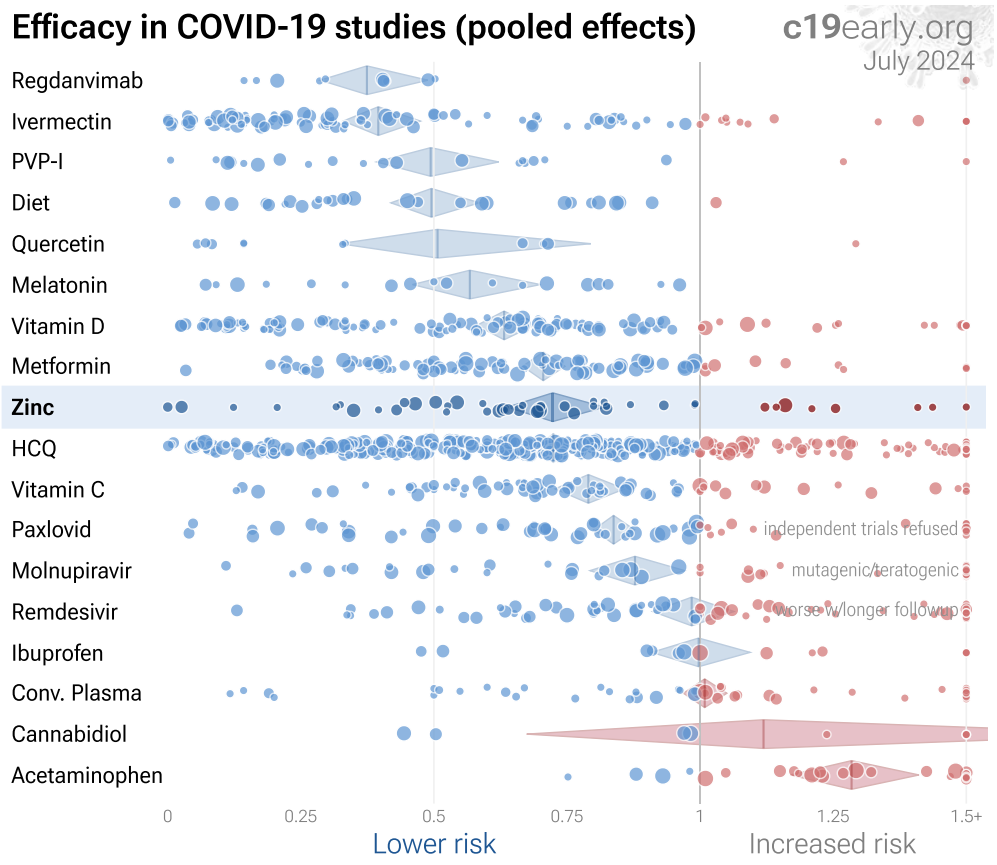


Figure 31. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy [128].

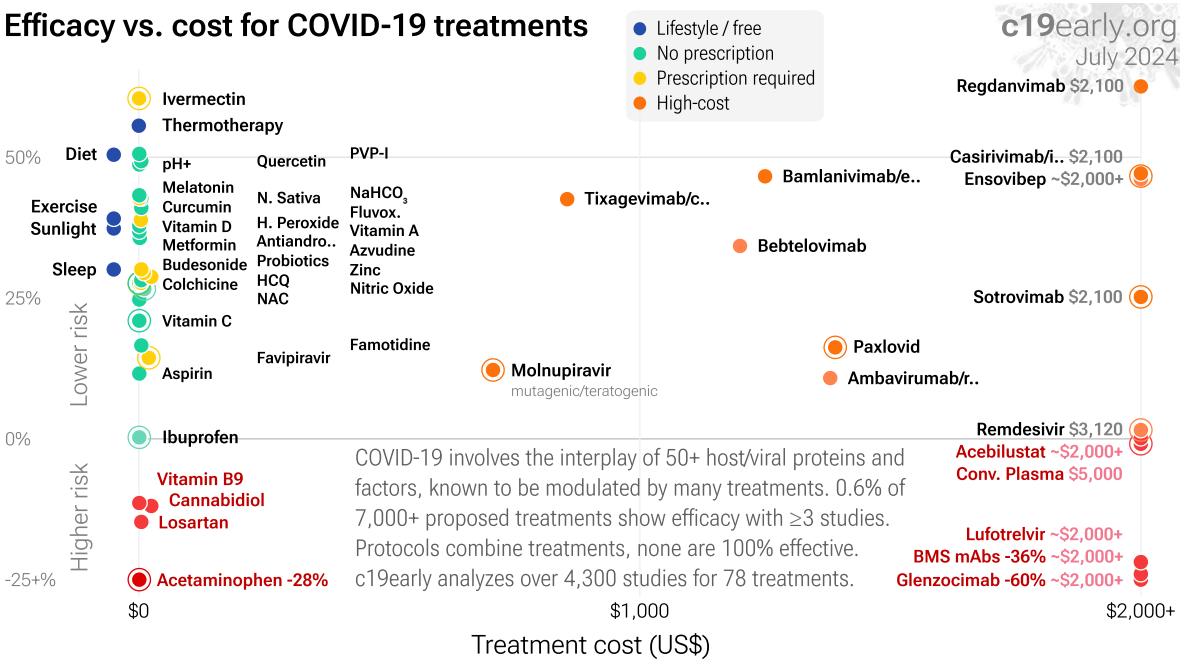


Figure 32. **Efficacy vs. cost for COVID-19 treatments.**

Conclusion

Zinc is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, ventilation, hospitalization, progression, recovery, and viral clearance. 18 studies from 18 independent teams in 9 countries show significant improvements. Meta analysis using the most serious outcome reported shows 28% [18-36%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, peer-reviewed studies, and after excluding studies using combined treatment. 17 sufficiency studies analyze outcomes based on serum levels, showing 74% [64-81%] lower risk for patients with higher zinc levels. Results are robust — in exclusion sensitivity analysis 20 of 45 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

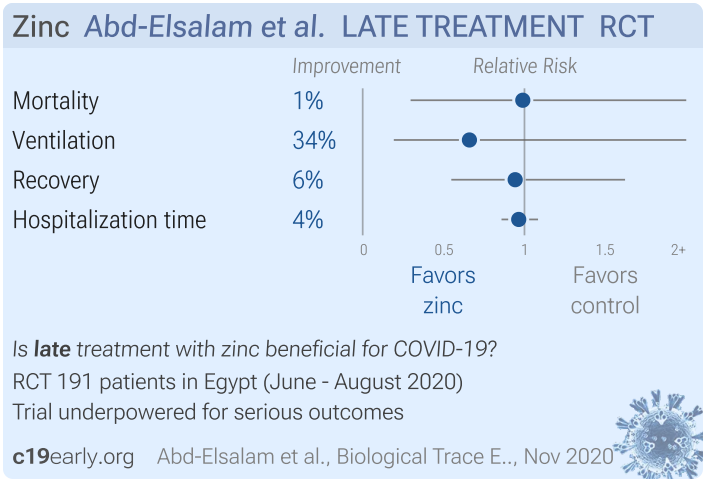
8 studies use combined treatments. After exclusion the risk reduction is 26% [16-35%] compared to 28% [18-36%].

The European Food Safety Authority has found evidence for a causal relationship between the intake of zinc and optimal immune system function[1,2]. Over-supplementation may be detrimental[3]. Bioaccessibility of supplements varies widely[4].

6 other meta analyses show significant improvements with zinc for mortality[7-11], severity[12], and cases[12].

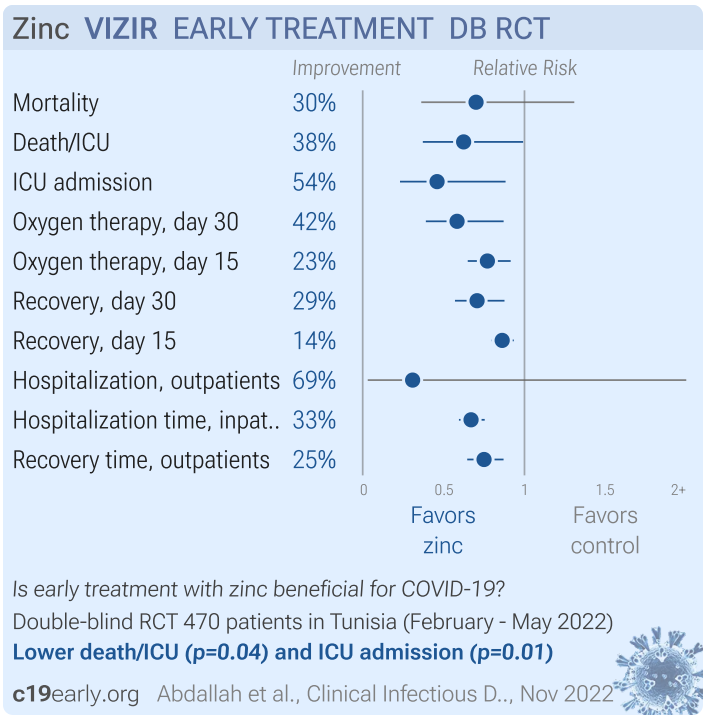
Study Notes

Abd-Elsalam



Abd-Elsalam: 191 patient RCT in Egypt comparing the addition of zinc to HCQ, not showing a significant difference. No information on baseline zinc values was recorded. Egypt has a low rate of zinc deficiency so supplementation may be less likely to be helpful[129,130]. For several issues with this trial, see[131]. See also[132]. The primary outcome was changed from viral clearance to "improvement or mortality" in the last month of the trial. The pre-specified outcome was not reported.

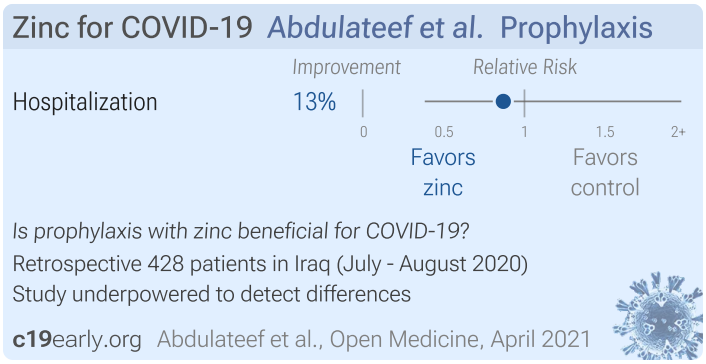
Abdallah



Abdallah: RCT 470 patients with symptoms ≤7 days, showing significantly lower ICU admission and combined mortality/ICU admission with zinc treatment. Greater benefit was seen for patients treated within 3 days. 25mg elemental zinc bid for 15 days.

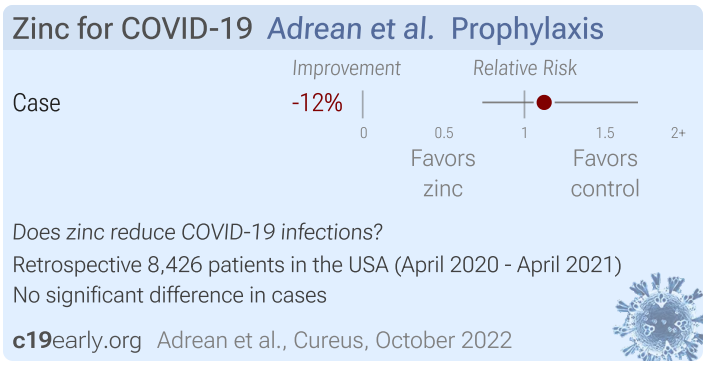
See also [133] and the author's reply [134].

Abdulateef



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.

Adrean

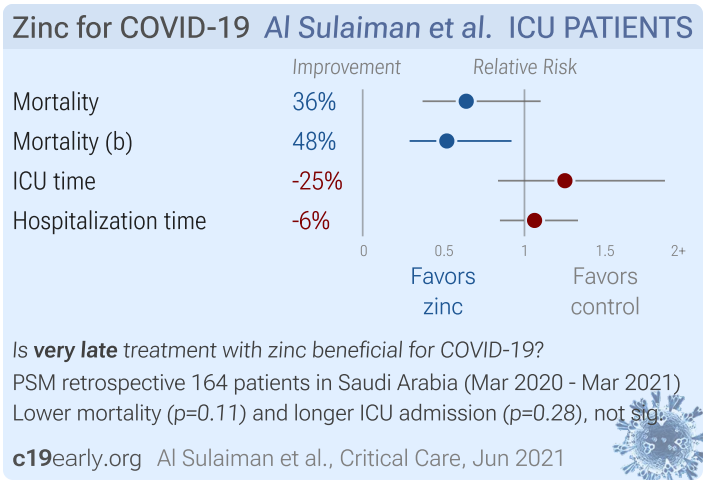


Adrean: Retrospective 8,426 patients in the USA, showing no significant difference in cases with zinc prophylaxis. Severity results were not reported due to the small number of events.

Ajili

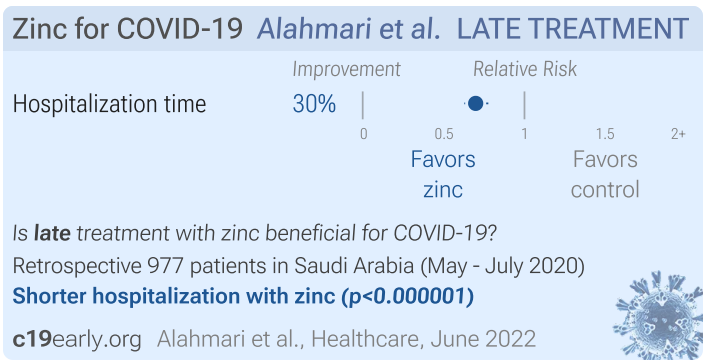
Ajili: Estimated 660 participant zinc prophylaxis RCT with results not reported over 3 years after estimated completion.

Al Sulaiman



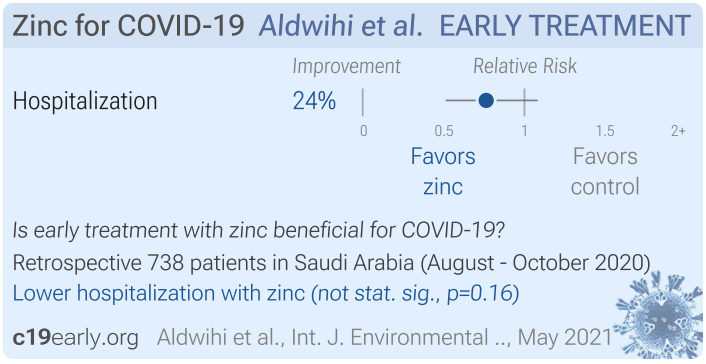
Al Sulaiman: Retrospective 266 ICU patients showing lower mortality with zinc treatment, reaching statistical significance only for 30 day mortality, and lower odds of acute kidney injury, without statistical significance. NRC21R/287/07.

Alahmari



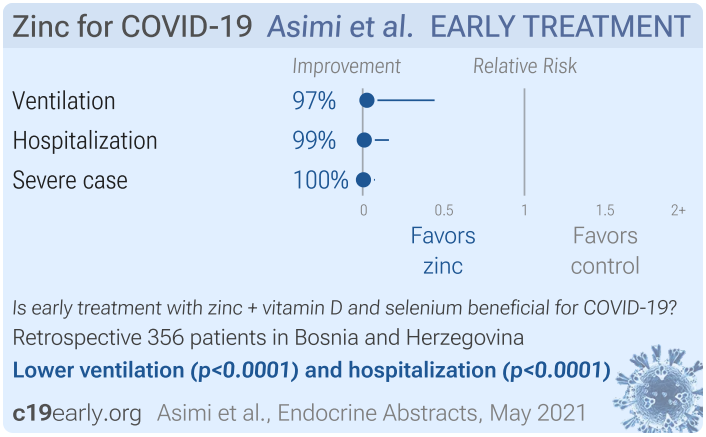
Alahmari: Retrospective 977 hospitalized patients in Saudi Arabia, showing significantly shorter hospitalization with zinc treatment.

Aldwihi



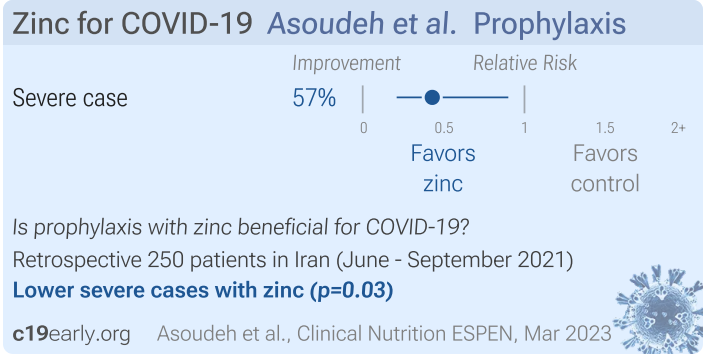
Aldwihi: Retrospective survey-based analysis of 738 COVID-19 patients in Saudi Arabia, showing lower hospitalization with vitamin C, turmeric, zinc, and nigella sativa, and higher hospitalization with vitamin D. For vitamin D, most patients continued prophylactic use. For vitamin C, the majority of patients 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.

Asimi



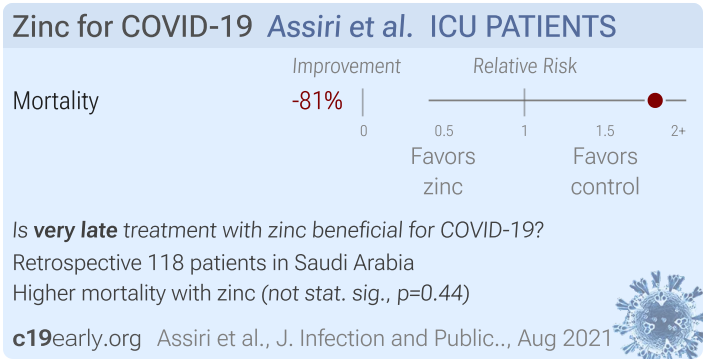
Asimi: Retrospective 356 Hashimoto's thyroiditis outpatients, 270 taking vitamin D, zinc, and selenium, showing significantly lower hospitalization with treatment. Authors adjust for age, gender, BMI, and smoking status, reporting statistically significant associations with p<0.001 for hospitalization and mechanical ventilation, however they do not report the adjusted risks.

Asoudeh



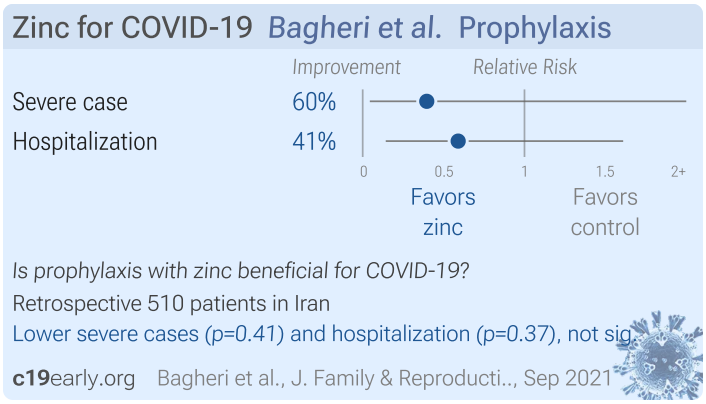
Asoudeh: Retrospective 250 recovered COVID-19 patients, showing lower risk of severe cases with higher zinc intake.

Assiri



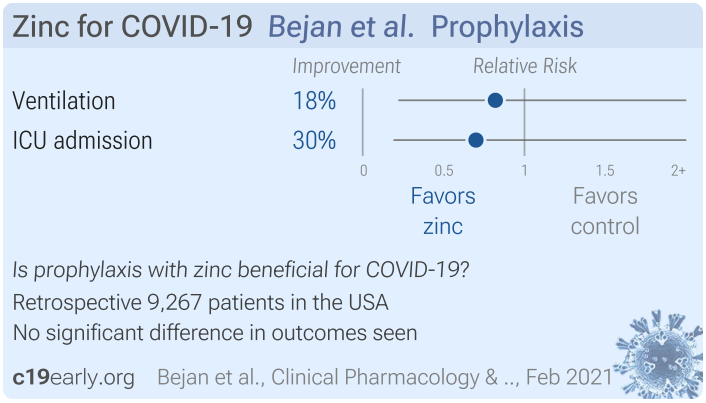
Assiri: Retrospective 118 ICU patients in Saudi Arabia showing no significant differences in unadjusted results with zinc, vitamin D, and favipiravir treatment.

Bagheri



Bagheri: Retrospective 510 patients in Iran, showing lower risk of severity with vitamin D (statistically significant) and zinc (not statistically significant) supplementation. IR.TUMS.VCR.REC.1398.1063.

Bejan

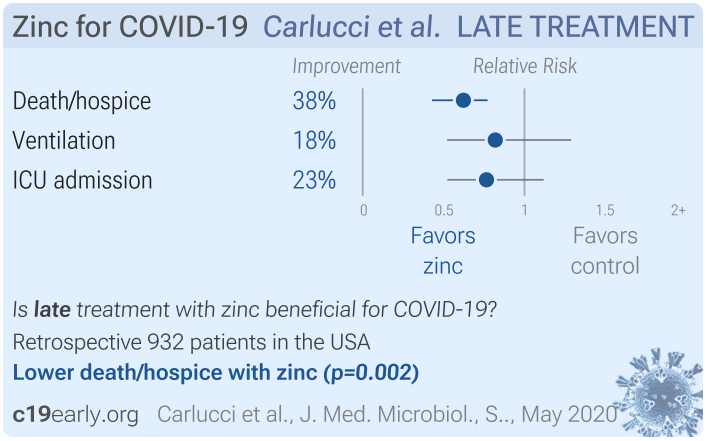


Bejan: Retrospective 9,748 COVID-19 patients in the USA showing lower ventilation and ICU admission with zinc prophylaxis, without statistical significance.

Boukef

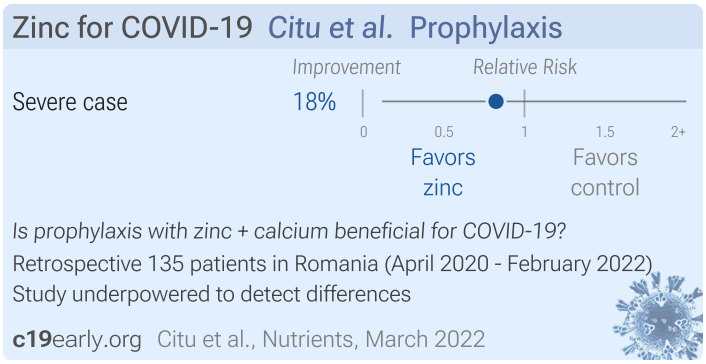
Boukef: 150 patient zinc early treatment RCT with results not reported over 1 year after completion.

Carlucci



Carlucci: Retrospective 932 patients showing that the addition of zinc to HCQ+AZ reduced mortality / transfer to hospice, ICU admission, and the need for ventilation.

Citu

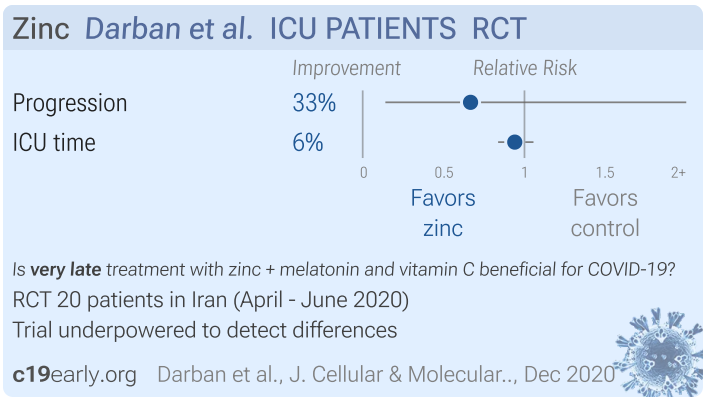


Citu: Retrospective 448 pregnant women with COVID-19. Patients with calcium, zinc, and magnesium supplementation, or magnesium only, had a significantly higher titer of SARS-CoV-2 anti-RBD antibodies. There was no statistically significant difference in severe cases based on supplementation.

Correa

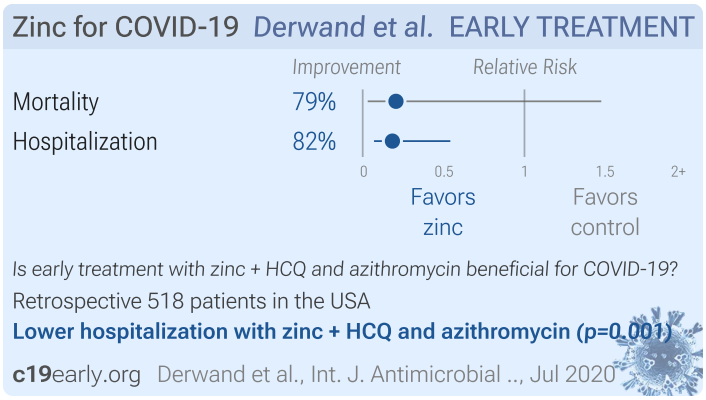
Correa: 105 patient zinc late treatment RCT with results not reported over 2 years after completion.

Darban



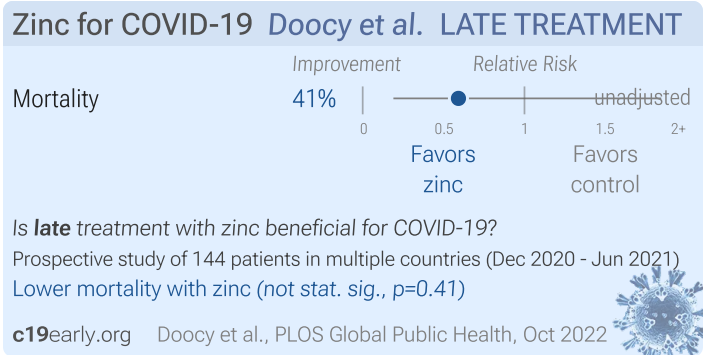
Darban: Small RCT in Iran with 20 ICU patients, 10 treated with high-dose vitamin C, melatonin, and zinc, not showing significant differences.

Derwand



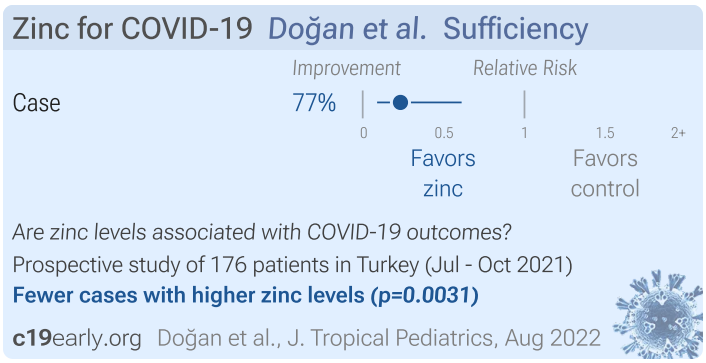
Derwand (B): 79% lower mortality and 82% lower hospitalization with early HCQ+AZ+Z. Retrospective 518 patients (141 treated, 377 control).

Doocy



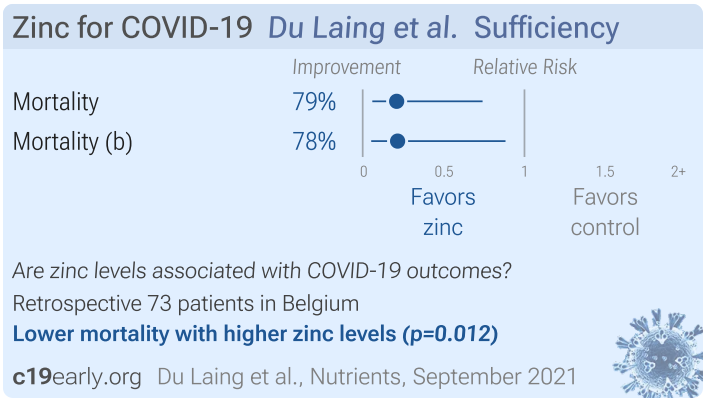
Doocy: Prospective study of 144 hospitalized COVID-19 patients in the DRC and South Sudan, showing lower mortality with zinc treatment, without statistical significance.

Doğan



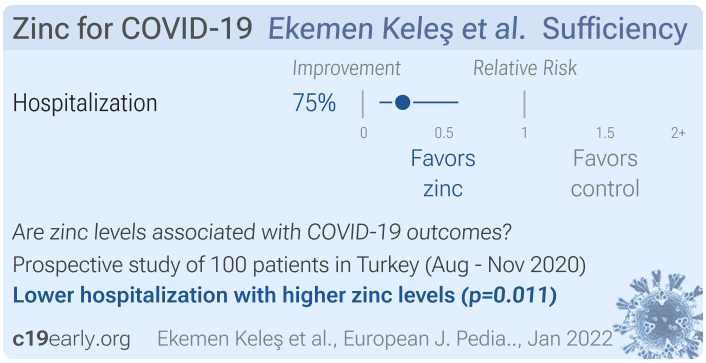
Doğan: Prospective study of 88 pediatric COVID-19 patients and 88 healthy controls, showing significantly lower zinc and vitamin D levels in COVID-19 patients.

Du Laing



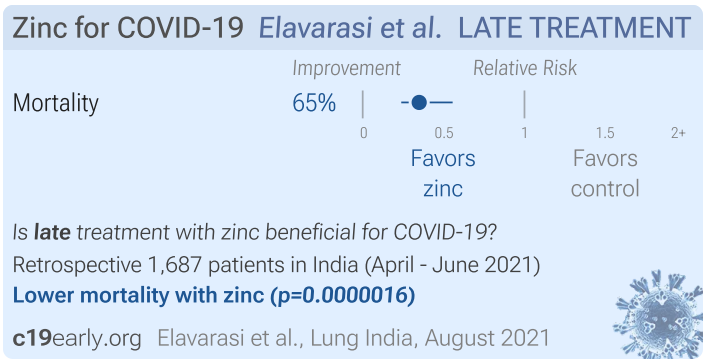
Du Laing: Retrospective 73 hospitalized COVID-19 patients in Belgium, showing higher risk of mortality with selenium deficiency and zinc deficiency.

Ekemen Keleş



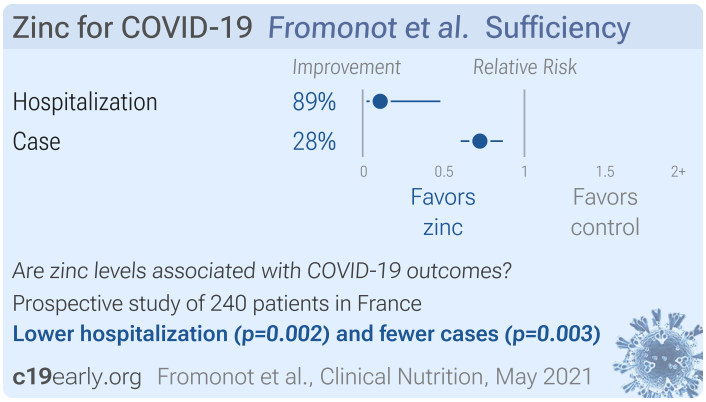
Ekemen Keleş: Prospective study of 100 COVID+ pediatric patients in Turkey, showing significantly increased risk of hospitalization for patients with zinc deficiency.

Elavarasi



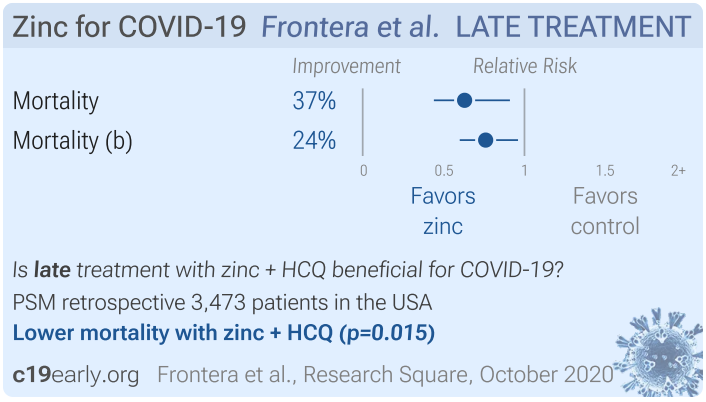
Elavarasi: Retrospective 2017 hospitalized patients in India, showing lower mortality with zinc treatment.

Fromonot



Fromonot: Analysis of 240 consecutive patients in France, showing significantly higher zinc deficiency in COVID-19 patients, and significantly greater risk of hospitalization for COVID-19 patients with zinc deficiency. 2020PI087.

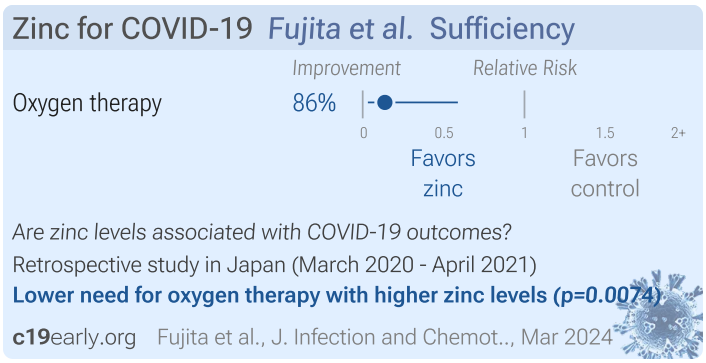
Frontera



Frontera: Retrospective 3,473 hospitalized patients showing 37% lower mortality with HCQ+zinc.

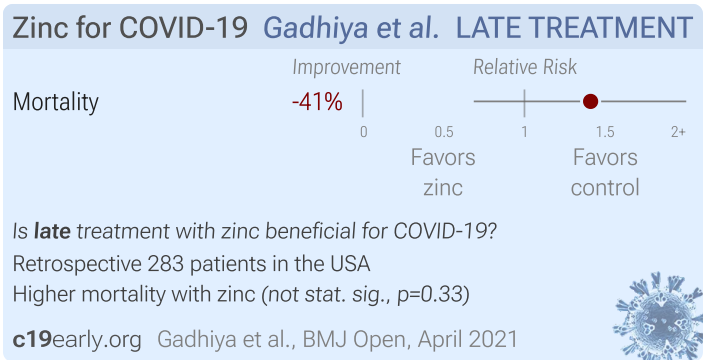
PSM aHR 0.63, p=0.015
regression aHR 0.76, p = 0.023

Fujita



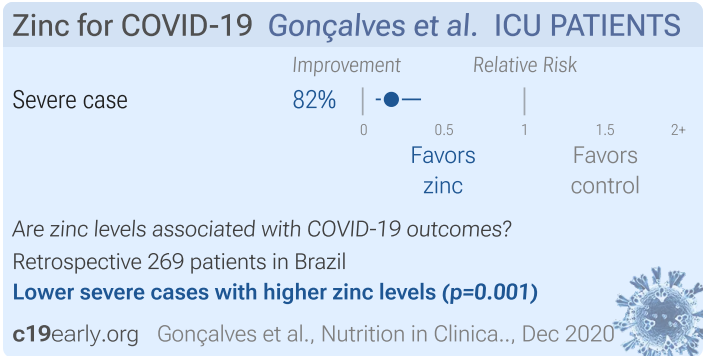
Fujita: Retrospective 60 hospitalized COVID-19 patients in Japan showing higher risk of progression to pneumonia requiring oxygen therapy with zinc deficiency at the time of diagnosis.

Gadhiya



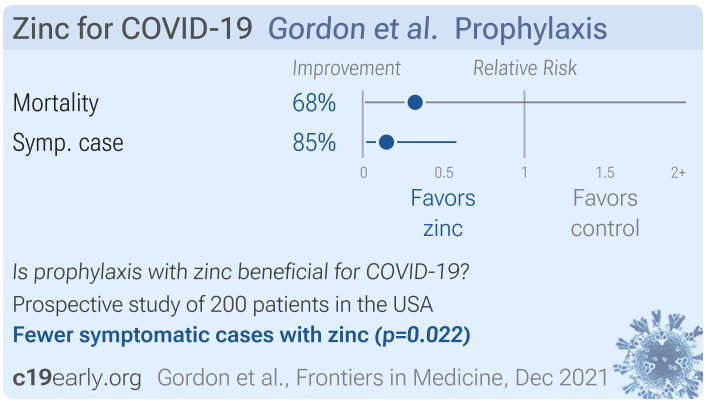
Gadhiya: Retrospective 283 patients in the USA showing higher mortality with all treatments (not statistically significant). Confounding by indication is likely. In the supplementary appendix, authors note that the treatments were usually given for patients that required oxygen therapy. Oxygen therapy 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.

Gonçalves



Gonçalves: Retrospective 169 ICU patients in Brazil, 214 with low zinc levels, showing an association between low zinc levels and severe ARDS. CAAE 30608,020.9.0000.8114.

Gordon

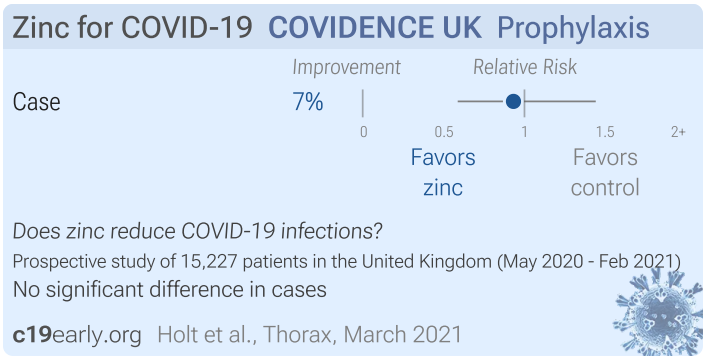


Gordon: Prospective study of zinc supplementation with 104 patients randomized to receive 10mg, 25mg, or 50mg of zinc picolinate daily, and a matched sample of 96 control patients from the adjacent clinic that did not routinely recommend/use zinc, showing significantly lower symptomatic COVID-19 with treatment.

Güerri-Fernández

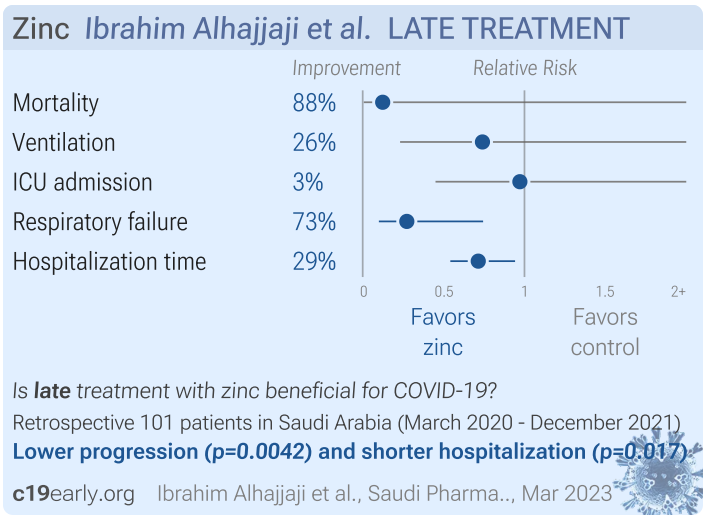
Güerri-Fernández: 75 patient zinc late treatment RCT with results not reported over 2 years after completion.

Holt



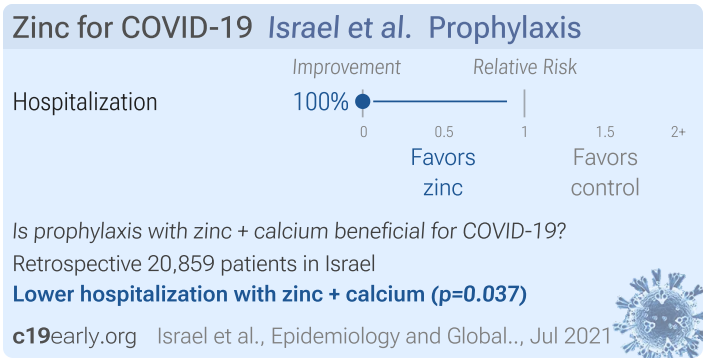
Holt: Prospective survey-based study with 15,227 people in the UK, showing lower risk of COVID-19 cases with vitamin A, vitamin D, zinc, selenium, probiotics, and inhaled corticosteroids; and higher risk with metformin and vitamin C. Statistical significance was not reached for any of these. Except for vitamin D, the results for treatments we follow were only adjusted for age, sex, duration of participation, and test frequency. NCT04330599. COVIDENCE UK.

Ibrahim Alhajjaji



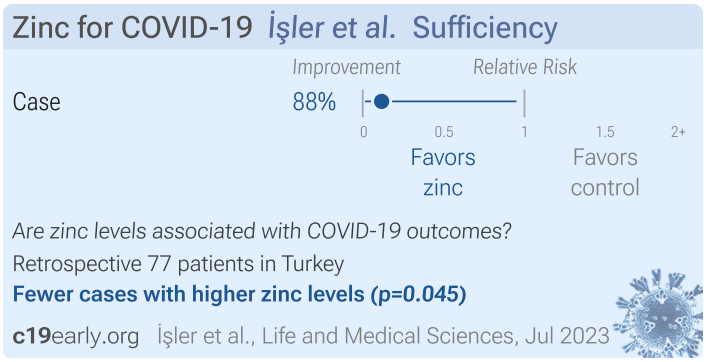
Ibrahim Alhajjaji: Retrospective 101 hospitalized pediatric patients in Saudi Arabia, showing zinc treatment associated with lower respiratory failure and shorter hospitalization in unadjusted results. Patients receiving zinc were older. Authors note elevated serum creatinine and the possibility of kidney injury.

Israel



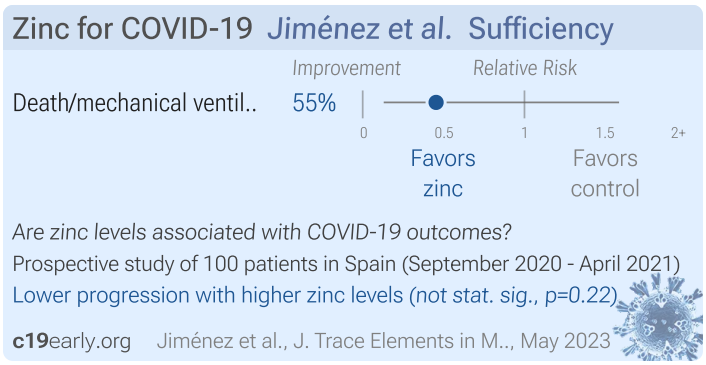
Israel: Case control study examining medication usage with a healthcare database in Israel, showing lower risk of hospitalization with calcium + zinc supplements (defined as being picked up within 35 days prior to PCR+), however only 10 patients took the supplements. Other patients may have acquired supplements outside of the healthcare system.

İşler



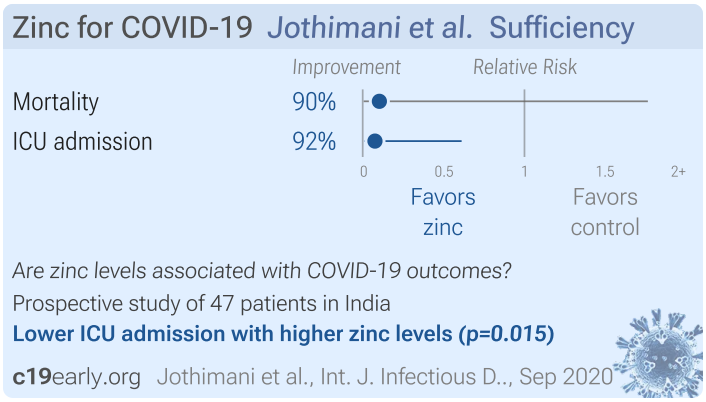
İşler: Retrospective 51 COVID-19 patients and 26 healthy controls in Turkey, showing significantly lower zinc levels in COVID-19 patients, and zinc deficiency associated with COVID-19 in unadjusted results.

Jiménez



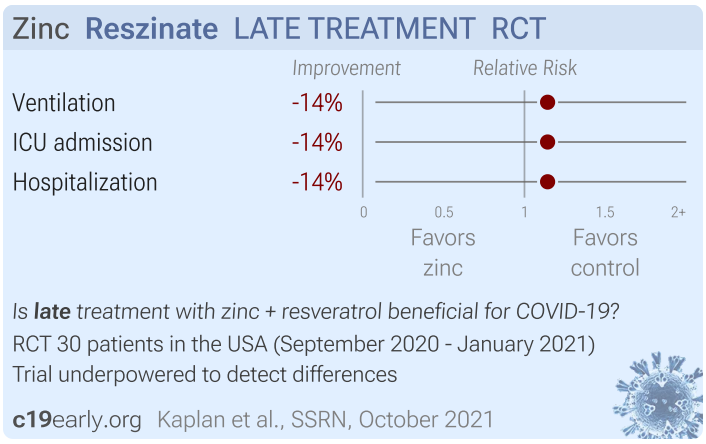
Jiménez: Prospective analysis of 100 hospitalized COVID-19 patients in Spain, showing higher risk of death/mechanical ventilation/ICU admission with zinc levels <79μg/dL, without statistical significance.

Jothimani



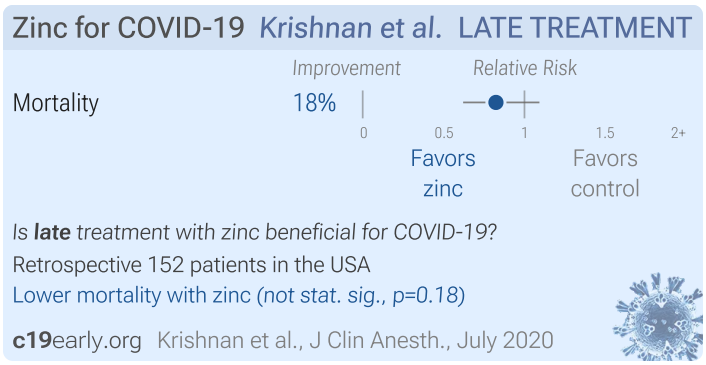
Jothimani: Prospective study of zinc levels in 47 hospitalized COVID-19 patients and 45 healthy controls. COVID-19 patients had significantly lower zinc levels (74.5 vs. 105.8 median µg/dl, p < 0.001). 57.4% of COVID-19 patients were zinc deficient, and they had higher rates of complications, ARDS, prolonged hospital stay, and increased mortality.

Kaplan



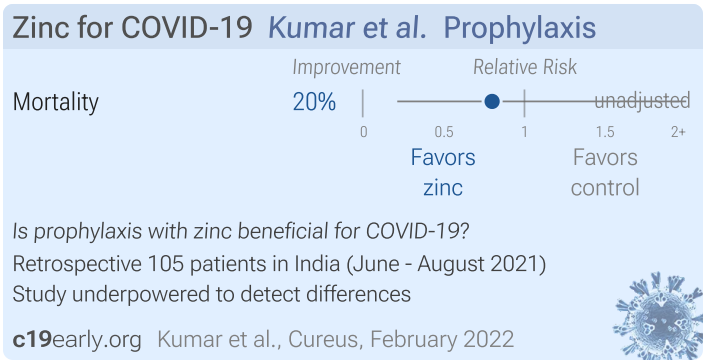
Kaplan: Small RCT of zinc plus resveratrol in COVID-19+ outpatients, showing no significant differences in viral clearance or symptoms. Although the treatment group was older (46.3 vs. 38.5) and had more severe baseline symptoms, they had similar symptomatic recovery by the second week.

Krishnan



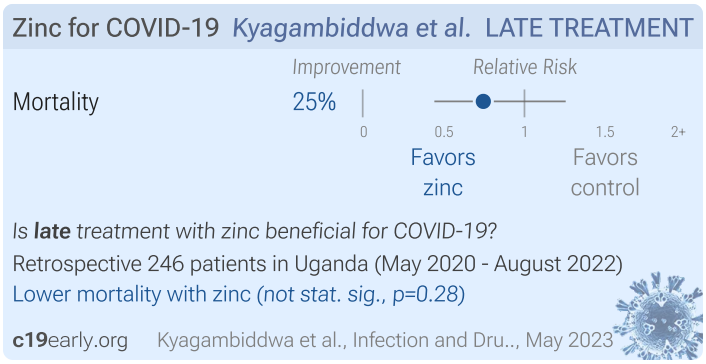
Krishnan: Retrospective 152 mechanically ventilated patients in the USA showing unadjusted lower mortality with vitamin C, vitamin D, HCQ, and zinc treatment, statistically significant only for vitamin C.

Kumar



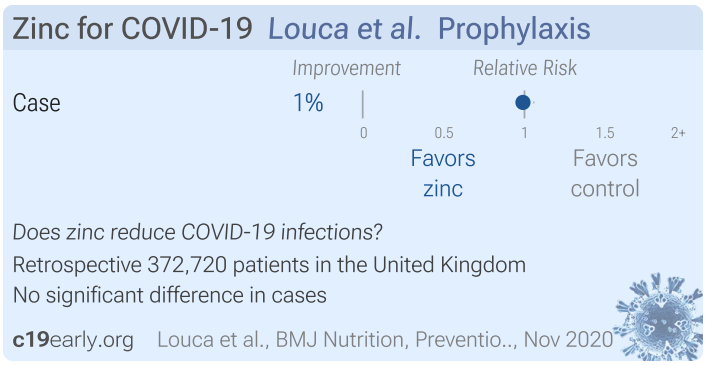
Kumar: Case control study of 105 COVID-19 patients in India, 55 with mucormycosis and 50 without, showing zinc prophylaxis and diabetes both associated with mucormycosis in unadjusted results. This is likely confounded because zinc supplementation is commonly used with diabetes [157], and Arora et al. show lower risk of mucormycosis with zinc prophylaxis, aOR 0.05 [0.01–0.19] [158]. There was no significant difference in mortality based on zinc prophylaxis in unadjusted results.

Kyagambiddwa



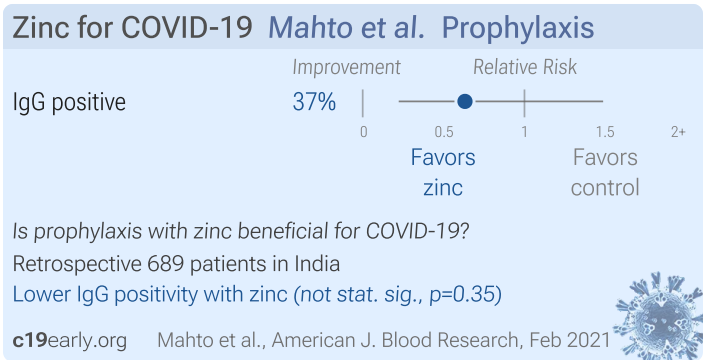
Kyagambiddwa: Retrospective 246 severe COVID-19 patients in Uganda, showing lower mortality with zinc treatment in unadjusted results, without statistical significance.

Louca



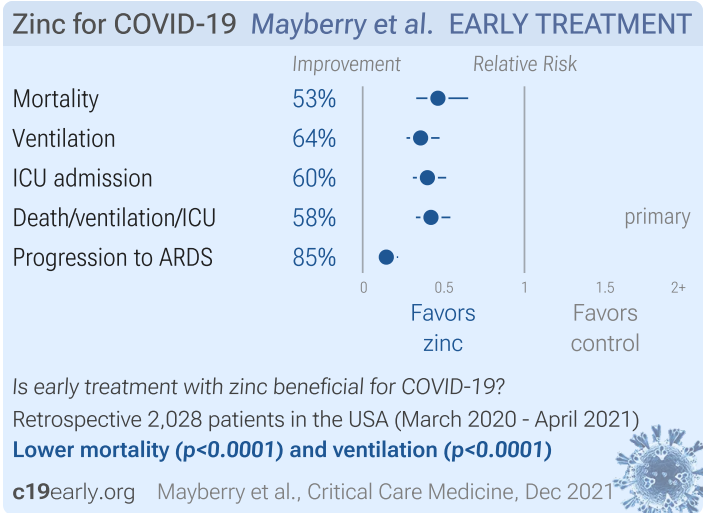
Louca: Survey analysis of dietary supplements showing no significant difference in PCR+ cases with zinc usage. These results are for PCR+ cases only, they do not reflect potential benefits for reducing the severity of cases. A number of biases could affect the results, for example users of the app may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

Mahto



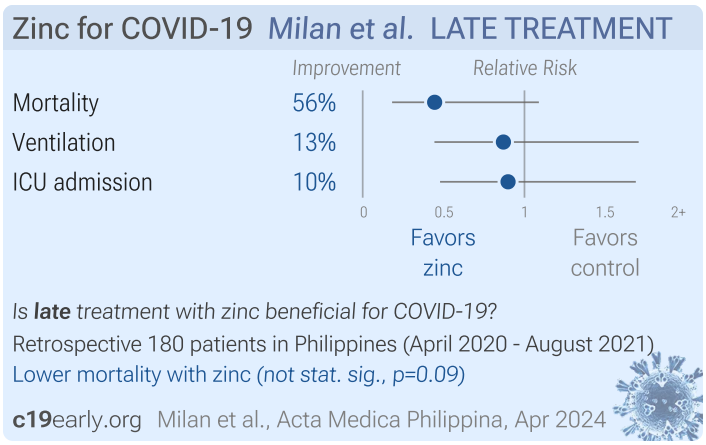
Mahto: Retrospective 689 healthcare workers in India, showing no significant difference in IgG positivity with zinc prophylaxis.

Mayberry



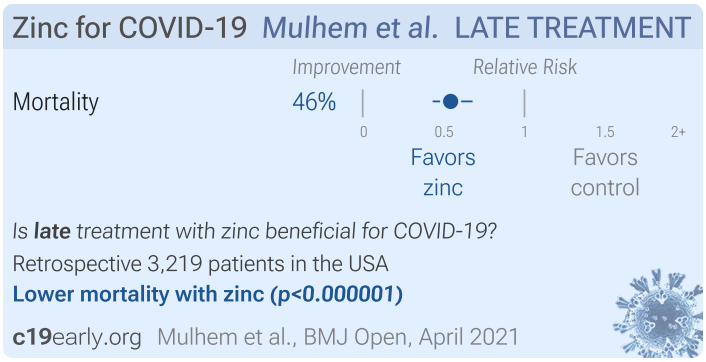
Mayberry: Retrospective 2,028 COVID patients in the USA, showing significantly lower mortality, ventilation, ICU admission, and progression to ARDS with zinc use, defined as at least one dose from one week prior to admission to 48 hours after admission.

Milan



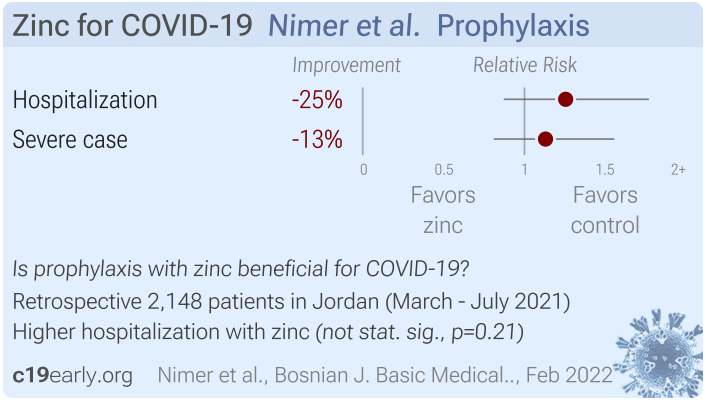
Milan: Retrospective 180 hospitalized pediatric COVID-19 patients in the Philippines showing lower mortality with vitamin D and zinc, and higher mortality with remdesivir, all without statistical significance. Remdesivir was given to few patients and authors do not provide information on the timing of treatment - confounding by indication may be significant.

Mulhem



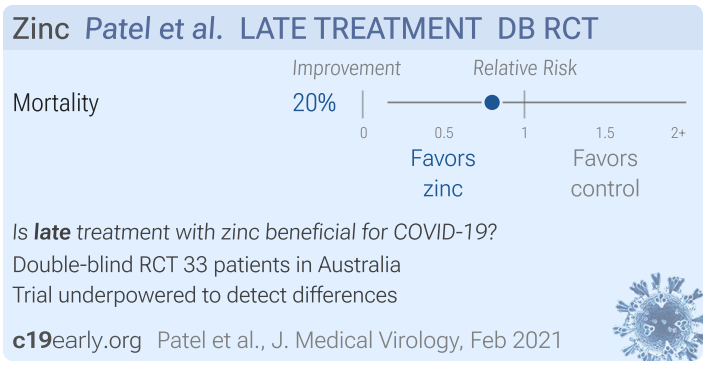
Mulhem: Retrospective database analysis of 3,219 hospitalized patients in the USA. Very different results in the time period analysis (Table S2), and results significantly different to other studies for the same medications (e.g., heparin OR 3.06 [2.44-3.83]) suggest significant confounding by indication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

Nimer



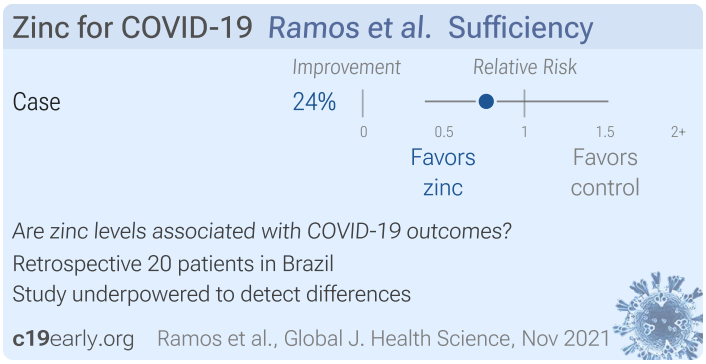
Nimer: Retrospective 2,148 COVID-19 recovered patients in Jordan, showing no significant differences in the risk of severity and hospitalization with zinc prophylaxis.

Patel



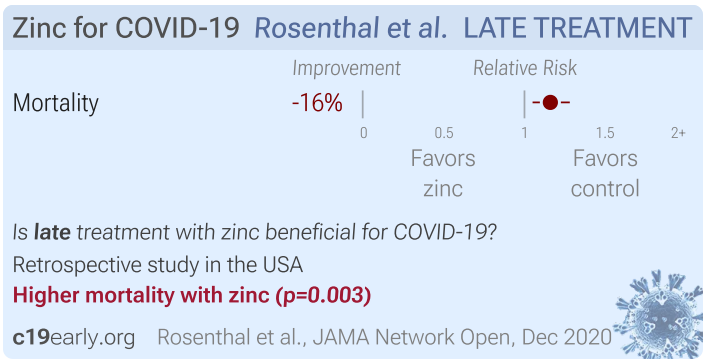
Patel: Small early terminated RCT with 33 hospitalized patients in Australia, 15 treated with zinc, showing no significant difference in clinical outcomes. Treatment increased zinc levels above the deficiency cutoff. Intravenous zinc 0.5mg/kg/day (elemental zinc concentration 0.24mg/kg/day) for up to 7 days. ACTRN12620000454976.

Ramos



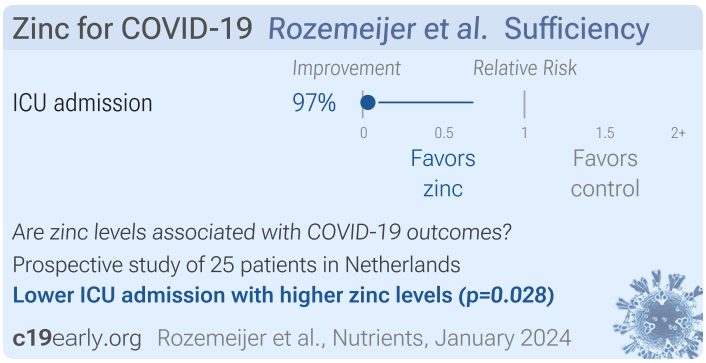
Ramos: Retrospective 13 COVID-19 patients and 7 controls in Brazil, showing no significant difference in zinc deficiency.

Rosenthal



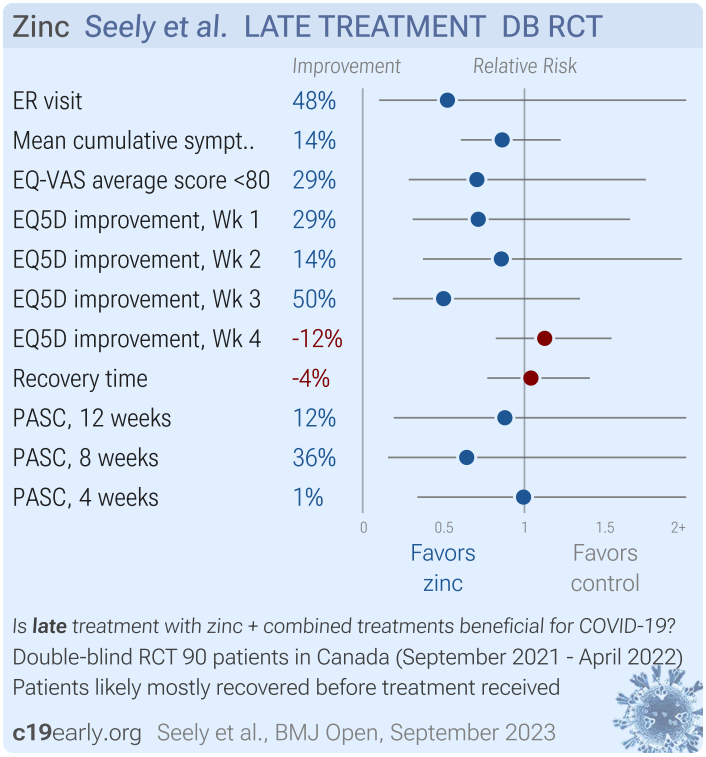
Rosenthal: Retrospective database analysis of 64,781 hospitalized patients in the USA, showing lower mortality with vitamin C or vitamin D (authors do not distinguish between the two), and higher mortality with zinc and HCQ, statistically significant for zinc. Authors excluded hospital-based outpatient visits, without explanation. Confounding by indication is likely, adjustments do not appear to include any information on COVID-19 severity at baseline.

Rozemeijer



Rozemeijer: Prospective pilot study of 20 critically ill COVID-19 ICU patients showing high deficiency rates of 50-100% for vitamins A, B6, and D; zinc; and selenium at admission. Deficiencies of vitamins B6 and D, and low iron status, persisted after 3 weeks. Plasma levels of vitamins A and E, zinc, and selenium increased over time as inflammation resolved, suggesting redistribution may explain some observed deficiencies. All patients received daily micronutrient administration. Additional intravenous and oral micronutrient administration for 10 patients did not significantly impact micronutrient levels or deficiency rates, however authors note that the administered doses may be too low. The form of vitamin D is not specified but may have been cholecalciferol which is expected to have a very long onset of action compared to more appropriate forms such as calcifediol or calcitriol.

Seely



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.

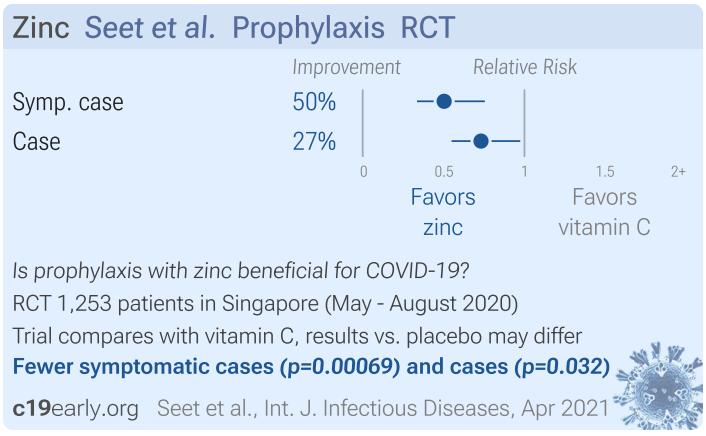
There was low compliance with completing surveys. Data from only 64% of patients was in the main analysis.

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.

Seet

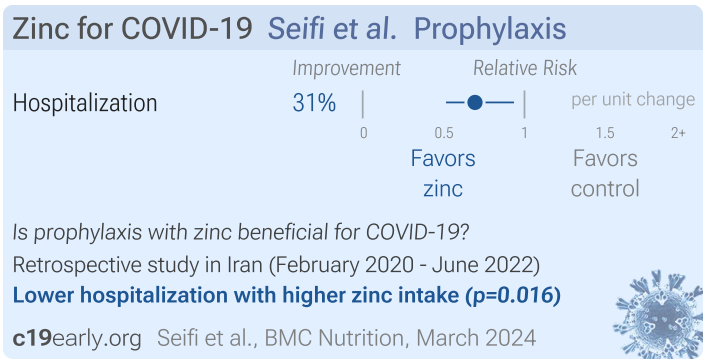


Seet: Prophylaxis RCT in Singapore with 3,037 low risk patients, showing lower serious cases, lower symptomatic cases, and lower confirmed cases of COVID-19 with all treatments (ivermectin, HCQ, PVP-I, and Zinc + vitamin C) compared to vitamin C.

Meta-analysis of vitamin C in 6 previous trials shows a benefit of 16%, so the actual benefit of ivermectin, HCQ, and PVP-I may be higher. Cluster RCT with 40 clusters.

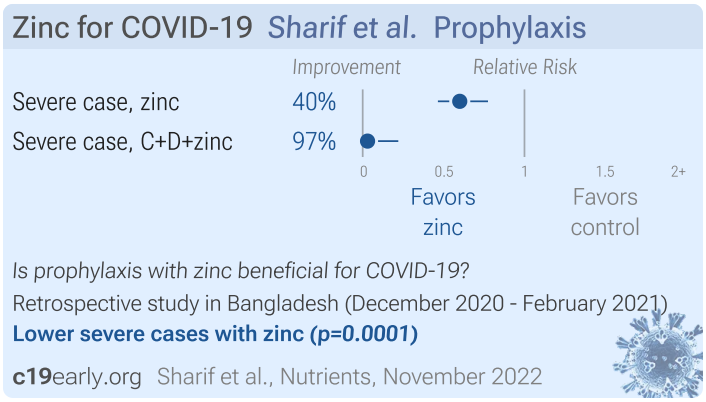
There were no hospitalizations and no deaths.

Seifi



Seifi: Analysis of 1,957 older adults showing lower risk of COVID-19 hospitalization with higher dietary zinc intake. Each unit increase in zinc intake was associated with a 31% reduction in the risk of COVID-19 hospitalization after adjustments. A dynamical system model showed that consumption of zinc < 9.7mg per day was associated with a 1.5 times greater risk of COVID-19 infection.

Sharif

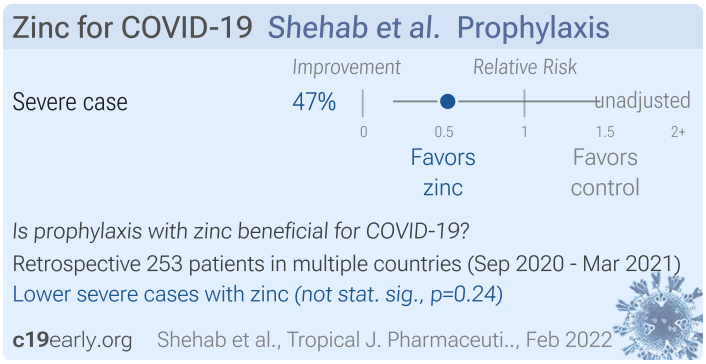


Sharif: Retrospective 962 COVID-19 patients in Bangladesh, showing significantly lower severity with vitamin C, vitamin D, and zinc supplementation, and improved results from the combination of all three.

Sharmin

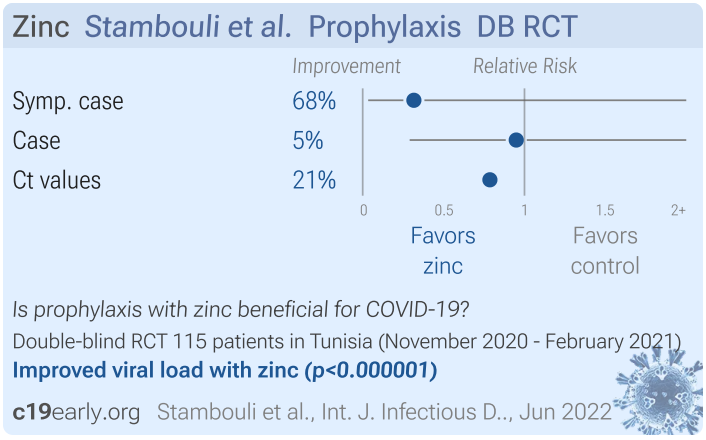
Sharmin: Estimated 50 patient zinc late treatment RCT with results not reported over 2 years after estimated completion.

Shehab



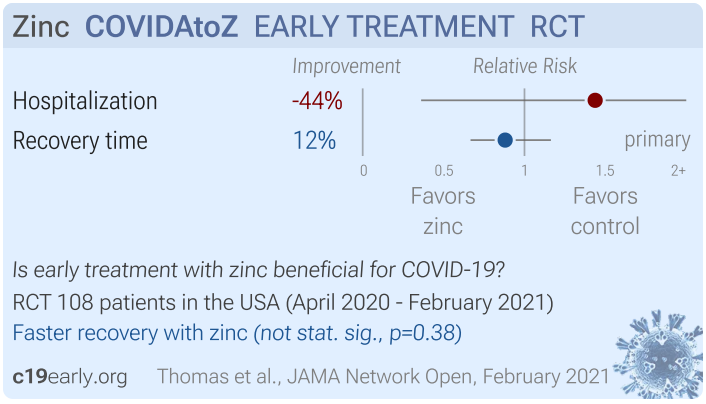
Shehab: Retrospective survey-based analysis of 349 COVID-19 patients, showing a lower risk of severe cases with vitamin D, zinc, turmeric, and honey prophylaxis in unadjusted analysis, without statistical significance. REC/UG/2020/03.

Stambouli



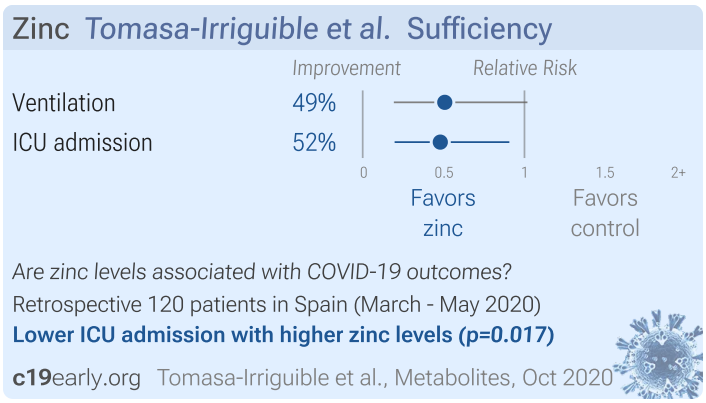
Stambouli: Prophylaxis RCT with 59 zinc + doxycycline, 56 doxycycline, and 57 placebo healthcare workers, showing lower symptomatic cases and significantly improved Ct values with the addition of zinc to doxycycline treatment. Doxycycline 100mg/day and zinc 15 mg/day.

Thomas



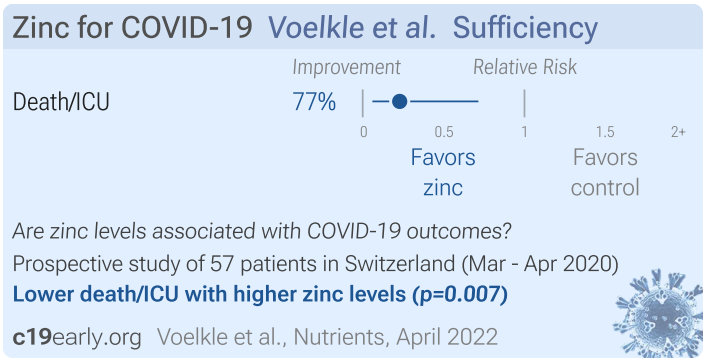
Thomas: Small 214 low-risk outpatient RCT showing non-statistically significant faster recovery with zinc and with vitamin C. Study performed in the USA where zinc deficiency is relatively uncommon. The zinc dosage is relatively low, 50mg zinc gluconate (7mg elemental zinc), one tenth of that shown to reduce the duration of colds in other studies [167].

Tomasa-Irriguible



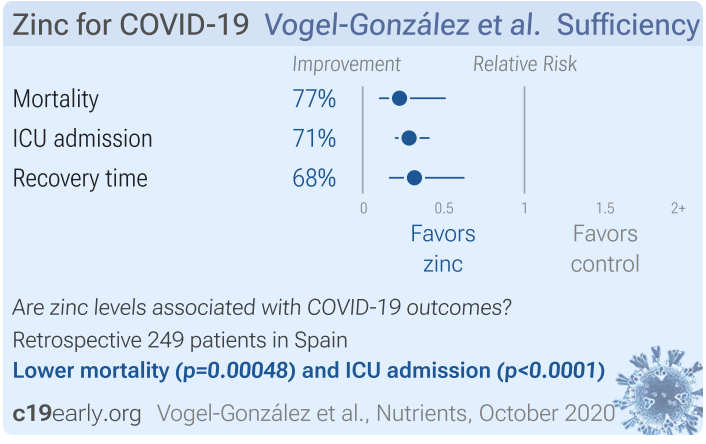
Tomasa-Irriguible: Retrospective 120 hospitalized patients in Spain showing zinc deficiency associated with higher ICU admission.

Voelkle



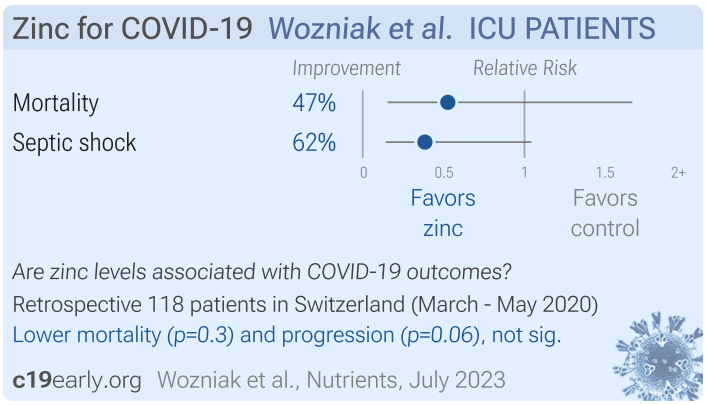
Voelkle: Prospective study of 57 consecutive hospitalized COVID-19 patients in Switzerland, showing higher risk of mortality/ICU admission with vitamin A, vitamin D, and zinc deficiency, with statistical significance only for vitamin A and zinc. Adjustments only considered age.

Vogel-González



Vogel-González: Retrospective 249 PCR+ hospitalized patients in Spain, 58 with zinc levels on admission <50 µg/dL, showing higher mortality and ICU admission, and slower recovery with low zinc levels.

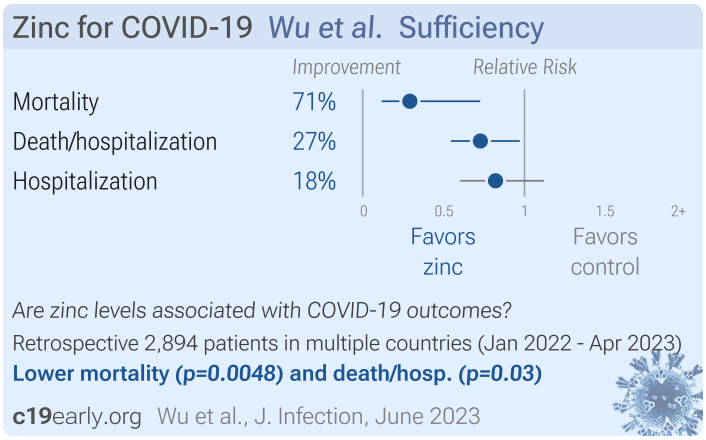
Wozniak



Wozniak: Retrospective 345 COVID-19 patients in Switzerland, showing significantly different zinc levels with ICU patients < hospitalized patients < outpatients.

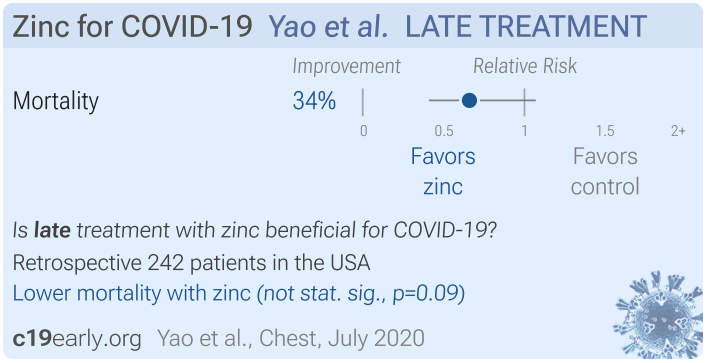
For ICU patients, there was higher mortality, septic shock, and mechanical ventilation days with lower zinc levels, without statistical significance.

Wu



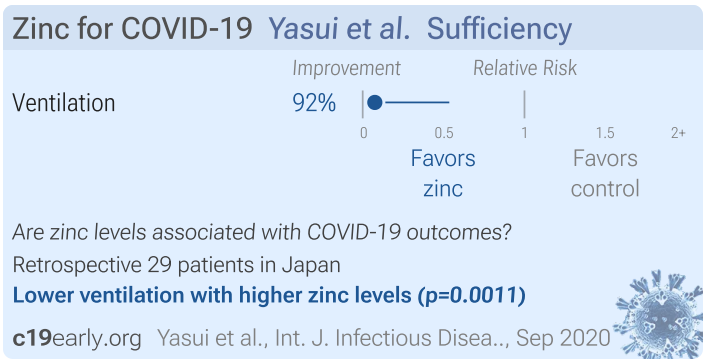
Wu: TriNetX PSM retrospective 10,935 COVID-19 patients, showing higher mortality with zinc deficiency.

Yao



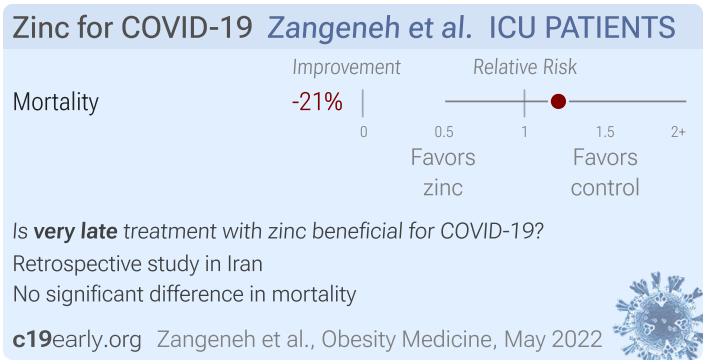
Yao: Retrospective 242 hospitalized patients in the USA showing adjusted hazard ratio for zinc treatment, aHR 0.66 [0.41-1.07].[174] notes that the study would be more informative if baseline serum zinc levels were known.

Yasui



Yasui: Retrospective 62 hospitalized patients, 29 with serum zinc data, showing significantly lower serum zinc levels for severe COVID-19 cases (intubation) compared with mild and moderate cases, p = 0.005. Authors recommend zinc supplementation.

Zangeneh



Zangeneh: Retrospective 193 ICU patients in Iran, showing no significant difference with zinc treatment.

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 zinc 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 zinc 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. This is a living analysis and is updated regularly.

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 both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used 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 test status. 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. 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 [177]. Reported confidence intervals and *p*-values were used when available, using adjusted values 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 [180]. 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 (3.12.4) with scipy (1.13.1), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.2), and plotly (5.22.0).

Forest plots are computed using PythonMeta [181] 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 0.8.0 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 [69,70].

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/zmeta.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.

Abdallah, 11/4/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Tunisia, peer-reviewed, mean age 54.2, 24 authors, study period 15 February, 2022 - 4 May, 2022, average treatment delay 4.6 days, trial NCT05212480 (history) (VIZIR).	risk of death, 29.9% lower, RR 0.70, *p* = 0.27, treatment 15 of 231 (6.5%), control 22 of 239 (9.2%), NNT 37, odds ratio converted to relative risk, day 30.
	risk of death/ICU, 37.6% lower, RR 0.62, *p* = 0.04, treatment 24 of 231 (10.4%), control 40 of 239 (16.7%), NNT 16, odds ratio converted to relative risk, day 30.
	risk of ICU admission, 54.0% lower, RR 0.46, *p* = 0.01, treatment 12 of 231 (5.2%), control 27 of 239 (11.3%), NNT 16, odds ratio converted to relative risk, day 30.
	risk of oxygen therapy, 41.7% lower, RR 0.58, *p* = 0.009, treatment 31 of 231 (13.4%), control 55 of 239 (23.0%), NNT

	10, grade III, day 30, Figure 3.
	risk of oxygen therapy, 22.9% lower, RR 0.77, $p = 0.003$, treatment 108 of 231 (46.8%), control 145 of 239 (60.7%), NNT 7.2, grade III, day 15, Figure 3.
	risk of no recovery, 29.3% lower, RR 0.71, $p = 0.002$, treatment 82 of 231 (35.5%), control 120 of 239 (50.2%), NNT 6.8, grade II/III, day 30.
	risk of no recovery, 13.8% lower, RR 0.86, $p < 0.001$, treatment 180 of 231 (77.9%), control 216 of 239 (90.4%), NNT 8.0, grade II/III, day 15.
	risk of hospitalization, 69.1% lower, RR 0.31, $p = 0.30$, treatment 1 of 85 (1.2%), control 4 of 100 (4.0%), NNT 35, odds ratio converted to relative risk, outpatients.
	hospitalization time, 33.0% lower, relative time 0.67, $p < 0.001$, treatment mean 7.1 (±3.4) n=146, control mean 10.6 (±2.8) n=134, inpatients.
	recovery time, 25.0% lower, relative time 0.75, $p < 0.001$, treatment mean 9.6 (±4.1) n=85, control mean 12.8 (±6.7) n=100, outpatients.
Aldwihi, 5/11/2021, retrospective, Saudi Arabia, peer-reviewed, survey, mean age 36.5, 8 authors, study period August 2020 - October 2020.	risk of hospitalization, 23.7% lower, RR 0.76, $p = 0.16$, treatment 53 of 199 (26.6%), control 184 of 539 (34.1%), NNT 13, adjusted per study, odds ratio converted to relative risk, multivariable.
Asimi, 5/22/2021, retrospective, Bosnia and Herzegovina, preprint, 3 authors, this trial uses multiple treatments in the treatment arm (combined with vitamin D and selenium) - results of individual treatments may vary, excluded in exclusion analyses: excessive unadjusted differences between groups.	risk of mechanical ventilation, 97.4% lower, RR 0.03, $p < 0.001$, treatment 0 of 270 (0.0%), control 9 of 86 (10.5%), NNT 9.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted.
	risk of hospitalization, 99.0% lower, RR 0.010, $p < 0.001$, treatment 0 of 270 (0.0%), control 24 of 86 (27.9%), NNT 3.6, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted.
	risk of severe case, 99.5% lower, RR 0.005, $p < 0.001$, treatment 0 of 270 (0.0%), control 51 of 86 (59.3%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), unadjusted.
Boukef, 2/28/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Tunisia, trial NCT05670444 (history).	150 patient RCT with results unknown and over 1 year late.
Derwand (B), 7/3/2020, retrospective, USA, peer-reviewed, 3 authors, this trial uses multiple treatments in the treatment arm (combined with HCQ and azithromycin) - results of individual treatments may vary.	risk of death, 79.4% lower, RR 0.21, $p = 0.12$, treatment 1 of 141 (0.7%), control 13 of 377 (3.4%), NNT 37, odds ratio converted to relative risk.
	risk of hospitalization, 81.6% lower, RR 0.18, $p < 0.001$, treatment 4 of 141 (2.8%), control 58 of 377 (15.4%), NNT 8.0, odds ratio converted to relative risk.

Mayberry, 12/16/2021, retrospective, USA, peer-reviewed, 14 authors, study period March 2020 - April 2021.	risk of death, 53.5% lower, OR 0.47, $p < 0.001$, treatment 938, control 1,090, adjusted per study, multivariable, RR approximated with OR.
	risk of mechanical ventilation, 64.2% lower, OR 0.36, $p < 0.001$, treatment 938, control 1,090, adjusted per study, multivariable, RR approximated with OR.
	risk of ICU admission, 60.0% lower, OR 0.40, $p < 0.001$, treatment 938, control 1,090, adjusted per study, multivariable, RR approximated with OR.
	death/ventilation/ICU, 57.8% lower, OR 0.42, $p < 0.001$, treatment 938, control 1,090, adjusted per study, multivariable, primary outcome, RR approximated with OR.
	progression to ARDS, 85.4% lower, OR 0.15, $p < 0.001$, treatment 938, control 1,090, adjusted per study, multivariable, RR approximated with OR.
Thomas, 2/12/2021, Randomized Controlled Trial, USA, peer-reviewed, 11 authors, study period 8 April, 2020 - 11 February, 2021, trial NCT04342728 (history) (COVIDAtoZ).	risk of hospitalization, 43.7% higher, RR 1.44, $p = 0.72$, treatment 5 of 58 (8.6%), control 3 of 50 (6.0%).
	recovery time, 11.9% lower, relative time 0.88, $p = 0.38$, treatment mean 5.9 (±4.9) n=58, control mean 6.7 (±4.4) n=50, mean time to a 50% reduction in symptoms, primary outcome.

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.

Abd-Elsalam, 11/29/2020, Randomized Controlled Trial, Egypt, peer-reviewed, 10 authors, study period 23 June, 2020 - 23 August, 2020, data issues, see notes, trial NCT04447534 (history), excluded in exclusion analyses: multiple potential data reliability issues.	risk of death, 1.0% lower, RR 0.99, $p = 0.99$, treatment 5 of 96 (5.2%), control 5 of 95 (5.3%), NNT 1824.
	risk of mechanical ventilation, 34.0% lower, RR 0.66, $p = 0.54$, treatment 4 of 96 (4.2%), control 6 of 95 (6.3%), NNT 47.
	risk of no recovery, 5.8% lower, RR 0.94, $p = 0.97$, treatment 20 of 96 (20.8%), control 21 of 95 (22.1%), NNT 79.
	hospitalization time, 3.6% lower, relative time 0.96, $p = 0.55$, treatment 96, control 95.
Al Sulaiman, 6/7/2021, retrospective, propensity score matching, Saudi Arabia, peer-reviewed, 11 authors, study period 1 March, 2020 - 31 March, 2021.	risk of death, 36.0% lower, HR 0.64, $p = 0.11$, treatment 23 of 82 (28.0%), control 32 of 82 (39.0%), NNT 9.1, adjusted per study, in-hospital, PSM, multivariable Cox proportional hazards.
	risk of death, 48.0% lower, HR 0.52, $p = 0.03$, treatment 19 of 82 (23.2%), control 31 of 82 (37.8%), NNT 6.8, adjusted per study, 30 day, PSM, multivariable Cox proportional hazards.
	ICU time, 25.0% higher, relative time 1.25, $p = 0.28$, treatment

	82, control 82.
	hospitalization time, 6.2% higher, relative time 1.06, $p = 0.61$, treatment 82, control 82.
Alahmari, 6/27/2022, retrospective, Saudi Arabia, peer-reviewed, 7 authors, study period 1 May, 2020 - 30 July, 2020.	**hospitalization time, 30.2% lower, relative time 0.70, $p < 0.001$**, treatment mean 6.39 (±0.76) n=130, control mean 9.15 (±0.27) n=847.
Assiri, 8/28/2021, retrospective, Saudi Arabia, peer-reviewed, 8 authors, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 80.8% higher, RR 1.81, $p = 0.44$**, treatment 10 of 60 (16.7%), control 4 of 58 (6.9%), inverted to make RR<1 favor treatment, odds ratio converted to relative risk.
Carlucci, 5/8/2020, retrospective, USA, peer-reviewed, 6 authors.	**risk of death/hospice, 37.7% lower, RR 0.62, $p = 0.002$**, treatment 54 of 411 (13.1%), control 119 of 521 (22.8%), NNT 10, adjusted per study, odds ratio converted to relative risk, multivariate logistic regression.
	risk of mechanical ventilation, 18.0% lower, RR 0.82, $p = 0.40$, treatment 29 of 411 (7.1%), control 62 of 521 (11.9%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression.
	risk of ICU admission, 23.5% lower, RR 0.77, $p = 0.17$, treatment 38 of 411 (9.2%), control 82 of 521 (15.7%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression.
Correa, 10/30/2021, Double Blind Randomized Controlled Trial, trial NCT04902976 (history).	105 patient RCT with results unknown and over 2 years late.
Darban, 12/15/2020, Randomized Controlled Trial, Iran, peer-reviewed, 8 authors, study period 7 April, 2020 - 8 June, 2020, this trial uses multiple treatments in the treatment arm (combined with melatonin and vitamin C) - results of individual treatments may vary, trial IRCT20151228025732N52.	**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.
Doocy, 10/19/2022, prospective, multiple countries, peer-reviewed, 6 authors, study period December 2020 - June 2021, trial NCT04568499 (history), excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 40.8% lower, RR 0.59, $p = 0.41$**, treatment 3 of 28 (10.7%), control 21 of 116 (18.1%), NNT 14, unadjusted.
Elavarasi, 8/12/2021, retrospective, India, peer-reviewed, 31 authors, study period April 2021 - June 2021.	**risk of death, 65.1% lower, RR 0.35, $p < 0.001$**, treatment 486, control 1,201, adjusted per study, odds ratio converted to relative risk, model 4, multivariate logistic regression, control prevalence approximated with overall prevalence.
Frontera, 10/26/2020, retrospective, propensity score matching, USA, preprint, median age 64.0, 14 authors, this trial uses multiple treatments in the treatment arm (combined with HCQ) - results of individual treatments may vary.	**risk of death, 37.0% lower, HR 0.63, $p = 0.01$**, treatment 121 of 1,006 (12.0%), control 424 of 2,467 (17.2%), NNT 19, adjusted per study, PSM.
	risk of death, 24.0% lower, HR 0.76, $p = 0.02$, treatment 121 of 1,006 (12.0%), control 424 of 2,467 (17.2%), NNT 19, adjusted per study, regression.

Gadhiya, 4/8/2021, retrospective, USA, peer-reviewed, 4 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of death, 40.9% higher, RR 1.41, $p = 0.33$, treatment 21 of 54 (38.9%), control 34 of 229 (14.8%), adjusted per study, odds ratio converted to relative risk, multivariate logistic regression.
Güerri-Fernández, 5/25/2022, Randomized Controlled Trial, Spain, trial NCT05778383 (history) (MARZINC).	75 patient RCT with results unknown and over 2 years late.
Ibrahim Alhajjaji, 3/4/2023, retrospective, Saudi Arabia, peer-reviewed, 8 authors, study period 1 March, 2020 - 31 December, 2021, excluded in exclusion analyses: excessive unadjusted differences between groups.	risk of death, 87.6% lower, RR 0.12, $p = 0.13$, treatment 0 of 44 (0.0%), control 4 of 57 (7.0%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 26.0% lower, RR 0.74, $p = 0.75$, treatment 4 of 44 (9.1%), control 7 of 57 (12.3%), NNT 31.
	risk of ICU admission, 2.8% lower, RR 0.97, $p = 1.00$, treatment 9 of 44 (20.5%), control 12 of 57 (21.1%), NNT 167.
	respiratory failure, 72.7% lower, RR 0.27, $p = 0.004$, treatment 4 of 44 (9.1%), control 19 of 57 (33.3%), NNT 4.1.
	hospitalization time, 28.6% lower, relative time 0.71, $p = 0.02$, treatment 44, control 57.
Kaplan, 10/1/2021, Randomized Controlled Trial, USA, preprint, 12 authors, study period 21 September, 2020 - 22 January, 2021, average treatment delay 5.9 days, this trial uses multiple treatments in the treatment arm (combined with resveratrol) - results of individual treatments may vary, trial NCT04542993 (history) (Reszinate).	risk of mechanical ventilation, 14.3% higher, RR 1.14, $p = 1.00$, treatment 1 of 14 (7.1%), control 1 of 16 (6.2%).
	risk of ICU admission, 14.3% higher, RR 1.14, $p = 1.00$, treatment 1 of 14 (7.1%), control 1 of 16 (6.2%).
	risk of hospitalization, 14.3% higher, RR 1.14, $p = 1.00$, treatment 1 of 14 (7.1%), control 1 of 16 (6.2%).
Krishnan, 7/20/2020, retrospective, USA, peer-reviewed, 13 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 17.6% lower, RR 0.82, $p = 0.18$, treatment 31 of 58 (53.4%), control 61 of 94 (64.9%), NNT 8.7.
Kyagambiddwa, 5/11/2023, retrospective, Uganda, peer-reviewed, mean age 39.0, 15 authors, study period May 2020 - August 2022, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 25.4% lower, RR 0.75, $p = 0.28$, treatment 20 of 89 (22.5%), control 22 of 73 (30.1%), NNT 13.
Milan, 4/30/2024, retrospective, Philippines, peer-reviewed, median age 11.0, 5 authors, study period 1 April, 2020 - 31 August, 2021.	risk of death, 55.5% lower, RR 0.44, $p = 0.09$, treatment 9 of 129 (7.0%), control 8 of 51 (15.7%), NNT 11, day 45.
	risk of mechanical ventilation, 13.0% lower, RR 0.87, $p = 0.67$, treatment 22 of 129 (17.1%), control 10 of 51 (19.6%), NNT 39, day 45.
	risk of ICU admission, 10.1% lower, RR 0.90, $p = 0.84$, treatment 25 of 129 (19.4%), control 11 of 51 (21.6%), NNT 46, day 45.

Mulhem, 4/7/2021, retrospective, database analysis, USA, peer-reviewed, 3 authors, 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, 45.6% lower, RR 0.54, $p < 0.001$, treatment 256 of 1,596 (16.0%), control 260 of 1,623 (16.0%), adjusted per study, odds ratio converted to relative risk, logistic regression.
Patel, 2/25/2021, Double Blind Randomized Controlled Trial, Australia, peer-reviewed, 12 authors.	risk of death, 20.0% lower, RR 0.80, $p = 1.00$, treatment 2 of 15 (13.3%), control 3 of 18 (16.7%), NNT 30.
Rosenthal, 12/10/2020, retrospective, database analysis, USA, peer-reviewed, 5 authors, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.	risk of death, 16.0% higher, OR 1.16, $p = 0.003$, adjusted per study, multivariable, RR approximated with OR.
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 2 years late.

Yao, 7/22/2020, retrospective, USA, peer-reviewed, 9 authors.	risk of death, 34.0% lower, RR 0.66, $p = 0.09$, treatment 73 of 196 (37.2%), control 21 of 46 (45.7%), adjusted per study, multivariate Cox regression.
Zangeneh, 5/13/2022, retrospective, Iran, peer-reviewed, 3 authors.	risk of death, 21.0% higher, HR 1.21, $p = 0.66$, Cox proportional hazards.

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, excluded in exclusion analyses: unadjusted results with no group details.	risk of hospitalization, 13.1% lower, RR 0.87, $p = 0.83$, treatment 7 of 111 (6.3%), control 23 of 317 (7.3%), NNT 105, unadjusted.
Adrean, 10/30/2022, retrospective, USA, peer-reviewed, survey, 6 authors, study period 1 April, 2020 - 9 April, 2021.	risk of case, 12.2% higher, RR 1.12, $p = 0.58$, treatment 30 of 2,111 (1.4%), control 80 of 6,315 (1.3%).
Ajili, 7/31/2020, Double Blind Randomized Controlled Trial, placebo-controlled, trial NCT04377646 (history) (COVID-Milit).	Estimated 660 patient RCT with results unknown and over 3 years late.
Asoudeh, 3/21/2023, retrospective, Iran, peer-reviewed, 10 authors, study period June 2021 - September 2021.	risk of severe case, 57.0% lower, OR 0.43, $p = 0.03$, adjusted per study, T3 vs. T1, multivariable, model 3, RR approximated with OR.
Bagheri, 9/1/2021, retrospective, Iran, peer-reviewed, 6 authors.	risk of severe case, 60.4% lower, OR 0.40, $p = 0.41$, treatment 33, control 477, adjusted per study, multinomial logistic regression, RR approximated with OR.
	risk of hospitalization, 41.0% lower, RR 0.59, $p = 0.37$, treatment 4 of 33 (12.1%), control 167 of 477 (35.0%), NNT 4.4, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, binary logistic regression.
Bejan, 2/28/2021, retrospective, USA, peer-reviewed, mean age 42.0, 6 authors.	risk of mechanical ventilation, 18.0% lower, OR 0.82, $p = 0.78$, treatment 155, control 9,074, adjusted per study, RR approximated with OR.
	risk of ICU admission, 30.0% lower, OR 0.70, $p = 0.60$, treatment 155, control 9,112, adjusted per study, RR approximated with OR.
Citu, 3/30/2022, retrospective, Romania, peer-reviewed, survey, 14 authors, study period 14 April, 2020 - 14 February, 2022, this trial uses multiple treatments in the treatment arm (combined with calcium) - results of individual treatments may vary.	risk of severe case, 17.6% lower, RR 0.82, $p = 1.00$, treatment 2 of 74 (2.7%), control 2 of 61 (3.3%), NNT 174, Ca+Mg+Zn vs. Mg.

Gordon, 12/13/2021, prospective, USA, peer-reviewed, 2 authors.	risk of death, 67.6% lower, RR 0.32, $p = 0.48$, treatment 0 of 104 (0.0%), control 1 of 96 (1.0%), NNT 96, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of symptomatic case, 85.3% lower, RR 0.15, $p = 0.02$, treatment 2 of 104 (1.9%), control 9 of 96 (9.4%), NNT 13, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk.
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, 6.8% lower, RR 0.93, $p = 0.77$, treatment 21 of 750 (2.8%), control 425 of 14,477 (2.9%), NNT 737, adjusted per study, odds ratio converted to relative risk, minimally adjusted, group sizes approximated.
Israel, 7/27/2021, retrospective, Israel, peer-reviewed, 10 authors, this trial uses multiple treatments in the treatment arm (combined with calcium) - results of individual treatments may vary, excluded in exclusion analyses: treatment or control group size extremely small.	risk of hospitalization, >99.99% lower, OR < 0.001, $p = 0.04$, treatment 0 of 6,953 (0.0%) cases, 10 of 13,906 (0.1%) controls, NNT 3.0, case control OR, PCR+, cohort 2.
Kumar, 2/23/2022, retrospective, India, peer-reviewed, 10 authors, study period June 2021 - August 2021, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 20.0% lower, RR 0.80, $p = 0.71$, treatment 6 of 75 (8.0%), control 3 of 30 (10.0%), NNT 50, unadjusted.
Louca, 11/30/2020, retrospective, United Kingdom, peer-reviewed, 26 authors.	risk of case, 0.9% lower, RR 0.99, $p = 0.80$, odds ratio converted to relative risk, United Kingdom, all adjustment model.
Mahto, 2/15/2021, retrospective, India, peer-reviewed, 6 authors.	risk of IgG positive, 36.8% lower, RR 0.63, $p = 0.35$, treatment 10 of 38 (26.3%), control 83 of 651 (12.7%), adjusted per study, odds ratio converted to relative risk, multivariable.
Nimer, 2/28/2022, retrospective, Jordan, peer-reviewed, survey, 4 authors, study period March 2021 - July 2021.	risk of hospitalization, 25.4% higher, RR 1.25, $p = 0.21$, treatment 41 of 326 (12.6%), control 178 of 1,822 (9.8%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of severe case, 13.0% higher, RR 1.13, $p = 0.46$, treatment 46 of 326 (14.1%), control 214 of 1,822 (11.7%), adjusted per study, odds ratio converted to relative risk, multivariable.
Seet, 4/14/2021, Cluster Randomized Controlled Trial, Singapore, peer-reviewed, 15 authors, study period 13 May, 2020 - 31 August, 2020, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04446104 (history).	risk of symptomatic case, 49.7% lower, RR 0.50, $p < 0.001$, treatment 33 of 634 (5.2%), control 64 of 619 (10.3%), NNT 19.
	risk of case, 26.9% lower, RR 0.73, $p = 0.03$, treatment 300 of 634 (47.3%), control 433 of 619 (70.0%), NNT 4.4, adjusted per study, odds ratio converted to relative risk, model 6.
Seifi, 3/4/2024, retrospective, Iran, peer-reviewed, mean age 49.7, 8 authors, study period February 2020 - June 2022, excluded in exclusion analyses:	risk of hospitalization, 30.6% lower, OR 0.69, $p = 0.02$, RR approximated with OR, per unit change, per unit change.

the hospitalization result is only provided with respect to continuous values and the confidence interval is not reported for the case result.	
Sharif, 11/26/2022, retrospective, Bangladesh, peer-reviewed, 14 authors, study period 13 December, 2020 - 4 February, 2021.	risk of severe case, 40.0% lower, OR 0.60, $p < 0.001$, 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, 47.4% lower, RR 0.53, $p = 0.24$, treatment 4 of 65 (6.2%), control 22 of 188 (11.7%), NNT 18, unadjusted, severe vs. mild cases.
Stambouli, 6/17/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Tunisia, peer-reviewed, 22 authors, study period 12 November, 2020 - 10 February, 2021, trial NCT04584567 (history).	risk of symptomatic case, 68.4% lower, RR 0.32, $p = 0.36$, treatment 1 of 59 (1.7%), control 3 of 56 (5.4%), NNT 27, zinc + doxycycline vs. doxycycline.
	risk of case, 5.1% lower, RR 0.95, $p = 1.00$, treatment 5 of 59 (8.5%), control 5 of 56 (8.9%), NNT 220, zinc + doxycycline vs. doxycycline.
	relative Ct values, 21.4% better, RR 0.79, $p < 0.001$, treatment mean 29.0 (±1.3) n=59, control mean 22.8 (±4.0) n=56, zinc + doxycycline vs. doxycycline.

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.

References

1. ***Galmés*** et al., *Suboptimal Consumption of Relevant Immune System Micronutrients Is Associated with a Worse Impact of COVID-19 in Spanish Populations*, Nutrients, doi:10.3390/nu14112254.
2. ***Galmés (B)*** et al., *Current State of Evidence: Influence of Nutritional and Nutrigenetic Factors on Immunity in the COVID-19 Pandemic Framework*, Nutrients, doi:10.3390/nu12092738.
3. ***karger.com***, www.karger.com/Article/FullText/528899.
4. ***Ośko*** et al., *Comparison of the Potential Relative Bioaccessibility of Zinc Supplements—In Vitro Studies*, Nutrients, doi:10.3390/nu15122813.

5. **Crawford** et al., *Analysis of Select Dietary Supplement Products Marketed to Support or Boost the Immune System*, JAMA Network Open, doi:10.1001/jamanetworkopen.2022.26040.

6. **Crighton** et al., *Toxicological screening and DNA sequencing detects contamination and adulteration in regulated herbal medicines and supplements for diet, weight loss and cardiovascular health*, Journal of Pharmaceutical and Biomedical Analysis, doi:10.1016/j.jpba.2019.112834.

7. **Tabatabaeizadeh**, S., *Zinc supplementation and COVID-19 mortality: a meta-analysis*, European Journal of Medical Research, doi:10.1186/s40001-022-00694-z.

8. **Olczak-Pruc** et al., *The effect of zinc supplementation on the course of COVID-19 – A systematic review and meta-analysis*, Annals of Agricultural and Environmental Medicine, doi:10.26444/aaem/155846.

9. **Xie** et al., *Micronutrient perspective on COVID-19: Umbrella review and reanalysis of meta-analyses*, Critical Reviews in Food Science and Nutrition, doi:10.1080/10408398.2023.2174948.

10. **Abuhelwa**, Z., *Do Zinc Supplements Reduce Mortality in Patients with COVID-19?*, Translation: The University of Toledo Journal of Medical Sciences, doi:10.46570/utjms.vol11-2023-749.

11. **Rheingold** et al., *Zinc Supplementation Associated With a Decrease in Mortality in COVID-19 Patients: A Meta-Analysis*, Cureus, doi:10.7759/cureus.40231.

12. **Fan** et al., *Zinc and selenium status in coronavirus disease 2019*, BioMetals, doi:10.1007/s10534-023-00501-0.

13. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.

14. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.

15. **Hampshire** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.

16. **Duloquin** et al., *Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2*, Journal of Clinical Medicine, doi:10.3390/jcm13051397.

17. **Sodagar** et al., *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, Biomolecules, doi:10.3390/biom12070971.

18. **Sagar** et al., *COVID-19-associated cerebral microbleeds in the general population*, Brain Communications, doi:10.1093/braincomms/fcae127.

19. **Verma** et al., *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, bioRxiv, doi:10.1101/2024.06.02.596989.

20. **Panagea** et al., *Neurocognitive Impairment in Long COVID: A Systematic Review*, Archives of Clinical Neuropsychology, doi:10.1093/arclin/acae042.

21. **Eberhardt** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.

22. **Malone** et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, Nature Reviews Molecular Cell Biology, doi:10.1038/s41580-021-00432-z.

23. **Murigneux** et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.

24. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.

25. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.

26. **Niarakis** et al., *Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1282859.

27. **c19early.org**, c19early.org/treatments.html.

28. **Abioye** et al., *Effect of micronutrient supplements on influenza and other respiratory tract infections among adults: a systematic review and meta-analysis*, BMJ Global Health, doi:10.1136/bmjgh-2020-003176.

29. **Hemilä** et al., *Zinc Acetate Lozenges May Improve the Recovery Rate of Common Cold Patients: An Individual Patient Data Meta-Analysis*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofx059.

30. **Agamah** et al., *Network-based multi-omics-disease-drug associations reveal drug repurposing candidates for COVID-19 disease phases*, ScienceOpen, doi:10.58647/DRUGARXIV.PR000010.v1.

31. **Lockwood**, T., *Coordination chemistry suggests that independently observed benefits of metformin and Zn2+ against COVID-19 are not independent*, BioMetals, doi:10.1007/s10534-024-00590-5.

32. **El-Megharbel** et al., *Chemical and spectroscopic characterization of (Artemisinin/Quercetin/ Zinc) novel mixed ligand complex with assessment of its potent high antiviral activity against SARS-CoV-2 and antioxidant capacity against toxicity induced by acrylamide in male rats*, PeerJ, doi:10.7717/peerj.15638.

33. **Bess** et al., *Identification of oral therapeutics using an AI platform against the virus responsible for COVID-19, SARS-CoV-2*, Frontiers in Pharmacology, doi:10.3389/fphar.2023.1297924.

34. **Pormohammad** et al., *Zinc and SARS-CoV-2: A molecular modeling study of Zn interactions with RNA-dependent RNA-polymerase and 3C-like proteinase enzymes*, International Journal of Molecular Medicine, doi:10.3892/ijmm.2020.4790.

35. **Hajdrik** et al., *In Vitro Determination of Inhibitory Effects of Humic Substances Complexing Zn and Se on SARS-CoV-2 Virus Replication*, Foods, doi:10.3390/foods11050694.

36. **Panchariya** et al., *Zinc2+ ion inhibits SARS-CoV-2 main protease and viral replication in vitro*, Chemical Communications, doi:10.1039/D1CC03563K.

37. **te Velthuis** et al., *Zn2+ Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture*, PLOS Pathogens 2010, 6:11, doi:10.1371/journal.ppat.1001176.

38. **Zeraatkar** et al., *Consistency of covid-19 trial preprints with published reports and impact for decision making: retrospective review*, BMJ Medicine, doi:10.1136/bmjmed-2022-0003091.

39. **Davidson** et al., *No evidence of important difference in summary treatment effects between COVID-19 preprints and peer-reviewed publications: a meta-epidemiological study*, Journal of Clinical Epidemiology, doi:10.1016/j.jclinepi.2023.08.011.

40. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings, Second Edition*, doi:10.1002/9780470691922.

41. **Gøtzsche**, P., *Bias in double-blind trials*, Doctoral Thesis, University of Copenhagen, www.scientificfreedom.dk/2023/05/16/bias-in-double-blind-trials-doctoral-thesis/.

42. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.

43. **Concato** et al., NEJM, 342:1887-1892, doi:10.1056/NEJM200006223422507.

44. **Anglemyer** et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews 2014, Issue 4, doi:10.1002/14651858.MR000034.pub2.

45. **Lee** et al., *Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines*, Arch Intern Med., 2011, 171:1, 18-22, doi:10.1001/archinternmed.2010.482.

46. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.

47. **Nichol** et al., *Challenging issues in randomised controlled trials*, Injury, 2010, doi: 10.1016/j.injury.2010.03.033, www.injuryjournal.com/article/S0020-1383(10)00233-0/fulltext.

48. **Boukef** et al., *Melatonin, Vitamins and Minerals Supplements for the Treatment of Covid-19 and Covid-like Illness: Results of a Prospective, Randomised, Double-blinded Multicentre Study*, NCT05670444, clinicaltrials.gov/study/NCT05670444.

49. **Güerri-Fernández** et al., *Zinc-based Nutritional Immunity to Lower Inflammation, Viral Load and COVID-19 Mortality During SARS-CoV-2 Infection.*, NCT05778383, clinicaltrials.gov/study/NCT05778383.

50. **Correa** et al., *Evaluation of SARS-COV-2 Viral Load of Covid-19 Patients After Rinsing With Oral Antimicrobial Mouthwashes*, NCT04902976, clinicaltrials.gov/study/NCT04902976.

51. **Sharmin** et al., *Randomized, Double -Blind, Placebo Controlled, Trial to Evaluate the Effect of Zinc and Ascorbic Acid Supplementation in COVID-19 Positive Hospitalized Patients in BSMMU*, NCT04558424, clinicaltrials.gov/study/NCT04558424.

52. **Ajili** et al., *A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers (COVID-Milit)*, NCT04377646, clinicaltrials.gov/study/NCT04377646.

53. **Abd-Elsalam** et al., *Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: a Randomized, Multicenter Trial*, Biological Trace Element Research, doi:10.1007/s12011-020-02512-1.

54. **Abdulateef** et al., *COVID-19 severity in relation to sociodemographics and vitamin D use*, Open Medicine, doi:10.1515/med-2021-0273.

55. **Asimi** et al., *Selenium, zinc, and vitamin D supplementation affect the clinical course of COVID-19 infection in Hashimoto's thyroiditis*, Endocrine Abstracts, doi:10.1530/endoabs.73.PEP14.2.

56. **Assiri** et al., *COVID-19 related treatment and outcomes among COVID-19 ICU patients: A retrospective cohort study*, Journal of Infection and Public Health, doi:10.1016/j.jiph.2021.08.030.

57. **Doocy** et al., *Clinical progression and outcomes of patients hospitalized with COVID-19 in humanitarian settings: A prospective cohort study in South Sudan and Eastern Democratic Republic of the Congo*, PLOS Global Public Health, doi:10.1371/journal.pgph.0000924.

58. **Gadhiya** et al., *Clinical characteristics of hospitalised patients with COVID-19 and the impact on mortality: a single-network, retrospective cohort study from Pennsylvania state*, BMJ Open, doi:10.1136/bmjopen-2020-042549.

59. **Holt** et al., *Risk factors for developing COVID-19: a population-based longitudinal study (COVIDENCE UK)*, Thorax, doi:10.1136/thoraxjnl-2021-217487.

60. **Ibrahim Alhajjaji** et al., *Effect of zinc supplementation on symptom reduction and length of hospital stay among pediatric patients with Coronavirus Disease 2019 (COVID-19)*, Saudi Pharmaceutical Journal, doi:10.1016/j.jsps.2023.02.011.

61. **Israel** et al., *Identification of drugs associated with reduced severity of COVID-19: A case-control study in a large population*, Epidemiology and Global Health Microbiology and Infectious Disease, doi:10.7554/eLife.68165.

62. **Krishnan** et al., *Clinical comorbidities, characteristics, and outcomes of mechanically ventilated patients in the State of Michigan with SARS-CoV-2 pneumonia*, J Clin Anesth., doi:10.1016/j.jclinane.2020.110005.

63. **Kumar** et al., *Role of Zinc and Clinicopathological Factors for COVID-19-Associated Mucormycosis (CAM) in a Rural Hospital of Central India: A Case-Control Study*, Cureus, doi:10.7759/cureus.22528.

64. **Kyagambiddwa** et al., *Thirty-Day Outcomes of Young and Middle-Aged Adults Admitted with Severe COVID-19 in Uganda: A Retrospective Cohort Study*, Infection and Drug Resistance, doi:10.2147/idr.s405256.

65. **Mulhem** et al., *3219 hospitalised patients with COVID-19 in Southeast Michigan: a retrospective case cohort study*, BMJ Open, doi:10.1136/bmjopen-2020-042042.

66. **Rosenthal** et al., *Risk Factors Associated With In-Hospital Mortality in a US National Sample of Patients With COVID-19*, JAMA Network Open, doi:10.1001/jamanetworkopen.2020.29058.

67. **Seifi** et al., *Dietary mineral intakes predict Coronavirus-disease 2019 (COVID-19) incidence and hospitalization in older adults*, BMC Nutrition, doi:10.1186/s40795-024-00821-5.

68. **Shehab** et al., *Immune-boosting effect of natural remedies and supplements on progress of, and recovery from COVID-19 infection*, Tropical Journal of Pharmaceutical Research, doi:10.4314/tjpr.v21i2.13.

69. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.

70. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.

71. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.

72. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.

73. **Kumar (B)** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, The Lancet Infectious Diseases, doi:10.1016/S1473-3099(21)00469-2.

74. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.3071.

75. **Korves** et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, medRxiv, doi:10.1101/2024.03.08.24303818.

76. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.

77. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.

78. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, medRxiv, doi:10.1101/2021.08.27.21262754.

79. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, Research Square, doi:10.21203/rs.3.rs-910467/v1.

80. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.

81. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.

82. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.

83. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.

84. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.

85. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.

86. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.

87. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.

88. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.

89. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.

90. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.

91. ***Fiaschi*** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.

92. ***Thairu*** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.

93. ***Williams***, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.

94. ***Xu*** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, Rapid Communications in Mass Spectrometry, doi:10.1002/rcm.9358.

95. ***Singh*** et al., *The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis*, Journal of Antimicrobial Chemotherapy, doi:10.1093/jac/dkae045.

96. ***Meneguesso***, A., *Médica defende tratamento precoce da Covid-19*, www.youtube.com/watch?v=X5FCrIm_19U.

97. ***Boulware***, D., *Comments regarding paper rejection*, twitter.com/boulware_dr/status/1311331372884205570.

98. ***Meeus***, G., *Online Comment*, twitter.com/gertmeeus_MD/status/1386636373889781761.

99. ***twitter.com***, twitter.com/KashPrime/status/1768487878454124914.

100. ***Rothstein***, H., *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*, www.wiley.com/en-ae/Publication+Bias+in+Meta+Analysis:+Prevention,+Assessment+and+Adjustments-p-9780470870143.

101. ***Stanley*** et al., *Meta-regression approximations to reduce publication selection bias*, Research Synthesis Methods, doi:10.1002/jrsm.1095.

102. ***Rücker*** et al., *Arcsine test for publication bias in meta-analyses with binary outcomes*, Statistics in Medicine, doi:10.1002/sim.2971.

103. ***Peters***, J., *Comparison of Two Methods to Detect Publication Bias in Meta-analysis*, JAMA, doi:10.1001/jama.295.6.676.

104. ***Moreno*** et al., *Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study*, BMC Medical Research Methodology, doi:10.1186/1471-2288-9-2.

105. ***Macaskill*** et al., *A comparison of methods to detect publication bias in meta-analysis*, Statistics in Medicine, doi:10.1002/sim.698.

106. ***Egger*** et al., *Bias in meta-analysis detected by a simple, graphical test*, BMJ, doi:10.1136/bmj.315.7109.629.

107. ***Harbord*** et al., *A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints*, Statistics in Medicine, doi:10.1002/sim.2380.

108. ***medicospelavidacovid19.com.br***, medicospelavidacovid19.com.br/editoriais/folha-de-s-paulo-revela-numeros-de-david-uip-veja-a-comparacao-com-medicos-que-fazem-tratamento-precoce/.

109. ***Jin*** et al., *The nutritional roles of zinc for immune system and COVID-19 patients*, Frontiers in Nutrition, doi:10.3389/fnut.2024.1385591.

110. ***Briassoulis*** et al., *The Anti-Oxidative, Anti-Inflammatory, Anti-Apoptotic, and Anti-Necroptotic Role of Zinc in COVID-19 and Sepsis*, Antioxidants, doi:10.3390/antiox12111942.

111. ***Schloss*** et al., *Nutritional deficiencies that may predispose to long COVID*, Inflammopharmacology, doi:10.1007/s10787-023-01183-3.

112. ***Arora*** et al., *Global Dietary and Herbal Supplement Use during COVID-19—A Scoping Review*, Nutrients, doi:10.3390/nu15030771.

113. ***Foshati*** et al., *Antioxidants and clinical outcomes of patients with coronavirus disease 2019: A systematic review of observational and interventional studies*, Food Science & Nutrition, doi:10.1002/fsn3.3034.

114. **DiGuilio** et al., *Micronutrient Improvement of Epithelial Barrier Function in Various Disease States: A Case for Adjuvant Therapy*, International Journal of Molecular Sciences, doi:10.3390/ijms23062995.

115. **Wessels** et al., *Zinc deficiency as a possible risk factor for increased susceptibility and severe progression of Corona Virus Disease 19*, British Journal of Nutrition, doi:10.1017/S0007114521000738.

116. **Sethuram** et al., *Potential Role of Zinc in the COVID-19 Disease Process and its Probable Impact on Reproduction*, Reproductive Sciences, doi:10.1007/s43032-020-00400-6.

117. **Joachimiak** et al., *Zinc against COVID-19? Symptom surveillance and deficiency risk groups*, PLOS Neglected Tropical Diseases, doi:10.1371/journal.pntd.0008895.

118. **Derwand** et al., *Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19?*, Medical Hypotheses, doi:10.1016/j.mehy.2020.109815.

119. **covid19treatmentguidelines.nih.gov**, www.covid19treatmentguidelines.nih.gov/therapies/supplements/zinc/.

120. **Abdallah** et al., *Twice daily oral zinc in the treatment of patients with Coronavirus Disease-19: A randomized double-blind controlled trial*, Clinical Infectious Diseases, doi:10.1093/cid/ciac807.

121. **Thomas** et al., *Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial*, JAMA Network Open, doi:10.1001/jamanetworkopen.2021.0369.

122. **Darban** et al., *Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial*, Journal of Cellular & Molecular Anesthesia, doi:10.22037/jcma.v6i2.32182.

123. **Kaplan** et al., *Resveratrol and Zinc in the Treatment of Outpatients With COVID-19 – The Reszinate Study - A Phase 1/2 Randomized Clinical Trial Utilizing Home Patient-Obtained Nasal and Saliva Viral Sampling*, SSRN, doi:10.2139/ssrn.3934228.

124. **Patel** et al., *A pilot double-blind safety and feasibility randomized controlled trial of high-dose intravenous zinc in hospitalized COVID-19 patients*, Journal of Medical Virology, doi:10.1002/jmv.26895.

125. **Seely** et al., *Dietary supplements to reduce symptom severity and duration in people with SARS-CoV-2: a double-blind randomised controlled trial*, BMJ Open, doi:10.1136/bmjopen-2023-073761.

126. **Seet** et al., *Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: an open-label randomized trial*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.04.035.

127. **Stambouli** et al., *COVID-19 prophylaxis with Doxycycline and Zinc in Health Care Workers: A prospective randomized double-blind clinical tria*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2022.06.016.

128. ***c19early.org (B)***, c19early.org/timeline.html.

129. ***ncbi.nlm.nih.gov***, www.ncbi.nlm.nih.gov/pmc/articles/PMC3510072/.

130. ***ncbi.nlm.nih.gov (B)***, www.ncbi.nlm.nih.gov/pmc/articles/PMC3510072/bin/pone.0050568.s003.xls.

131. ***osf.io***, osf.io/vjcnp/.

132. ***link.springer.com***, link.springer.com/article/10.1007/s12011-023-03807-9.

133. ***academic.oup.com***, academic.oup.com/cid/article-abstract/77/4/662/7128481.

134. ***academic.oup.com (B)***, academic.oup.com/cid/article-abstract/77/4/662/7129959.

135. **Adrean** et al., *Does Prophylactic Oral Zinc Reduce the Risk of Contracting COVID-19?*, Cureus, doi:10.7759/cureus.30881.

136. **Al Sulaiman** et al., *Evaluation of Zinc Sulfate as an Adjunctive Therapy in COVID-19 Critically Ill Patients: a Two Center Propensity-score Matched Study*, Critical Care, doi:10.1186/s13054-021-03785-1.

137. **Alahmari** et al., *Factors Associated with Length of Hospital Stay among COVID-19 Patients in Saudi Arabia: A Retrospective Study during the First Pandemic Wave*, Healthcare, doi:10.3390/healthcare10071201.

138. **Aldwihi** et al., *Patients' Behavior Regarding Dietary or Herbal Supplements before and during COVID-19 in Saudi Arabia*, International Journal of Environmental Research and Public Health, doi:10.3390/ijerph18105086.

139. **Asoudeh** et al., *The association between dietary intakes of zinc, vitamin C and COVID-19 severity and related symptoms: A cross-sectional study*, Clinical Nutrition ESPEN, doi:10.1016/j.clnesp.2023.03.013.

140. **Bagheri** et al., *Supplement Usage Pattern in a Group of COVID-19 Patients in Tehran*, Journal of Family & Reproductive Health, doi:10.18502/jfrh.v14i3.4668.

141. **Bejan** et al., *DrugWAS: Drug-wide Association Studies for COVID-19 Drug Repurposing*, Clinical Pharmacology & Therapeutics, doi:10.1002/cpt.2376.

142. **Carlucci** et al., *Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients*, J. Med. Microbiol., Sep 15, 2020, doi: 10.1099/jmm.0.001250 (preprint 5/8), www.microbiologyresearch.org/content/journal/jmm/10.1099/jmm.0.001250.

143. **Citu** et al., *Calcium, Magnesium, and Zinc Supplementation during Pregnancy: The Additive Value of Micronutrients on Maternal Immune Response after SARS-CoV-2 Infection*, Nutrients, doi:10.3390/nu14071445.

144. **Derwand (B)** et al., *COVID-19 Outpatients – Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2020.106214.

145. **Doğan** et al., *The Clinical Significance of Vitamin D and Zinc Levels with Respect to Immune Response in COVID-19 Positive Children*, Journal of Tropical Pediatrics, doi:10.1093/tropej/fmac072.

146. **Du Laing** et al., *Course and Survival of COVID-19 Patients with Comorbidities in Relation to the Trace Element Status at Hospital Admission*, Nutrients, doi:10.3390/nu13103304.

147. **Ekemen Keleş** et al., *Serum zinc levels in pediatric patients with COVID-19*, European Journal of Pediatrics, doi:10.1007/s00431-021-04348-w.

148. **Elavarasi** et al., *Clinical features, demography, and predictors of outcomes of SARS-CoV-2 infection at a tertiary care hospital in India: A cohort study*, Lung India, doi:10.4103/lungindia.lungindia_493_21.

149. **Fromonot** et al., *Hypozincemia in the early stage of COVID-19 is associated with an increased risk of severe COVID-19*, Clinical Nutrition, doi:10.1016/j.clnu.2021.04.042.

150. **Frontera** et al., *Treatment with Zinc is Associated with Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study*, Research Square, doi:10.21203/rs.3.rs-94509/v1.

151. **Fujita** et al., *Zinc deficiency is a potential risk factor for COVID-19 progression to pneumonia requiring oxygen therapy*, Journal of Infection and Chemotherapy, doi:10.1016/j.jiac.2024.03.007.

152. **Gonçalves** et al., *Association Between Low Zinc Levels and Severity of Acute Respiratory Distress Syndrome by New Coronavirus SARS-CoV-2*, Nutrition in Clinical Practice, doi:10.1002/ncp.10612.

153. **Gordon** et al., *A Case-Control Study for the Effectiveness of Oral Zinc in the Prevention and Mitigation of COVID-19*, Frontiers in Medicine, doi:10.3389/fmed.2021.756707.

154. **İşler** et al., *Evaluation of the Serum Zinc Level in Patients Followed in Hospital with the Diagnosis of COVID-19 in Samsun Province, Türkiye*, Life and Medical Sciences, doi:10.54584/lms.2023.39.

155. **Jiménez** et al., *Zinc Levels of Patients With A Moderate to Severe COVID-19 Infection at Hospital Admission and After 4th Days of Ward Hospitalization and Their Clinical Outcome*, Journal of Trace Elements in Medicine and Biology, doi:10.1016/j.jtemb.2023.127200.

156. **Jothimani** et al., *COVID-19: Poor outcomes in patients with zinc deficiency*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2020.09.014.

157. **academic.oup.com (C)**, academic.oup.com/ajcn/article/110/1/76/5510583.

158. **Arora (B)** et al., *Risk factors for Coronavirus disease-associated mucormycosis*, Journal of Infection, doi:10.1016/j.jinf.2021.12.039.

159. **Louca** et al., *Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app*, BMJ Nutrition, Prevention & Health, doi:10.1136/bmjnph-2021-000250.

160. **Mahto** et al., *Seroprevalence of IgG against SARS-CoV-2 and its determinants among healthcare workers of a COVID-19 dedicated hospital of India*, American Journal of Blood Research, 11:1, www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8010601/.

161. **Mayberry** et al., *Zinc use is associated with improved outcomes in COVID-19: results from the CRUSH-COVID registry*, Critical Care Medicine, doi:10.1097/01.ccm.0000807104.82650.d6.

162. **Milan** et al., *Factors Associated with Adverse Outcomes among SARS-CoV-2 Positive Children in a Tertiary Government COVID-19 Referral Hospital in the Philippines*, Acta Medica Philippina, doi:10.47895/amp.v58i7.8392.

163. **Nimer** et al., *The impact of vitamin and mineral supplements usage prior to COVID-19 infection on disease severity and hospitalization*, Bosnian Journal of Basic Medical Sciences, doi:10.17305/bjbms.2021.7009.

164. **Ramos** et al., *Vitamin D, Zinc and Iron in Adult Patients with Covid-19 and Their Action in the Immune Response as Biomarkers*, Global Journal of Health Science, doi:10.5539/gjhs.v14n1p1.

165. **Rozemeijer** et al., *Micronutrient Status of Critically Ill Patients with COVID-19 Pneumonia*, Nutrients, doi:10.3390/nu16030385.

166. **Sharif** et al., *Impact of Zinc, Vitamins C and D on Disease Prognosis among Patients with COVID-19 in Bangladesh: A Cross-Sectional Study*, Nutrients, doi:10.3390/nu14235029.

167. **patrickholford.com**, www.patrickholford.com/blog/vitamin-c-speeds-up-covid-recovery.

168. **Tomasa-Irriguible** et al., *Low Levels of Few Micronutrients May Impact COVID-19 Disease Progression: An Observational Study on the First Wave*, Metabolites, doi:10.3390/metabo11090565.

169. **Voelkle** et al., *Prevalence of Micronutrient Deficiencies in Patients Hospitalized with COVID-19: An Observational Cohort Study*, Nutrients, doi:10.3390/nu14091862.

170. **Vogel-González** et al., *Low Zinc Levels at Admission Associates with Poor Clinical Outcomes in SARS-CoV-2 Infection*, Nutrients, doi:10.3390/nu13020562.

171. **Wozniak** et al., *Association of Trace Element Levels with Outcomes in Critically Ill COVID-19 Patients*, Nutrients, doi:10.3390/nu15153308.

172. **Wu** et al., *The association between zinc deficiency, and clinical outcomes of COVID-19*, Journal of Infection, doi:10.1016/j.jinf.2023.06.021.

173. **Yao** et al., *The Minimal Effect of Zinc on the Survival of Hospitalized Patients With COVID-19*, Chest, doi:10.1016/j.chest.2020.06.082.

174. **ncbi.nlm.nih.gov (C)**, www.ncbi.nlm.nih.gov/pmc/articles/PMC7836617/.

175. **Yasui** et al., *Analysis of the predictive factors for a critical illness of COVID-19 during treatment — relationship between serum zinc level and critical illness of COVID-19*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2020.09.008.

176. **Zangeneh** et al., *Survival analysis based on body mass index in patients with Covid-19 admitted to the intensive care unit of Amir Al-Momenin Hospital in Arak – 2021*, Obesity Medicine, doi:10.1016/j.obmed.2022.100420.

177. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.

178. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.

179. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.

180. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.

181. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.