Curcumin for COVID-19: real-time meta analysis of 26 studies

@CovidAnalysis, March 2024, Version 42

https://c19early.org/tmeta.html

Abstract

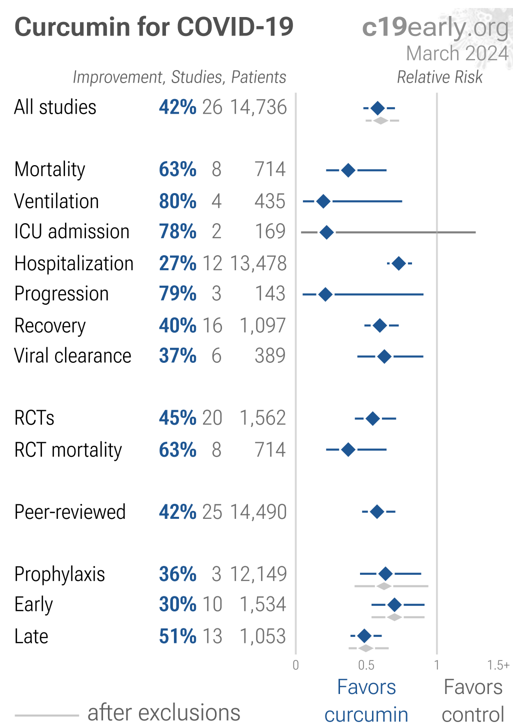
Statistically significant lower risk is seen for mortality, ventilation, hospitalization, progression, recovery, and viral clearance. 18 studies from 16 independent teams in 8 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 42% [30-52%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies.

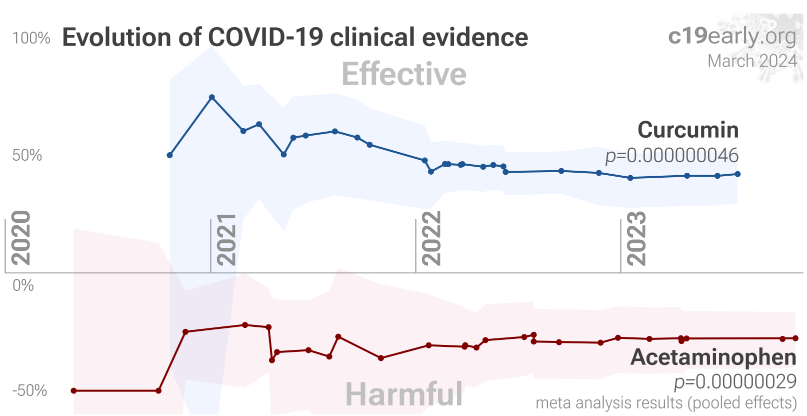
Results are robust — in exclusion sensitivity analysis 24 of 26 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Studies typically use advanced formulations for greatly improved bioavailability.

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 may be more effective. The quality of non-prescription supplements can vary widely Crawford, Crighton.



All data to reproduce this paper and sources are in the appendix. Other meta analyses show significant improvements with curcumin for mortality Kow, Shafiee, Shojaei, Vahedian-Azimi, hospitalization Shojaei, Vahedian-Azimi, recovery Shafiee, and symptoms Vahedian-Azimi.



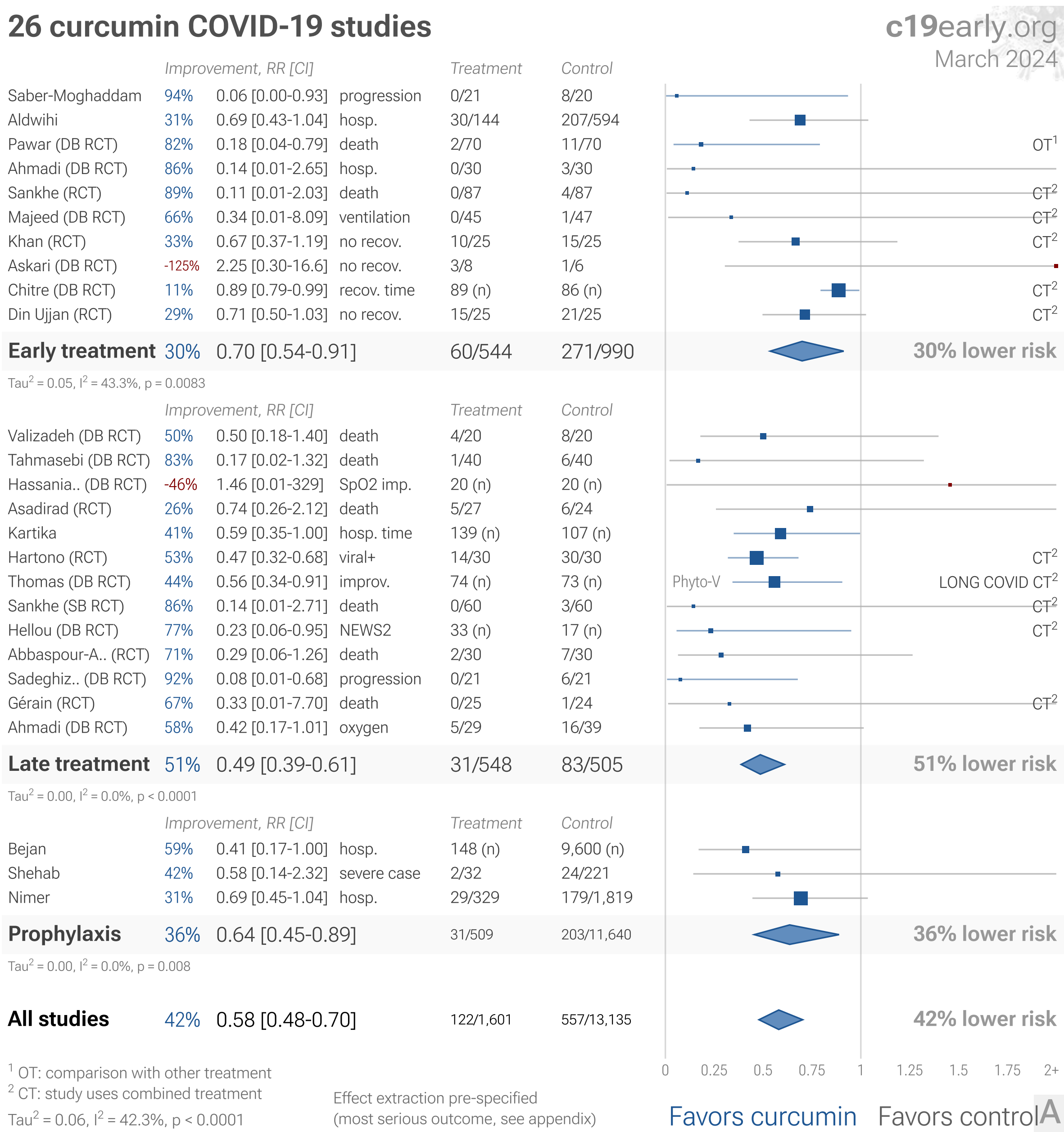
HIGHLIGHTS

Curcumin reduces risk for COVID-19 with very high confidence for mortality, hospitalization, recovery, and in pooled analysis, high confidence for ventilation, progression, and viral clearance, and low confidence for ICU admission. Studies typically use advanced formulations for greatly improved bioavailability.

Curcumin was the 15th treatment shown effective with ≥3 clinical studies in February 2021, now known with p = 0.000000046 from 26 studies.

We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.



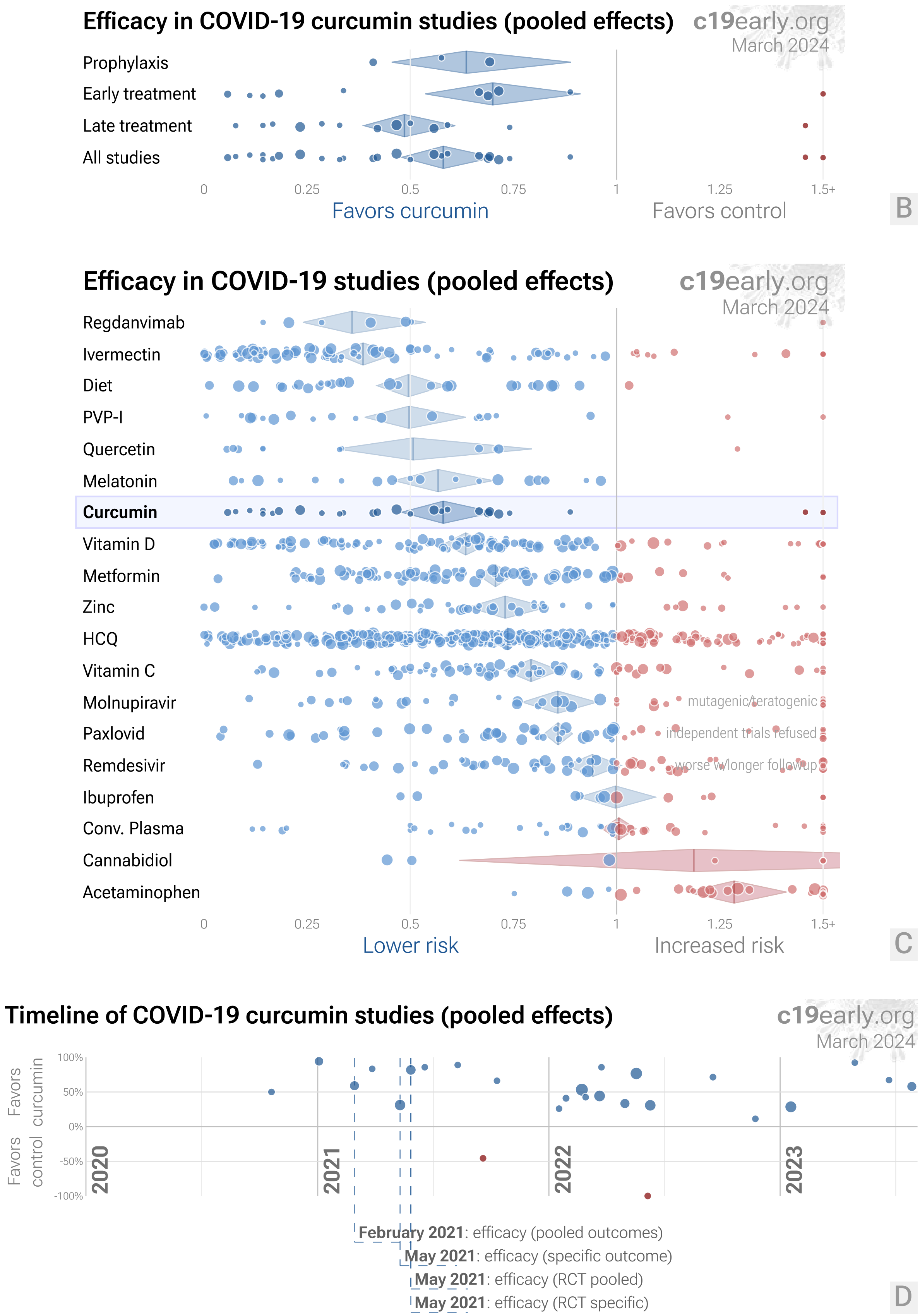


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. 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. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. Timeline of**

results in curcumin 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, pooled outcomes in RCTs, and one or more specific outcome in RCTs. Efficacy based on RCTs only was delayed by 2.9 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 2.4 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 issues [Scardua-Silva, Yang], cardiovascular complications [Eberhardt], 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 [Note A, Malone, Murigneux, Lv, Lui], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk [c19early.org (B)], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research. *In Silico* studies predict inhibition of SARS-CoV-2 with curcumin or metabolites via binding to the spike [Note B, Nag, Moschovou, Kandeil, Singh] (and specifically the receptor binding domain [Note C, Kant, Srivastava, Eleraky]), M^{pro} [Note D, Moschovou, Kandeil, Srivastava, Naderi Beni, Rajagopal, Rampogu, Sekiou, Singh (B), Winih Kinasih, Thapa, Bahun, Eleraky], RNA-dependent RNA polymerase [Note E, Singh (C), Eleraky], ACE2 [Note F, Singh, Thapa, Alkafaas], nucleocapsid [Note G, Hidayah, Suravajhala], and nsp10 [Note H, Suravajhala] proteins. *In Vitro* studies demonstrate inhibition of the spike [Note B, Mohd Abd Razak] (and specifically the receptor binding domain [Note C, Goc]), M^{pro} [Note D, Bahun, Guijarro-Real, Mohd Abd Razak, Wu], ACE2 [Note F, Goc], and TMPRSS2 [Note I, Goc] proteins. *In Vitro* studies demonstrate efficacy in Calu-3 [Note J, Bormann], A549 [Note K, Mohd Abd Razak], 293T [Note L, Zhang], HEK293-hACE2 [Note M, Nittayananta, Wu], 293T/hACE2/TMPRSS2 [Note N, Septisetyani], and Vero E6 [Note O, Bormann, Eleraky, Kandeil, Leka, Mohd Abd Razak, Nittayananta, Singh (B), Teshima, Marín-Palma] cells. Curcumin is predicted to inhibit the interaction between the SARS-CoV-2 spike protein receptor binding domain and the human ACE2 receptor for the delta and omicron variants [Kant], decreases pro-inflammatory cytokines induced by SARS-CoV-2 in peripheral blood mononuclear cells [Marín-Palma], and alleviates SARS-CoV-2 spike protein-induced mitochondrial membrane damage and oxidative stress [Zhang].

Analysis. We analyze all significant controlled studies of curcumin 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.

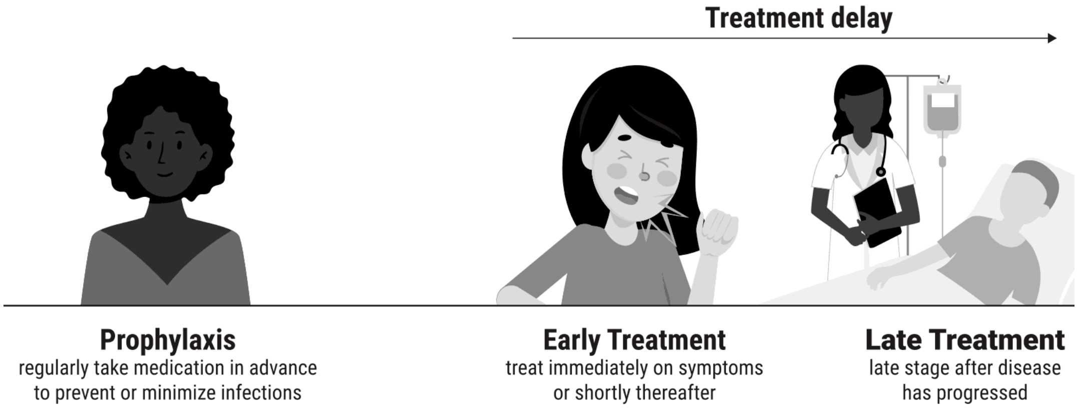


Figure 2. Treatment stages.

Mechanisms of Action

Table 1 shows potential mechanisms of action for the treatment of COVID-19 using curcumin.

3CL^{pro} inhibitor	Curcumin inhibits SARS-CoV-2 3CL^{pro} *Bahun, Eleraky, Guijarro-Real, Kandeil, Mohd Abd Razak, Moschovou, Naderi Beni, Rajagopal, Rampogu, Sekiou, Singh (B), Srivastava, Thapa, Winih Kinasih, Wu*.
RdRp inhibitor	SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) inhibition *Eleraky, Singh (C)*.
ACE2 inhibitor	Curcumin inhibits ACE2 activity. SARS-CoV-2 viral entry requires host cell surface proteins ACE2 and TMPRSS2 *Jena, Patel*.
TMPRSS2 downregulation	Curcumin downregulates transmembrane serine protease 2 (TMPRSS2). SARS-CoV-2 viral entry requires host cell surface proteins ACE2 and TMPRSS2 *Goc*.
Cathepsin L inhibitor	Curcumin inhibits cathepsin L activity. Cathepsin L plays a key role in viral entry *Goc*.
Anti-inflammatory	Curcumin shows anti-inflammatory effects *Daily, Derosa, Gupta, Marín-Palma, Rattis, Sahebkar*.
Inhibition in Vero E6 cells demonstrated	*In Vitro* research shows curcumin inhibits SARS-CoV-2 in Vero E6 cells *Bormann, Eleraky, Kandeil, Leka, Marín-Palma, Mohd Abd Razak, Nittayananta, Singh (B), Teshima*.
Inhibition in Calu-3 cells demonstrated	*In Vitro* research shows curcumin inhibits SARS-CoV-2 in Calu-3 cells *Bormann*.

Table 1. Curcumin mechanisms of action.

Preclinical Research

In Silico studies predict inhibition of SARS-CoV-2 with curcumin or metabolites via binding to the spike *Note B, Nag, Moschovou, Kandeil, Singh* (and specifically the receptor binding domain *Note C, Kant, Srivastava, Eleraky*), M^{pro} *Note D, Moschovou, Kandeil, Srivastava, Naderi Beni, Rajagopal, Rampogu, Sekiou, Singh (B), Winih Kinasih, Thapa, Bahun, Eleraky*, RNA-dependent RNA polymerase *Note E, Singh (C), Eleraky*, ACE2 *Note F, Singh, Thapa, Alkafaas*, nucleocapsid *Note G, Hidayah, Suravajhala*, and nsp10 *Note H, Suravajhala* proteins. *In Vitro* studies demonstrate inhibition of the spike *Note B, Mohd Abd Razak* (and specifically the receptor binding domain [Note C, Goc]), M^{pro} [Note D, Bahun, Guijarro-Real, Mohd Abd Razak, Wu], ACE2 [Note F, Goc], and TMPRSS2 [Note I, Goc] proteins. *In Vitro* studies demonstrate efficacy in Calu-3 [Note J, Bormann], A549 [Note K, Mohd Abd Razak], 293T [Note L, Zhang], HEK293-hACE2 [Note M, Nittayananta, Wu], 293T/hACE2/TMPRSS2 [Note N, Septisetyani], and Vero E6 [Note O, Bormann, Eleraky, Kandeil, Leka, Mohd Abd Razak, Nittayananta, Singh (B), Teshima, Marín-Palma] cells. Curcumin is predicted to inhibit the interaction between the SARS-CoV-2 spike protein receptor binding domain and the human ACE2 receptor for the delta and omicron variants [Kant], decreases pro-inflammatory cytokines induced by SARS-CoV-2 in peripheral blood mononuclear cells [Marín-Palma], and alleviates SARS-CoV-2 spike protein-induced mitochondrial membrane damage and oxidative stress [Zhang].

20 *In Silico* studies support the efficacy of curcumin [Alkafaas, Eleraky, Hidayah, Kandeil, Kant, Moschovou, Naderi Beni, Nag, Rajagopal, Rampogu, Sekiou, Singh, Singh (B), Singh (C), Srivastava, Suravajhala, Thapa, Winih Kinasih, Wu, Zhang].

16 *In Vitro* studies support the efficacy of curcumin [Bahun, Bormann, Eleraky, Goc, Goc (B), Guijarro-Real, Kandeil, Leka, Marín-Palma, Mohd Abd Razak, Nittayananta, Septisetyani, Singh (B), Teshima, Wu, Zhang].

2 studies investigate novel formulations of curcumin that may be more effective for COVID-19 [Eleraky, Panda].

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 2 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 3 shows results by treatment stage. Figure 3, 4, 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, viral clearance, and peer reviewed studies.

	Improvement	Studies	Patients	Authors
All studies	42% [30-52%] ****	26	14,736	225
After exclusions	40% [27-50%] ****	24	14,423	205
Peer-reviewed studies	42% [29-53%] ****	25	14,490	219
Randomized Controlled Trials	45% [29-58%] ****	20	1,562	185
Mortality	63% [36-78%] ***	8	714	83
Ventilation	80% [25-95%] *	4	435	30
ICU admission	78% [-27-96%]	2	169	18
Hospitalization	27% [18-35%] ****	12	13,478	92
Recovery	40% [27-51%] ****	16	1,097	140
Viral	37% [10-56%] *	6	389	46
RCT mortality	63% [36-78%] ***	8	714	83
RCT hospitalization	20% [9-29%] ***	7	557	59

Table 2. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the 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	**30%** [9-46%] **	**51%** [39-61%] ****	**36%** [11-55%] **
After exclusions	**30%** [9-46%] **	**50%** [34-63%] ****	**37%** [6-58%] *
Peer-reviewed studies	**30%** [9-46%] **	**54%** [40-64%] ****	**36%** [11-55%] **
Randomized Controlled Trials	**27%** [2-46%] *	**54%** [40-64%] ****	
Mortality	**84%** [39-96%] **	**56%** [19-76%] **	
Ventilation	**72%** [-65-95%]	**88%** [3-98%] *	
ICU admission		**78%** [-27-96%]	
Hospitalization	**30%** [7-48%] *	**24%** [13-34%] ***	**37%** [6-58%] *
Recovery	**30%** [15-43%] ***	**58%** [37-72%] ****	
Viral	**36%** [-26-67%]	**43%** [22-58%] ***	
RCT mortality	**84%** [39-96%] **	**56%** [19-76%] **	
RCT hospitalization	**32%** [-69-73%]	**22%** [10-33%] ***	

Table 3. **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.

26 curcumin COVID-19 studies

c19early.org
March 2024

Study	Improvement	RR [CI]	Outcome	Treatment	Control	Note
Saber-Moghaddam	94%	0.06 [0.00-0.93]	progression	0/21	8/20	
Aldwihi	31%	0.69 [0.43-1.04]	hosp.	30/144	207/594	
Pawar (DB RCT)	82%	0.18 [0.04-0.79]	death	2/70	11/70	OT[1]
Ahmadi (DB RCT)	86%	0.14 [0.01-2.65]	hosp.	0/30	3/30	
Sankhe (RCT)	89%	0.11 [0.01-2.03]	death	0/87	4/87	CT[2]
Majeed (DB RCT)	66%	0.34 [0.01-8.09]	ventilation	0/45	1/47	CT[2]
Khan (RCT)	33%	0.67 [0.37-1.19]	no recov.	10/25	15/25	CT[2]
Askari (DB RCT)	-125%	2.25 [0.30-16.6]	no recov.	3/8	1/6	
Chitre (DB RCT)	11%	0.89 [0.79-0.99]	recov. time	89 (n)	86 (n)	CT[2]
Din Ujjan (RCT)	29%	0.71 [0.50-1.03]	no recov.	15/25	21/25	CT[2]
Early treatment	30%	0.70 [0.54-0.91]		60/544	271/990	30% lower risk

Tau^2 = 0.05, I^2 = 43.3%, p = 0.0083

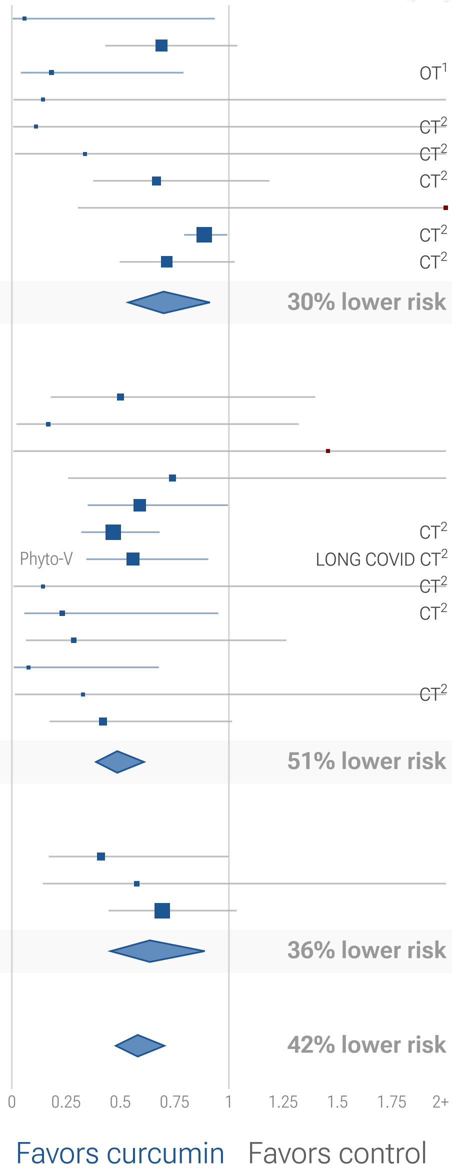
Study	Improvement	RR [CI]	Outcome	Treatment	Control	Note
Valizadeh (DB RCT)	50%	0.50 [0.18-1.40]	death	4/20	8/20	
Tahmasebi (DB RCT)	83%	0.17 [0.02-1.32]	death	1/40	6/40	
Hassania.. (DB RCT)	-46%	1.46 [0.01-329]	SpO2 imp.	20 (n)	20 (n)	
Asadirad (RCT)	26%	0.74 [0.26-2.12]	death	5/27	6/24	
Kartika	41%	0.59 [0.35-1.00]	hosp. time	139 (n)	107 (n)	
Hartono (RCT)	53%	0.47 [0.32-0.68]	viral+	14/30	30/30	CT[2]
Thomas (DB RCT)	44%	0.56 [0.34-0.91]	improv.	74 (n)	73 (n)	Phyto-V, LONG COVID CT[2]
Sankhe (SB RCT)	86%	0.14 [0.01-2.71]	death	0/60	3/60	CT[2]
Hellou (DB RCT)	77%	0.23 [0.06-0.95]	NEWS2	33 (n)	17 (n)	CT[2]
Abbaspour-A.. (RCT)	71%	0.29 [0.06-1.26]	death	2/30	7/30	
Sadeghiz.. (DB RCT)	92%	0.08 [0.01-0.68]	progression	0/21	6/21	
Gérain (RCT)	67%	0.33 [0.01-7.70]	death	0/25	1/24	CT[2]
Ahmadi (DB RCT)	58%	0.42 [0.17-1.01]	oxygen	5/29	16/39	
Late treatment	51%	0.49 [0.39-0.61]		31/548	83/505	51% lower risk

Tau^2 = 0.00, I^2 = 0.0%, p < 0.0001

Study	Improvement	RR [CI]	Outcome	Treatment	Control	Note
Bejan	59%	0.41 [0.17-1.00]	hosp.	148 (n)	9,600 (n)	
Shehab	42%	0.58 [0.14-2.32]	severe case	2/32	24/221	
Nimer	31%	0.69 [0.45-1.04]	hosp.	29/329	179/1,819	
Prophylaxis	36%	0.64 [0.45-0.89]		31/509	203/11,640	36% lower risk

Tau^2 = 0.00, I^2 = 0.0%, p = 0.008

All studies	42%	0.58 [0.48-0.70]		122/1,601	557/13,135	42% lower risk



[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
Tau^2 = 0.06, I^2 = 42.3%, p < 0.0001

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

Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

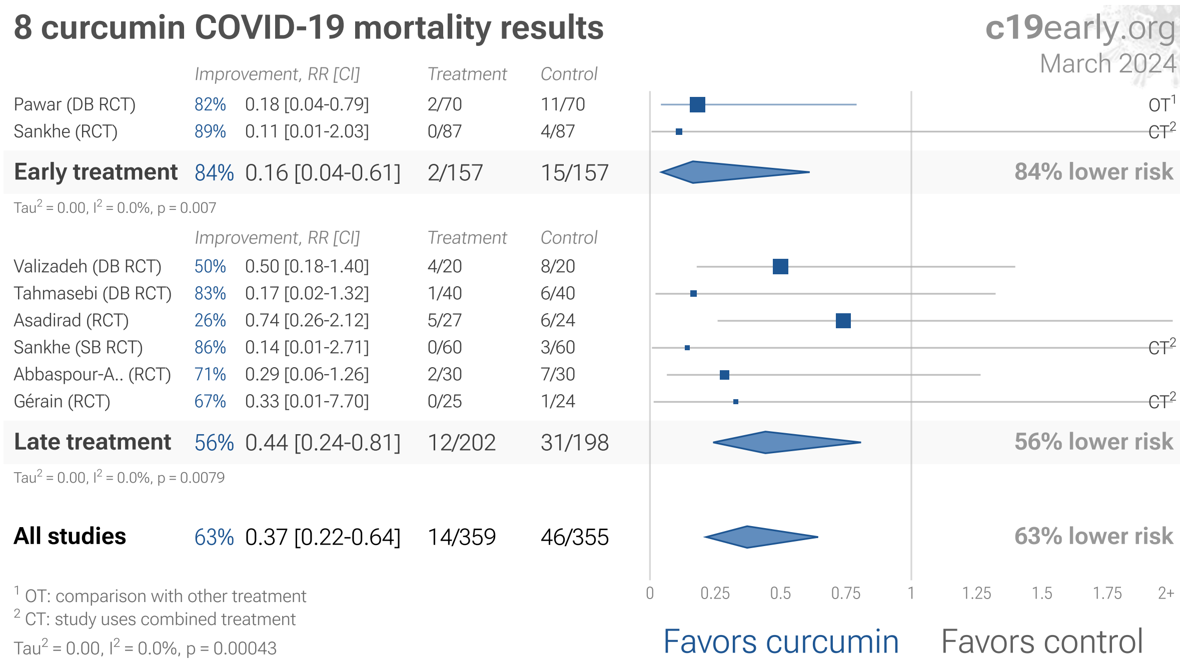


Figure 4. Random effects meta-analysis for mortality results.

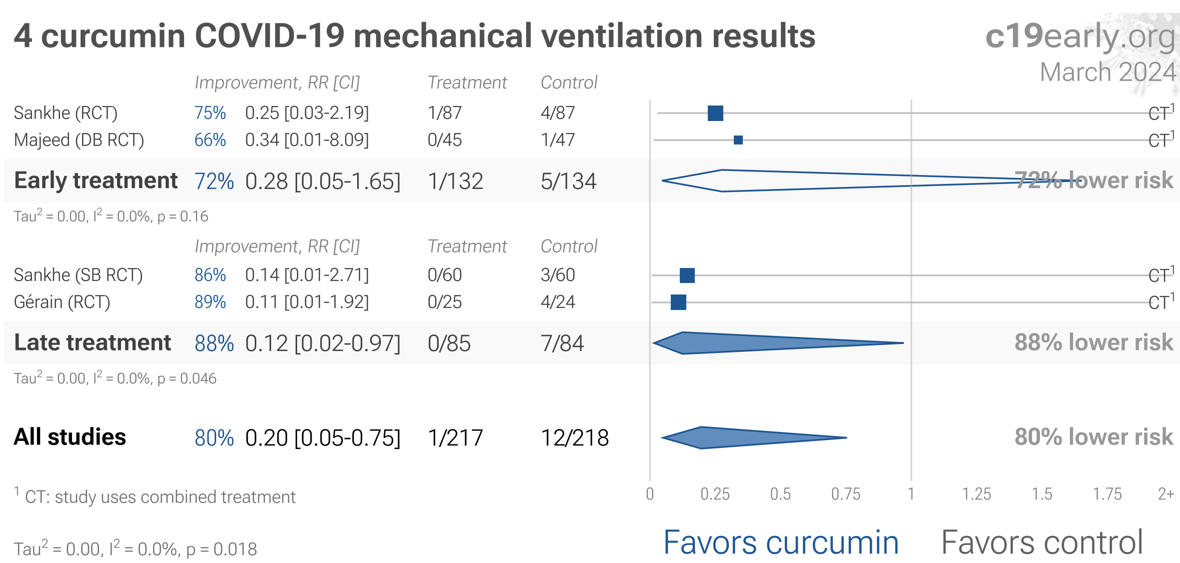


Figure 5. Random effects meta-analysis for ventilation.

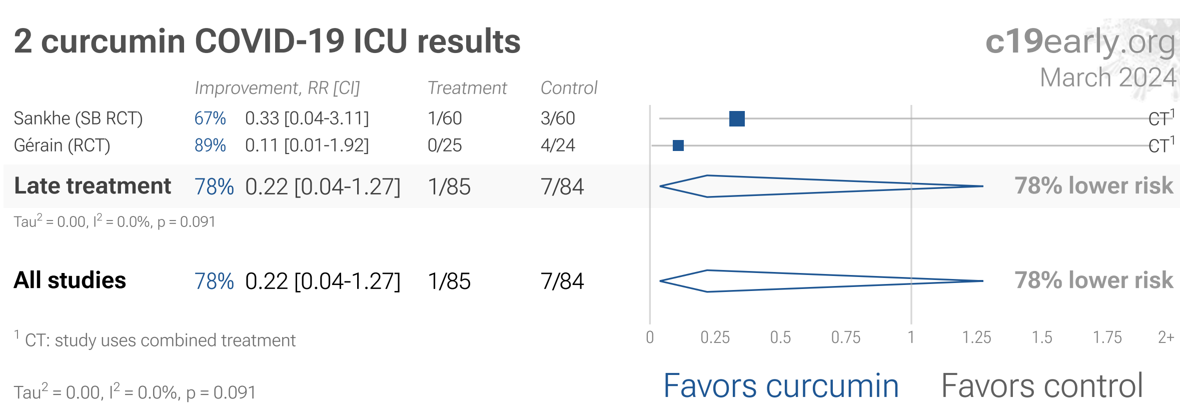


Figure 6. Random effects meta-analysis for ICU admission.

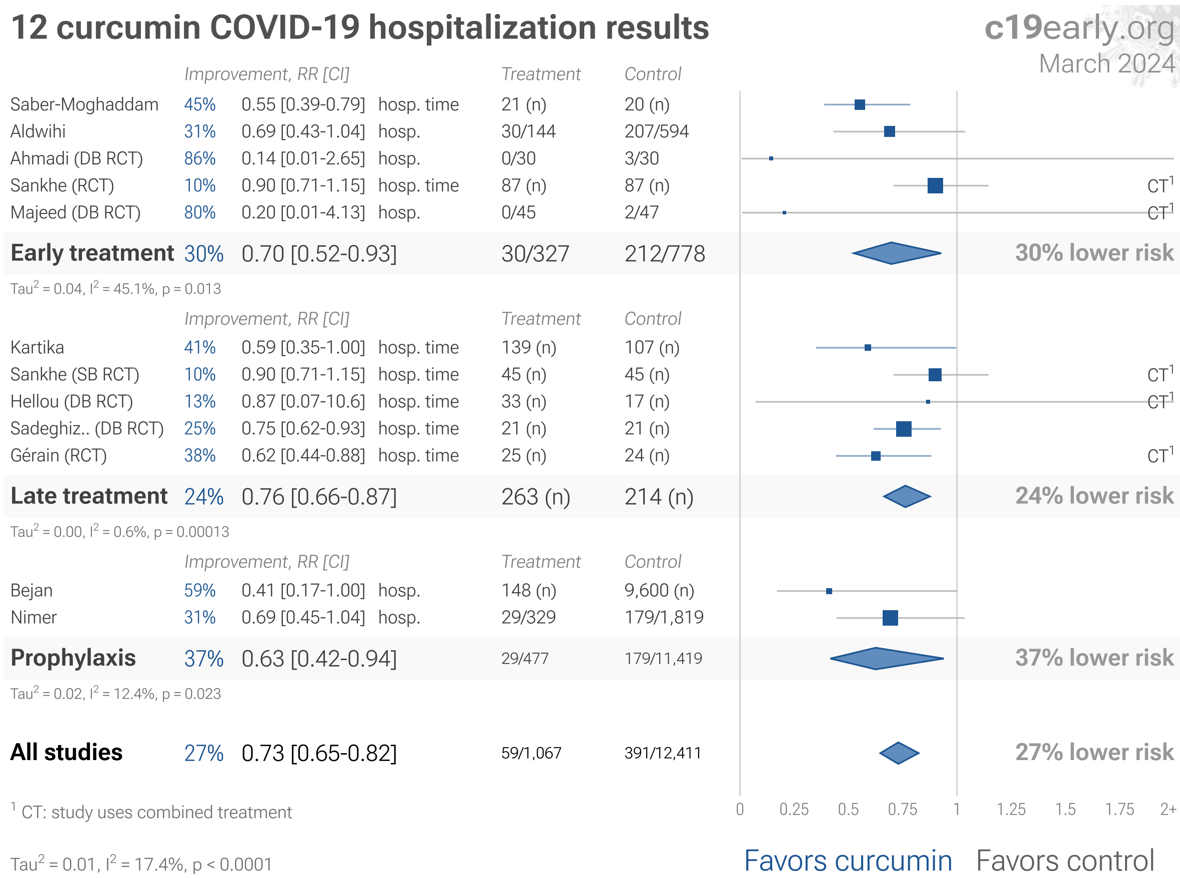


Figure 7. Random effects meta-analysis for hospitalization.

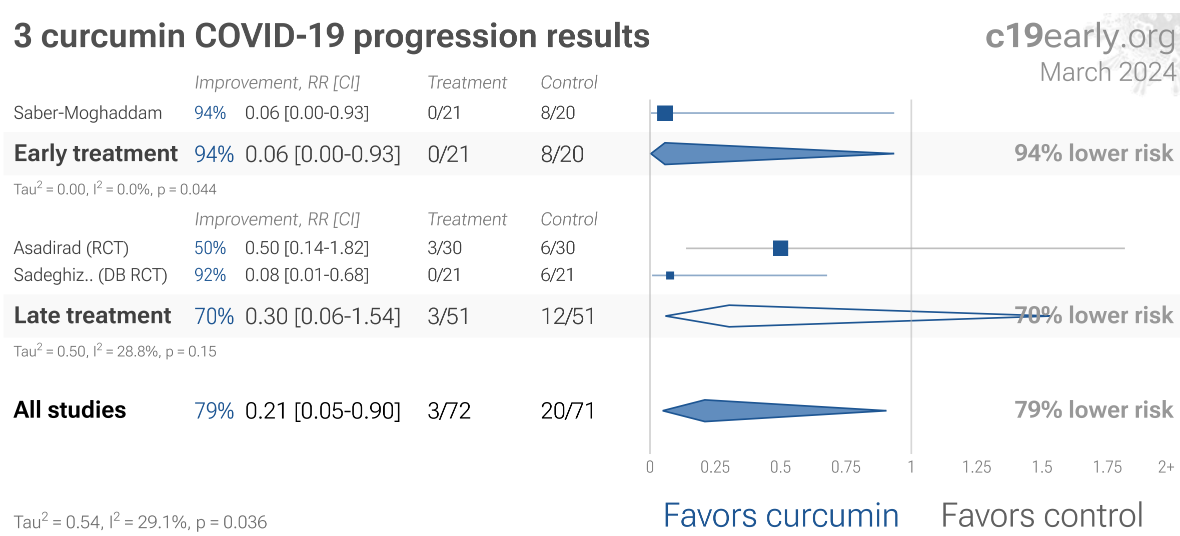


Figure 8. Random effects meta-analysis for progression.

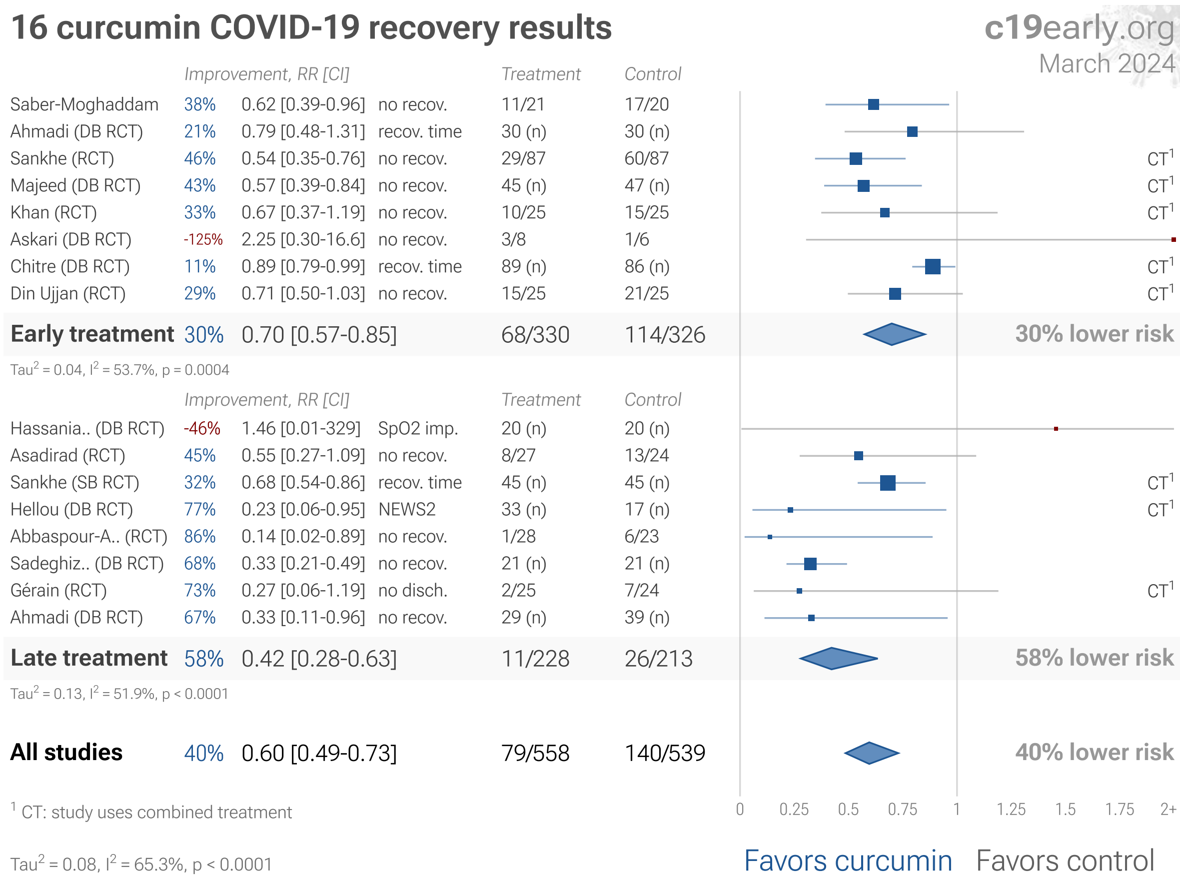


Figure 9. Random effects meta-analysis for recovery.

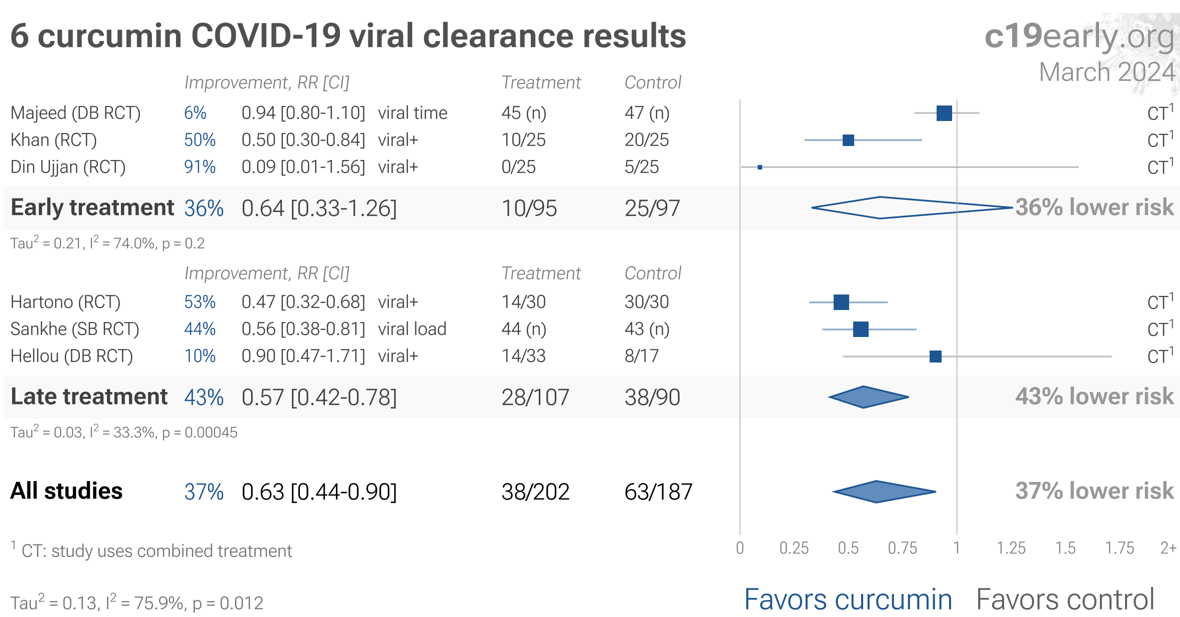


Figure 10. Random effects meta-analysis for viral clearance.

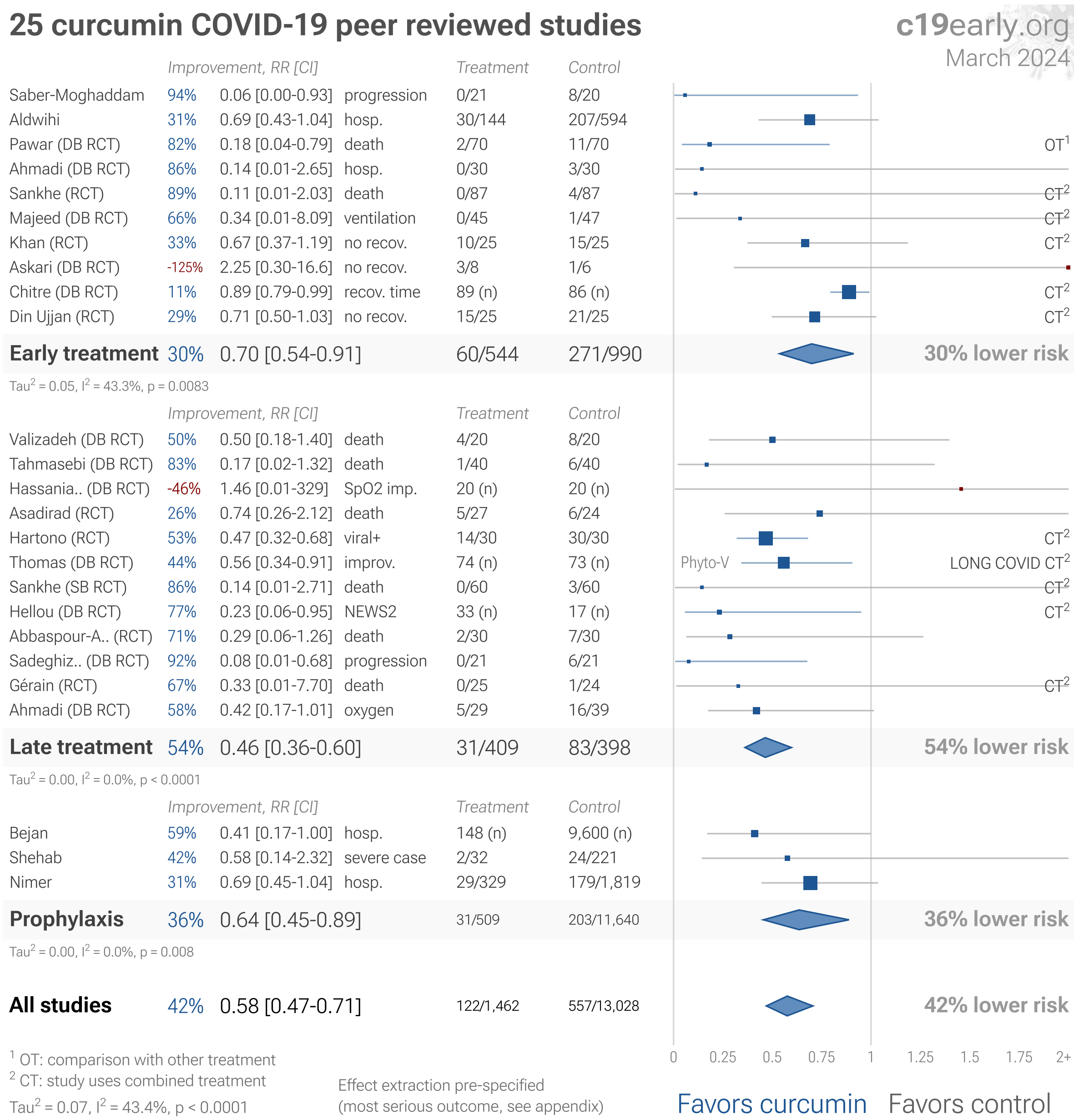


Figure 11. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with 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.

Randomized Controlled Trials (RCTs)

Figure 12 shows a comparison of results for RCTs and non-RCT studies. The median effect size for RCTs is 62% improvement, compared to 42% for other studies. Figure 13, 14, and 15 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 2 and Table 3.

RCTs have many potential biases. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases [Jadad], and analysis of double-blind RCTs has identified extreme levels of bias *Gøtzsche*. 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, 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 66 treatments we have analyzed, 63% 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 trials 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 could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see *Deaton, Nichol*.

Using all studies identifies efficacy 5.7+ months faster for COVID-19. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 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.

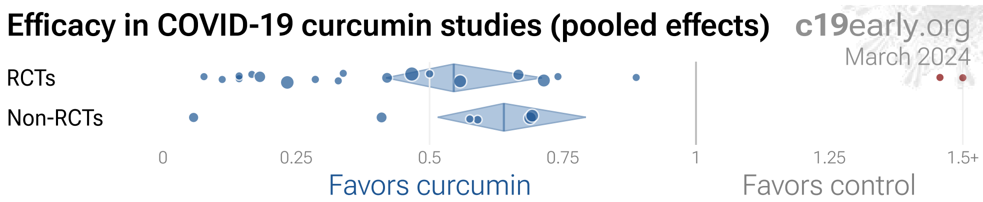


Figure 12. **Results for RCTs and non-RCT studies.**

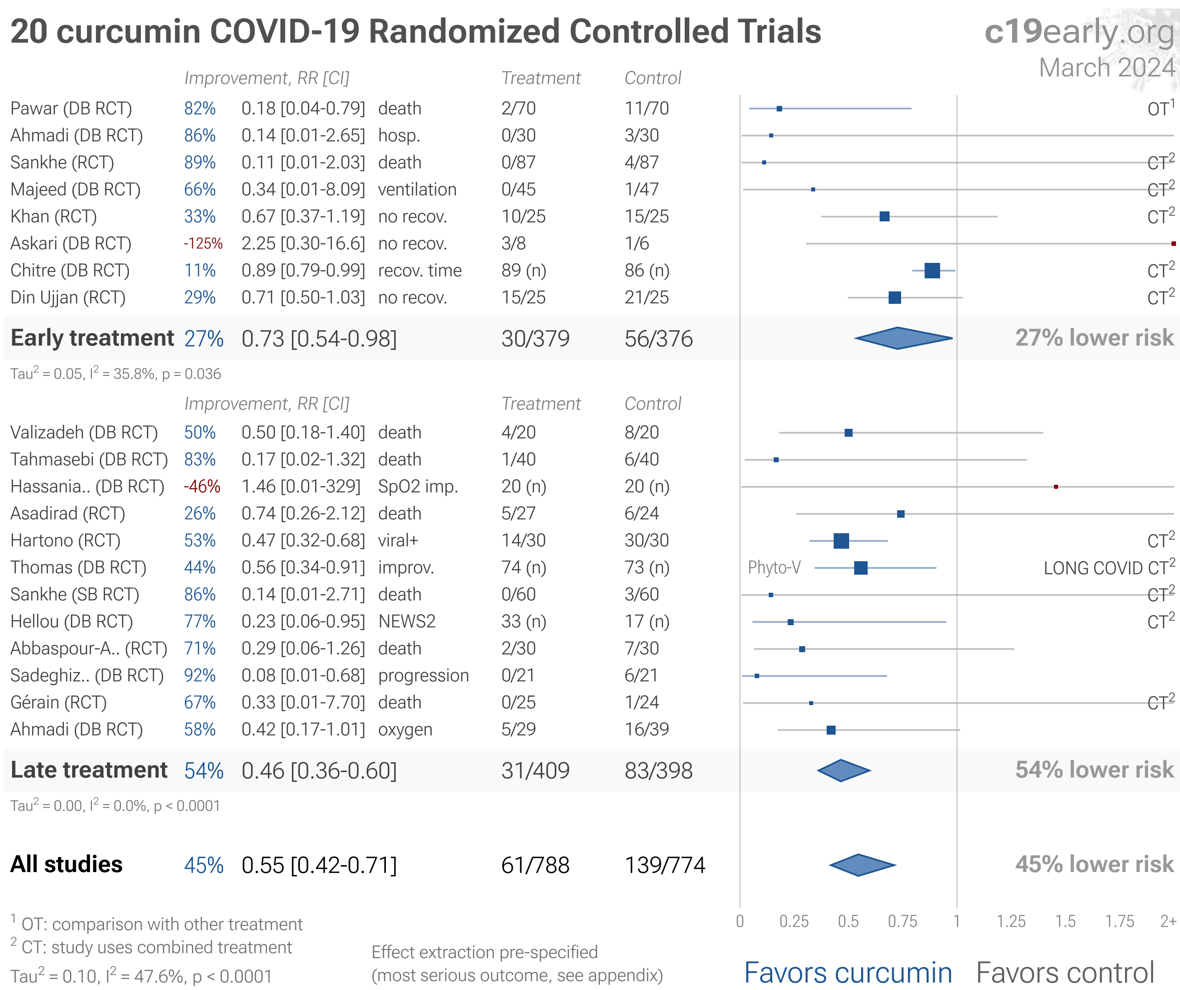


Figure 13. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

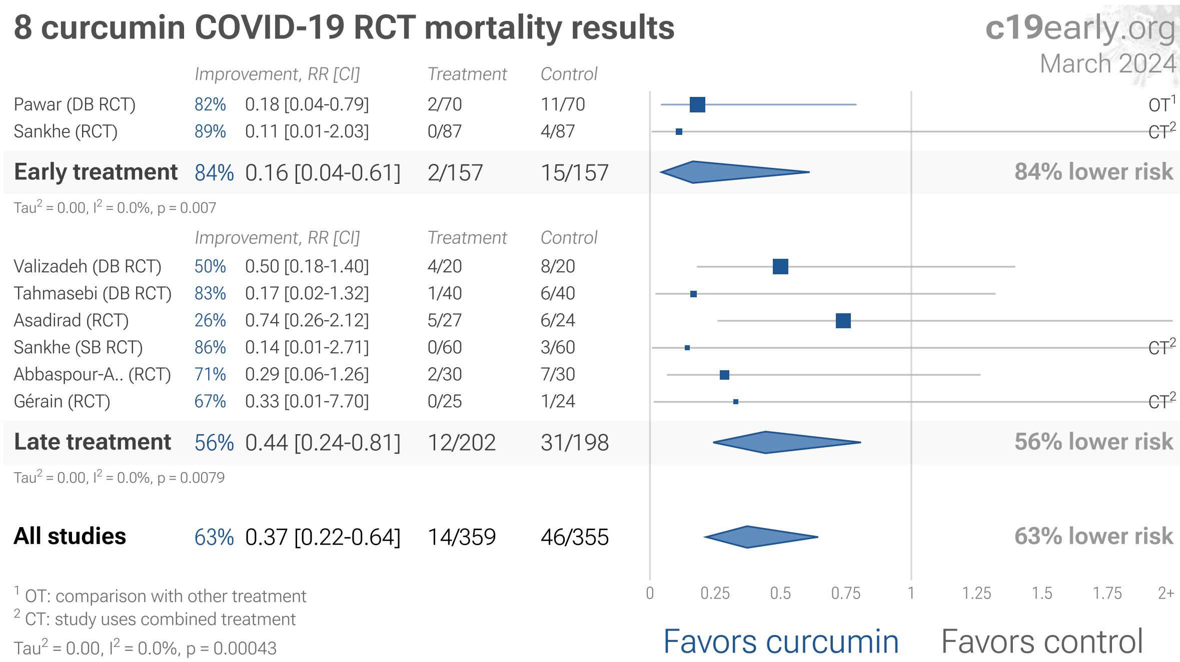


Figure 14. **Random effects meta-analysis for RCT mortality results.**

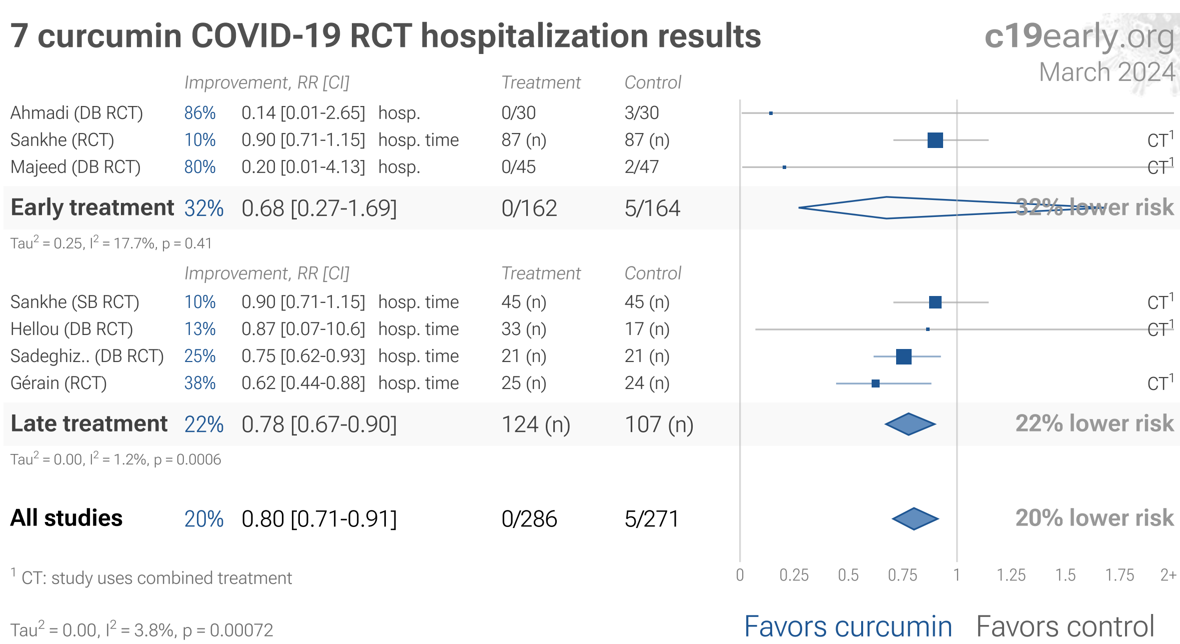


Figure 15. **Random effects meta-analysis for RCT hospitalization results.**

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 may underemphasize serious issues not captured in the checklists, overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size), and can be easily influenced by potential bias.

The studies excluded are as below. Figure 16 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Hartono, randomization resulted in significant baseline differences that were not adjusted for.

Shehab, unadjusted results with no group details.

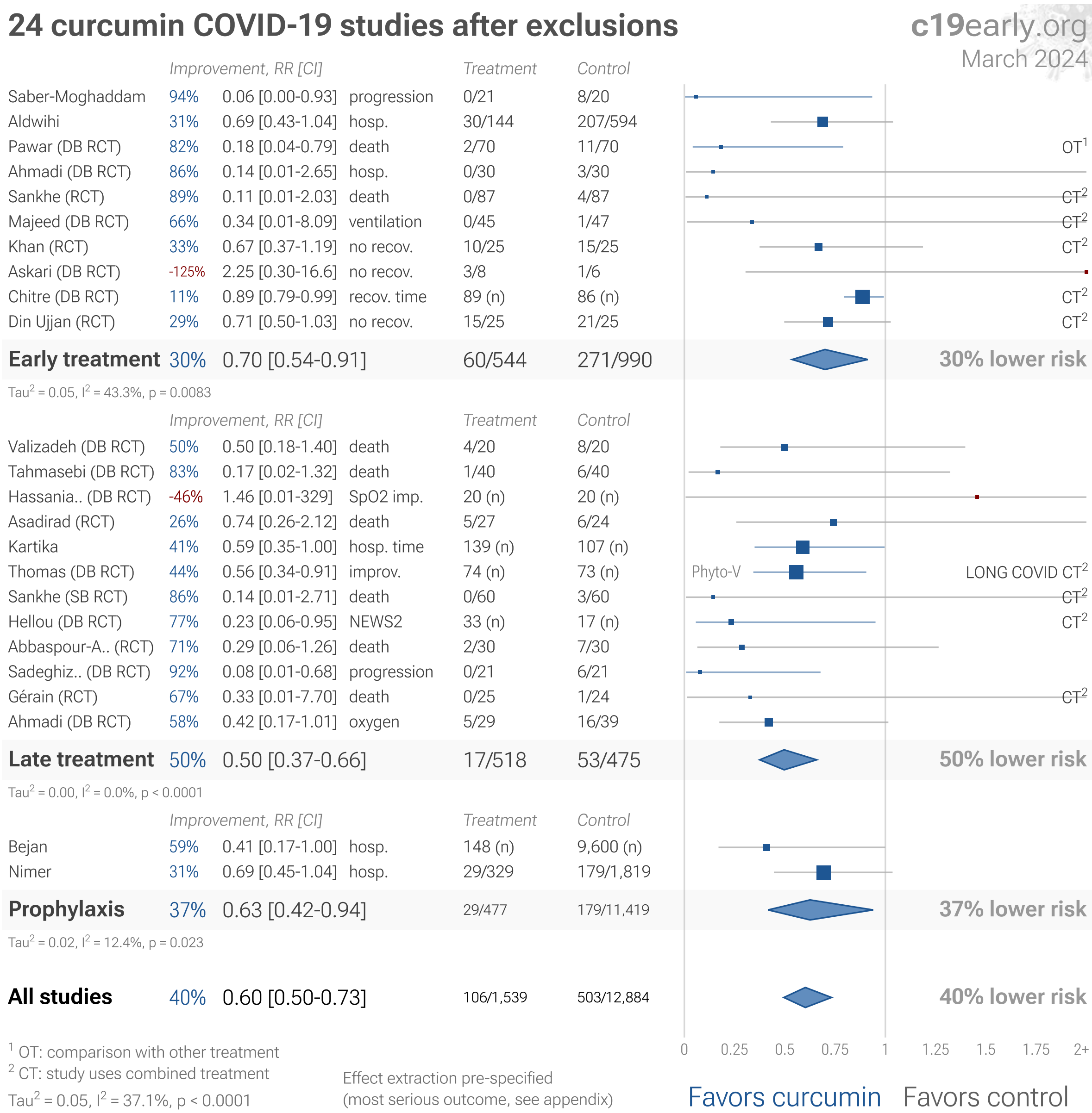


Figure 16. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction 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 McLean, Treanor. Baloxavir studies for influenza also show that treatment delay is critical

— *Ikematsu* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* 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* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post exposure prophylaxis	86% fewer cases *Ikematsu*
<24 hours	-33 hours symptoms *Hayden*
24-48 hours	-13 hours symptoms *Hayden*
Inpatients	-2.5 hours to improvement *Kumar*

Table 4. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 17 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

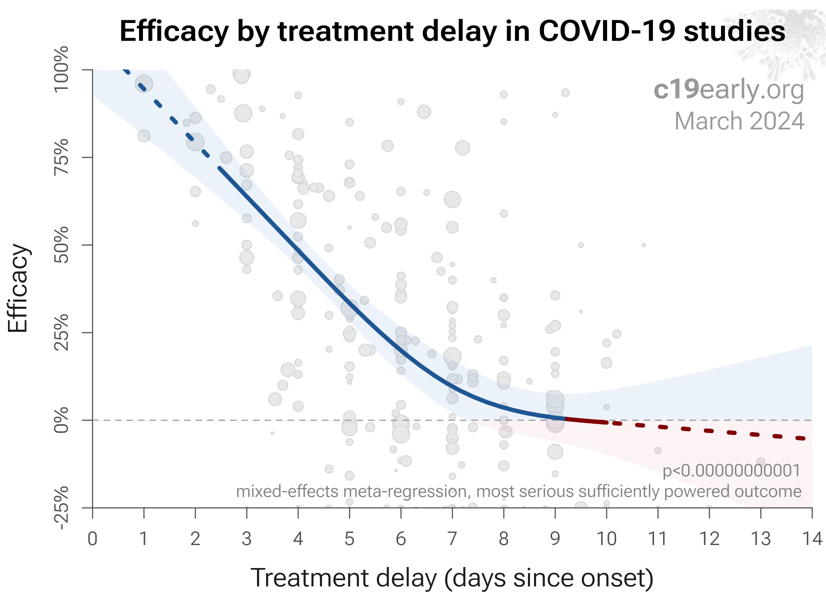


Figure 17. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 (as in *López-Medina*).

Effect measured. Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

Variants. There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics *Faria, Karita, Nonaka, Zavascki*. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective *Peacock, Willett*.

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

Other treatments. The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

Medication quality. The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu* 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 *Crawford, Crighton*.

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 18. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral replication or early stage disease could show no efficacy in pooled analysis if most studies only examine viral clearance. While we present pooled results, we also present individual outcome analyses, which may be more informative for specific use cases.

Pooled outcomes identify efficacy faster. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

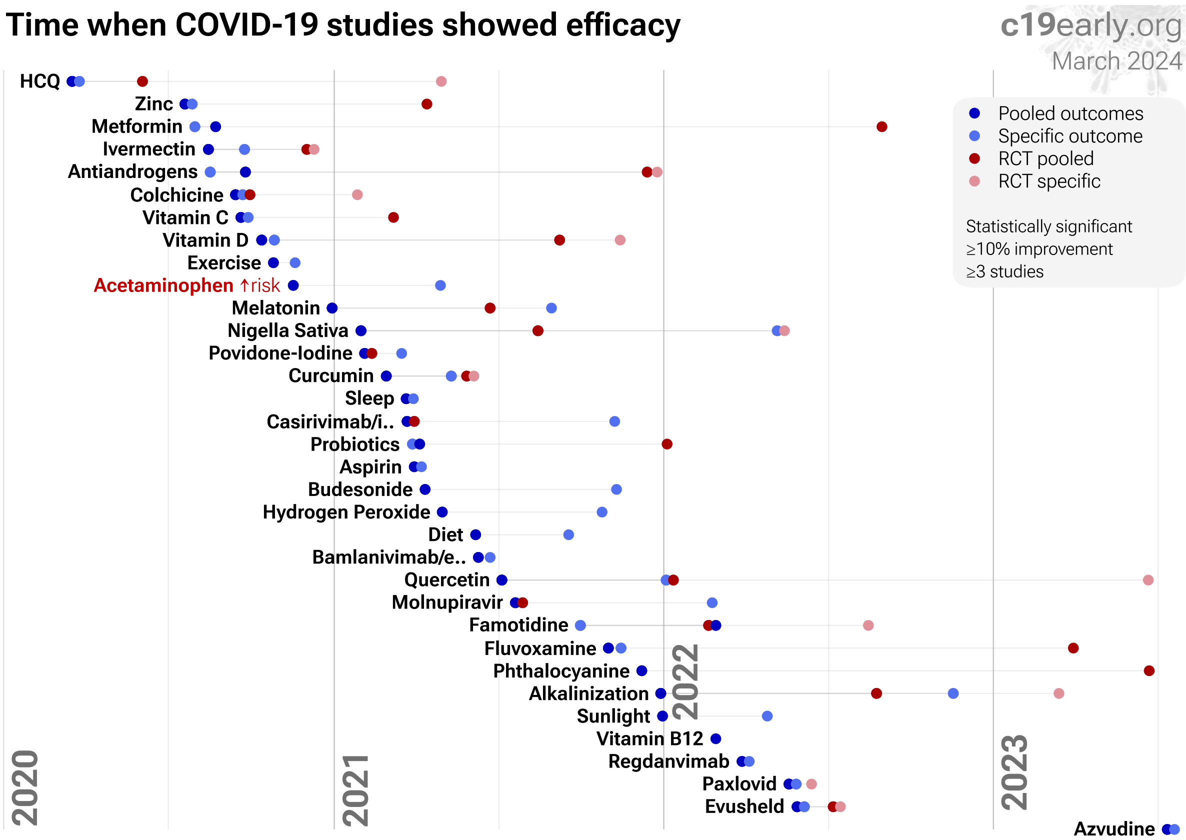


Figure 18. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

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.

Discussion

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 Boulware, Meeus, Meneguesso. For curcumin, there is currently not enough data to evaluate publication bias with high confidence.

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 19 shows a scatter plot of results for prospective and retrospective studies. 40% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 76% of prospective studies, consistent with a bias toward publishing negative results. The median effect size for retrospective studies is 41% improvement, compared to 66% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

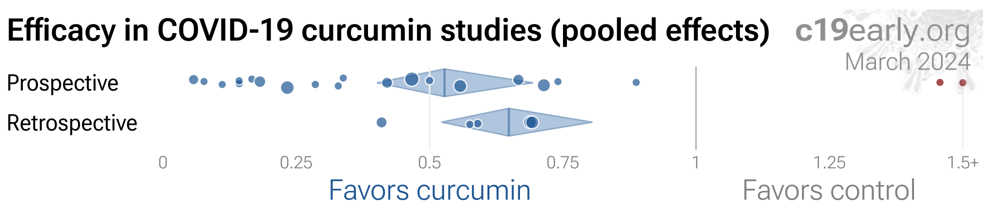


Figure 19. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 20 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 Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley. 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.

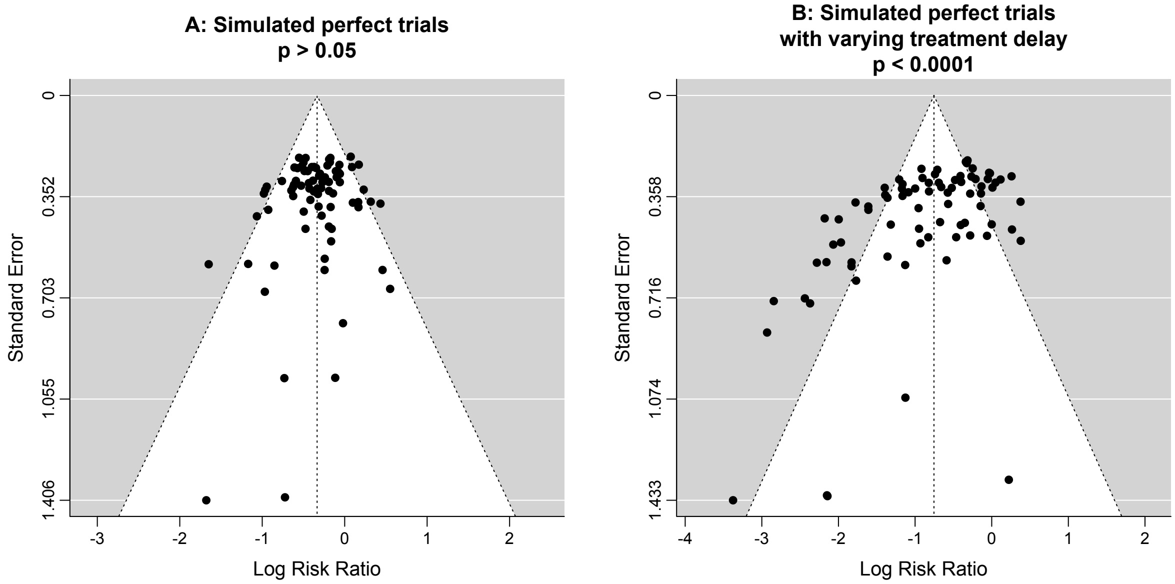


Figure 20. **Example funnel plot analysis for simulated perfect trials.**

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

Limitations. Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses by 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 affiliated with special interests 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 [*Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*]. 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, vaccine, 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 26 studies compare against other treatments, which may reduce the effect seen. 10 of 26 studies combine treatments. The results of curcumin alone may differ. 10 of 20 RCTs use combined treatment. Other meta analyses show significant improvements with curcumin for mortality [Kow, Shafiee, Shojaei, Vahedian-Azimi], hospitalization [Shojaei, Vahedian-Azimi], recovery [Shafiee], and symptoms [Vahedian-Azimi].

Reviews. Many reviews cover curcumin for COVID-19, presenting additional background on mechanisms, formulations, and related results, including [Arab, Daskou, Halma, Hegde, Hulscher, Kritis, Law, Rattis].

Conclusion

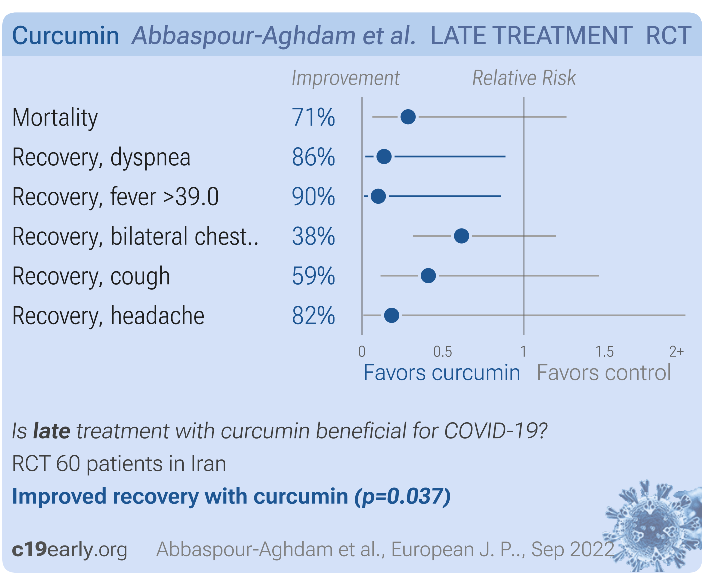
Curcumin is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, ventilation, hospitalization, progression, recovery, and viral clearance. 18 studies from 16 independent teams in 8 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 42% [30‑52%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Results are robust — in exclusion sensitivity analysis 24 of 26 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Studies typically use advanced formulations for greatly improved bioavailability.

Other meta analyses show significant improvements with curcumin for mortality [Kow, Shafiee, Shojaei, Vahedian-Azimi], hospitalization [Shojaei, Vahedian-Azimi], recovery [Shafiee], and symptoms [Vahedian-Azimi].

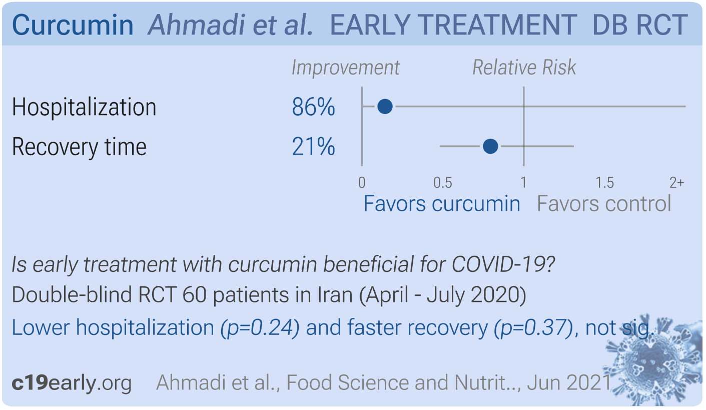
Study Notes

Abbaspour-Aghdam



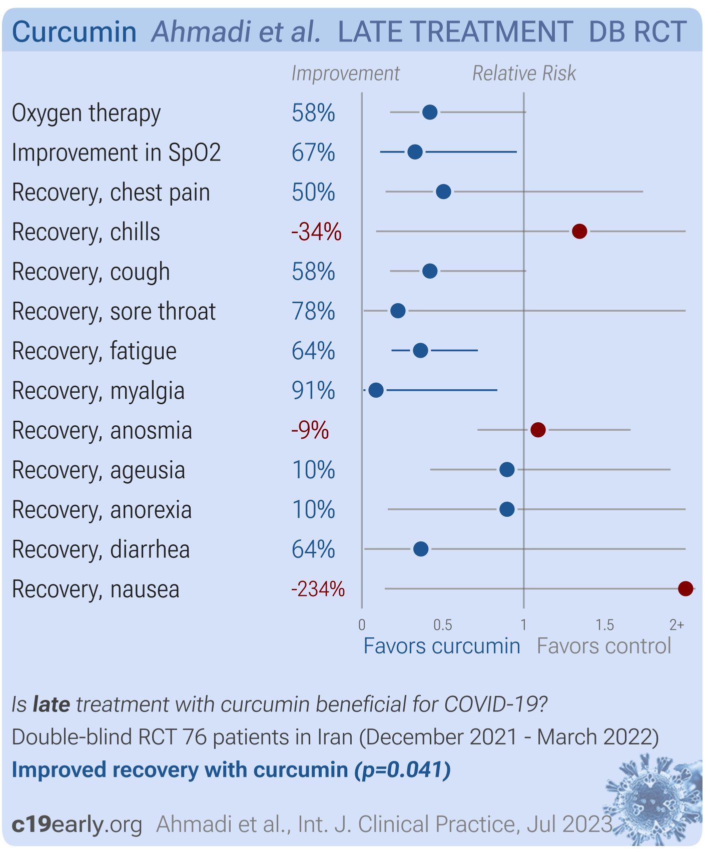
Abbaspour-Aghdam: RCT with 30 nanocurcumin and 30 control patients in Iran, showing lower mortality and improved recovery, without statistical significance, and improved NK cell function. 160mg nanocurcumin for 21 days.

Ahmadi



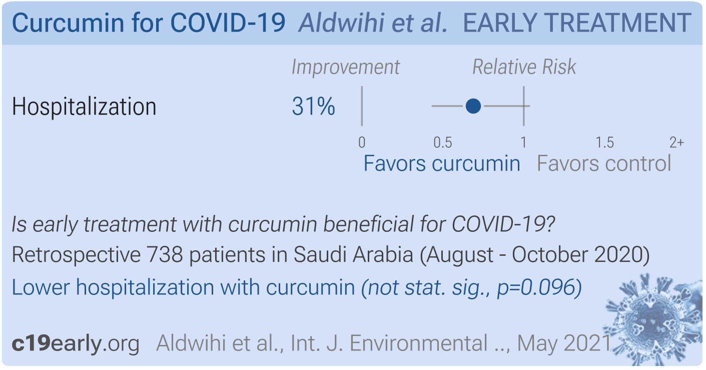
Ahmadi: RCT 60 outpatients in Iran, 30 treated with nano-curcumin showing lower hospitalization and faster recovery with treatment.

Ahmadi



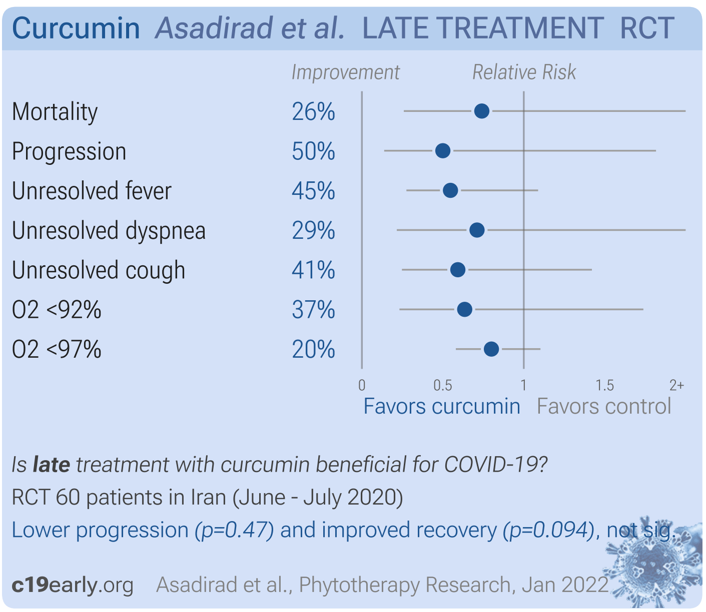
Ahmadi (B): RCT 76 hospitalized patients, showing improved recovery with nanocurcumin. Authors note that pure curcumin is limited due to rapid metabolism, low bio-availability, weak aqueous solubility, and systemic deletion, and that the nanocurcumin formulation used improves curcumin's solubility, stability, half-life, and bioavailability. The dropout rate was higher in the curcumin group, in part due to discontinuation for side effects. Authors do not provide detailed discharge criteria.

Aldwihi



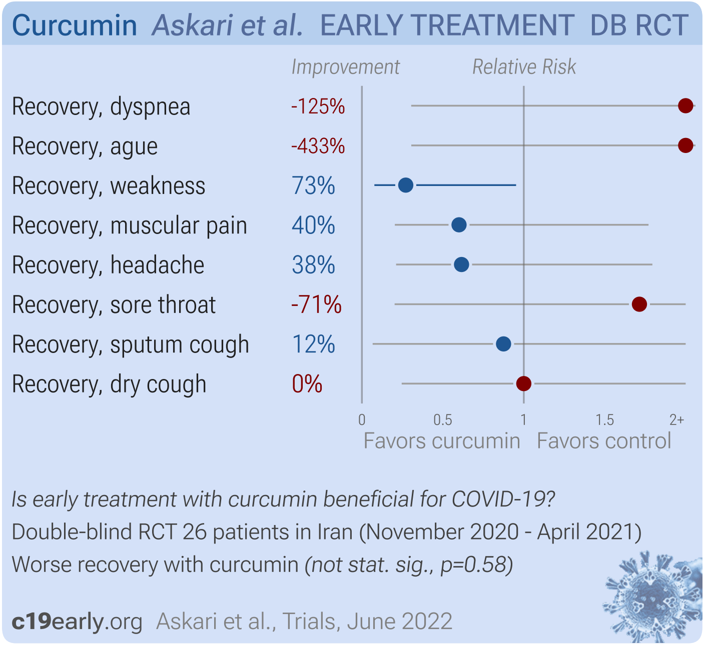
Aldwihi: Retrospective survey-based analysis of 738 COVID-19 patients in Saudi Arabia, showing lower hospitalization with vitamin C, turmeric, zinc, and nigella sativa, and higher hospitalization with vitamin D. For vitamin D, most patients continued prophylactic use. For vitamin C, the majority of patients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

Asadirad



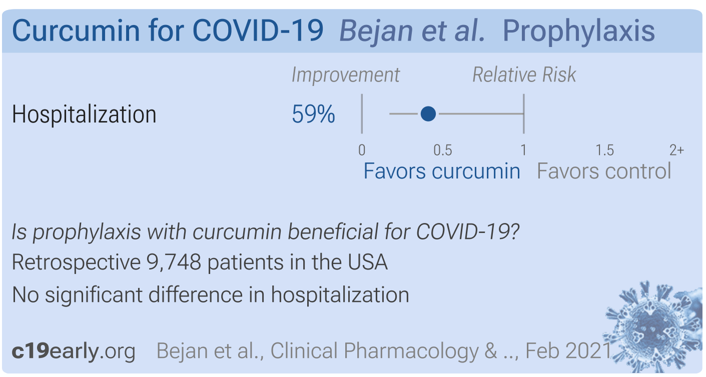
Asadirad: RCT 60 hospitalized patients in Iran, 30 treated with nano-curcumin, showing significant improvements in inflammatory cytokines, and improvements in clinical outcomes without statistical significance. 240mg/day nano-curcumin for 7days.

Askari



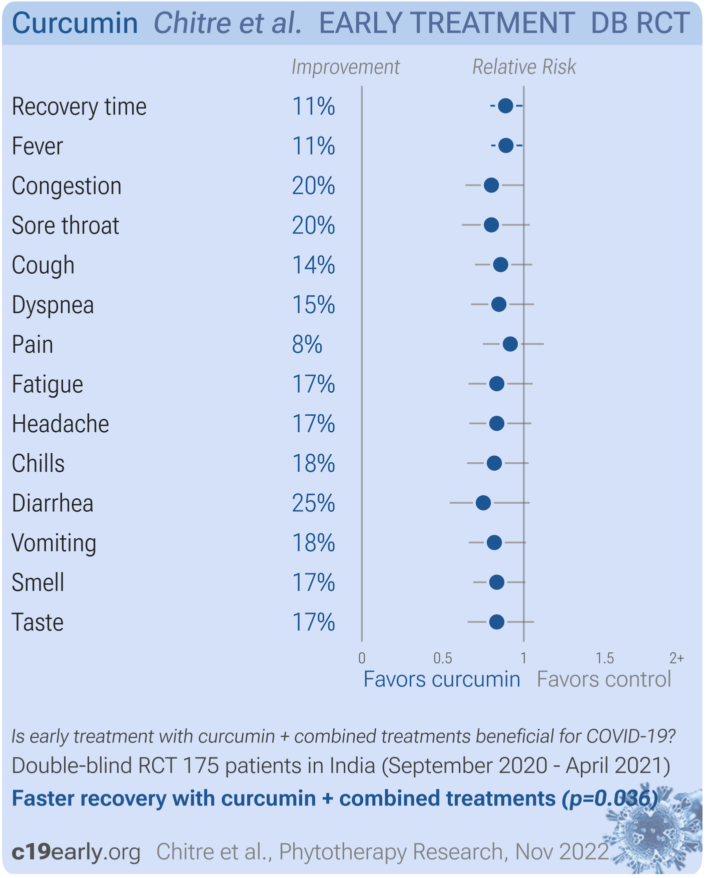
Askari: Small RCT 46 outpatients in Iran, 23 treated with curcimin-piperine, showing no significant differences in recovery. 1000mg curcumin and 10mg piperine/day for 14 days.

Bejan



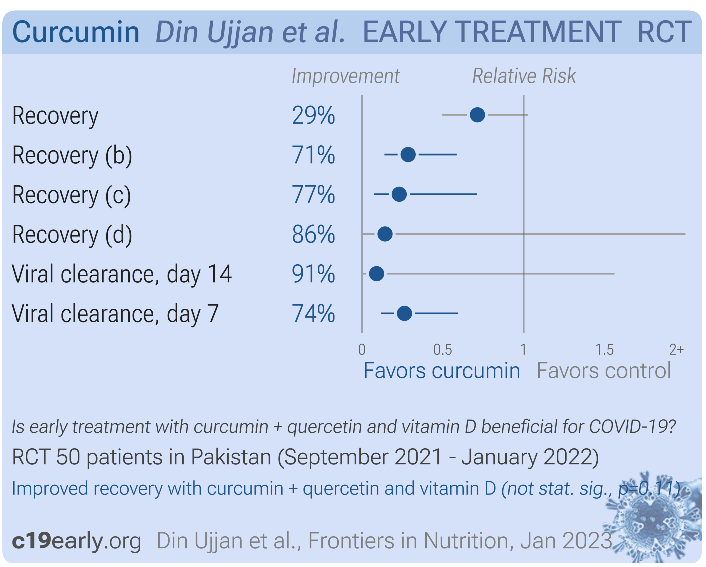
Bejan: Retrospective 9,748 COVID-19 patients in the USA showing lower hospitalization with turmeric extract.

Chitre



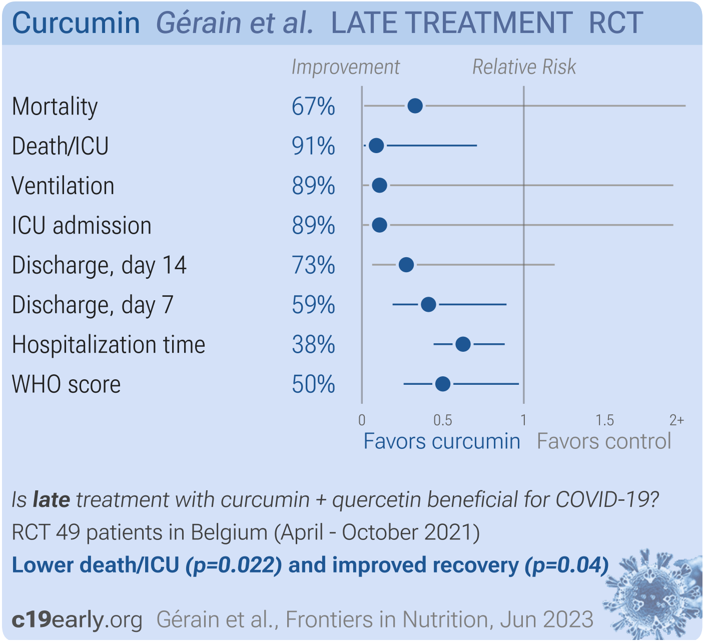
Chitre: RCT 208 moderate COVID-19 patients in India, 103 treated with a combination of turmeric, ashwagandha, boswellia, and ginger, showing improved recovery with treatment. The dose of curcumin is unknown and bioavailability may be poor.

Din Ujjan



Din Ujjan: Small RCT with 50 outpatients, 25 treated with curcumin, quercetin, and vitamin D, showing improved recovery and viral clearance with treatment. 168mg curcumin, 260mg, 360IU vitamin D3 daily for 14 days.

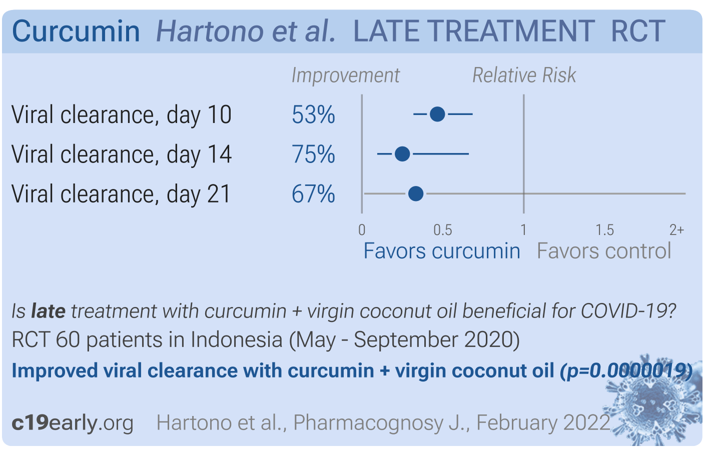
Gérain



Gérain: RCT 49 hospitalized COVID-19 patients, 25 treated with curcumin and quercetin, shower lower mortality/ICU admission and improved recovery with treatment. All patients received vitamin D.

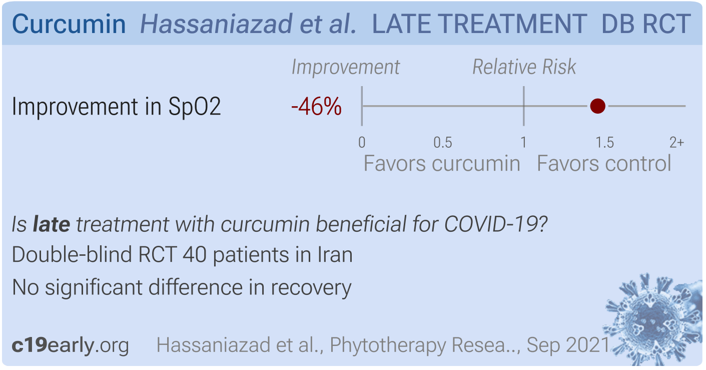
336mg curcumin, 520mg quercetin, and 18µg vitamin D3 daily for 14 days. The control arm received 20µg vitamin D3 daily. Baseline fever favored treatment while vaccination favored control.

Hartono



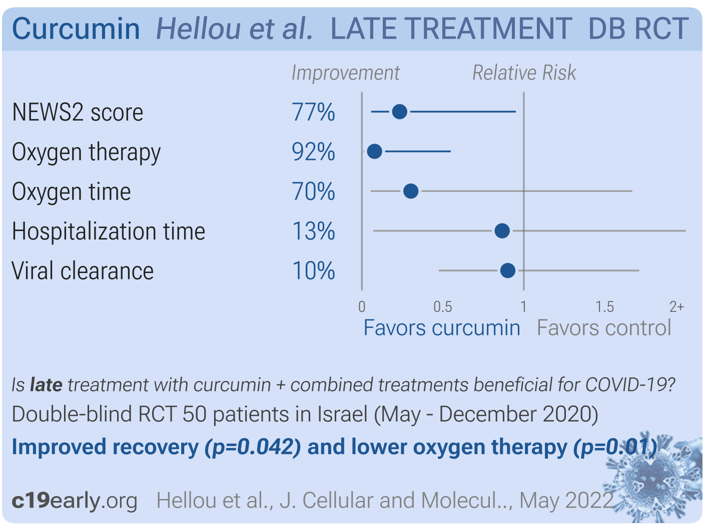
Hartono: RCT with 30 patients treated with curcumin and virgin coconut oil (VCO), and 30 SOC patients in Indonesia, showing faster viral clearance with treatment. Treatment also reduced IL-1β, IL-2, IL-6, IL-18, and IFN-β levels. VCO improves the bioavailability of curcumin. There were large unadjusted differences in baseline severity and age, for example 20% vs. 47% of patients >50. VCO 30ml and curcumin 1g tid for 21 days. 066/UN27.06.6.1/KEPK/EC/2020.

Hassaniazad



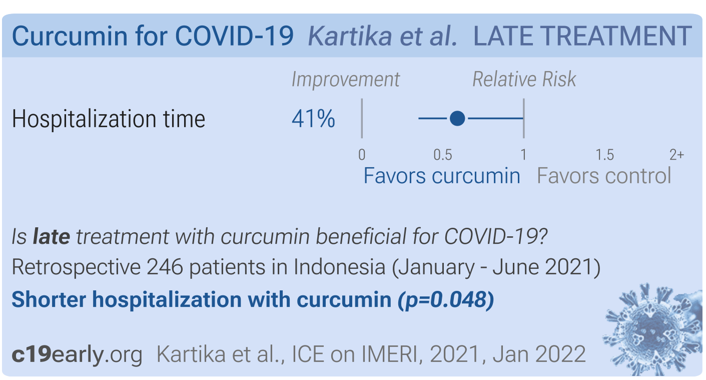
Hassaniazad: Small RCT with 40 low risk patients in Iran, 20 treated with nano-curcumin, showing no significant difference in outcomes with treatment. Authors note that treatment can improve peripheral blood inflammatory indices and modulate immune response by decreasing Th1 and Th17 responses, increasing T regulatory responses, further reducing IL-17 and IFN-γ, and increasing suppressive cytokines TGF-β and IL-4.

Hellou



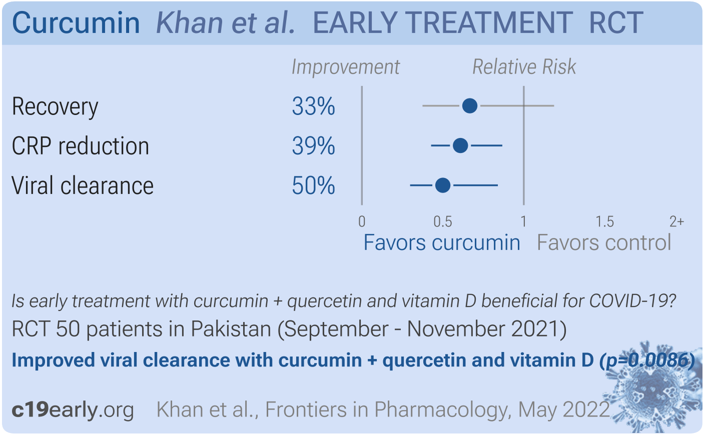
Hellou: RCT 50 hospitalized patients in Israel, 33 treated with curcumin, vitamin C, artemisinin, and frankincense oral spray, showing improved recovery with treatment.

Kartika



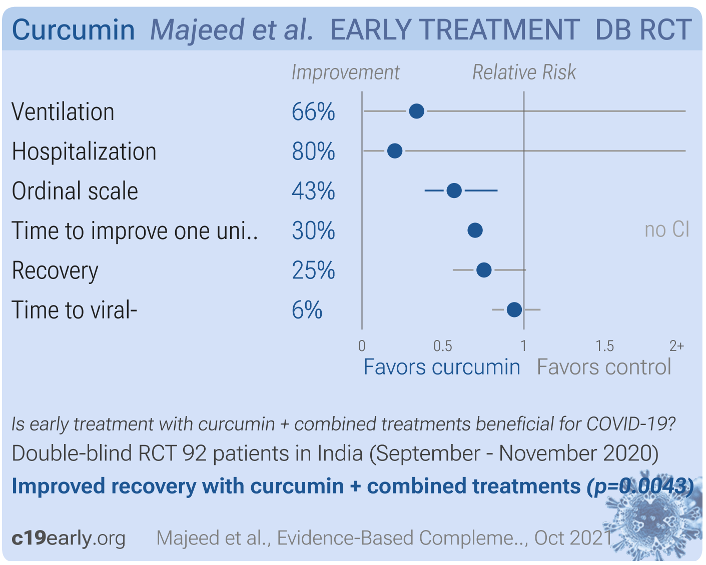
Kartika: Retrospective 246 hospitalized patients in Indonesia, 136 treated with curcumin, showing shorter hospitalization time with treatment. All patients received vitamin C, D, and zinc.

Khan



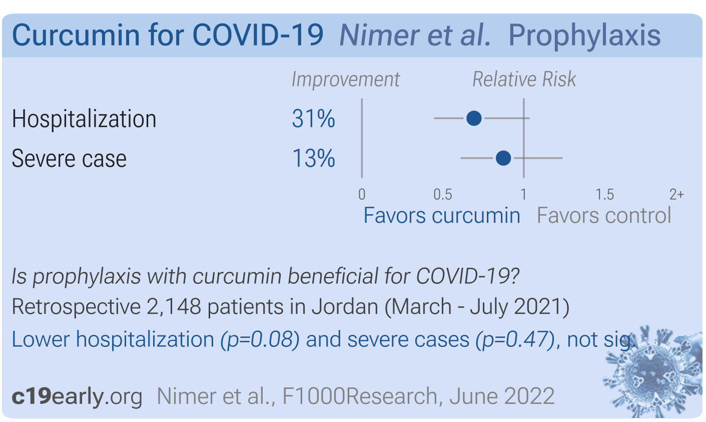
Khan: RCT 50 COVID+ outpatients in Pakistan, 25 treated with curcumin, quercetin, and vitamin D, showing significantly faster viral clearance, significantly improved CRP, and faster resolution of acute symptoms (p=0.154). 168mg curcumin, 260mg quercetin and 360IU cholecalciferol.

Majeed



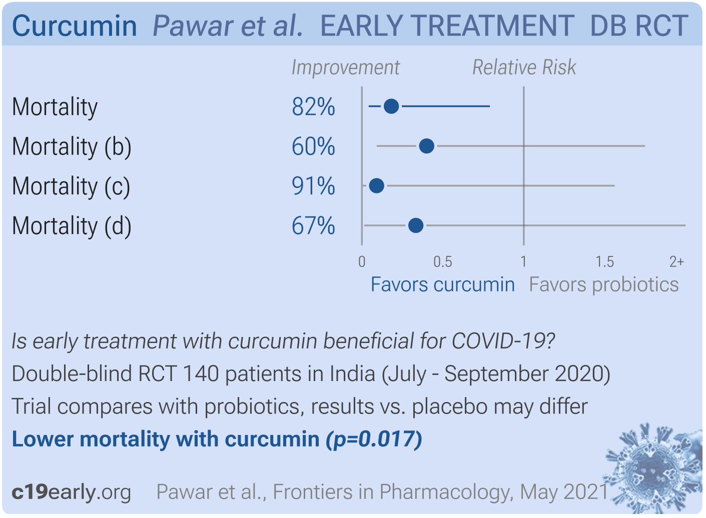
Majeed: RCT 100 patients in India, 50 treated with ImmuActive (curcumin, andrographolides, resveratrol, zinc, selenium, and piperine), showing improved recovery with treatment.

Nimer



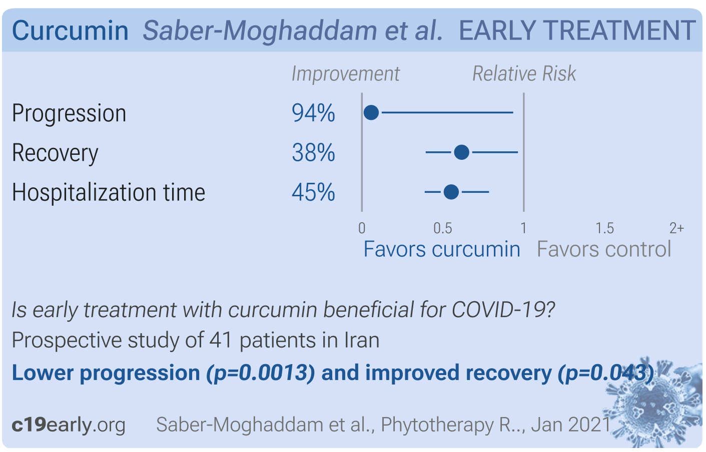
Nimer: Survey 2,148 COVID-19 recovered patients in Jordan, showing lower hospitalization with turmeric prophylaxis, not reaching statistical significance.

Pawar



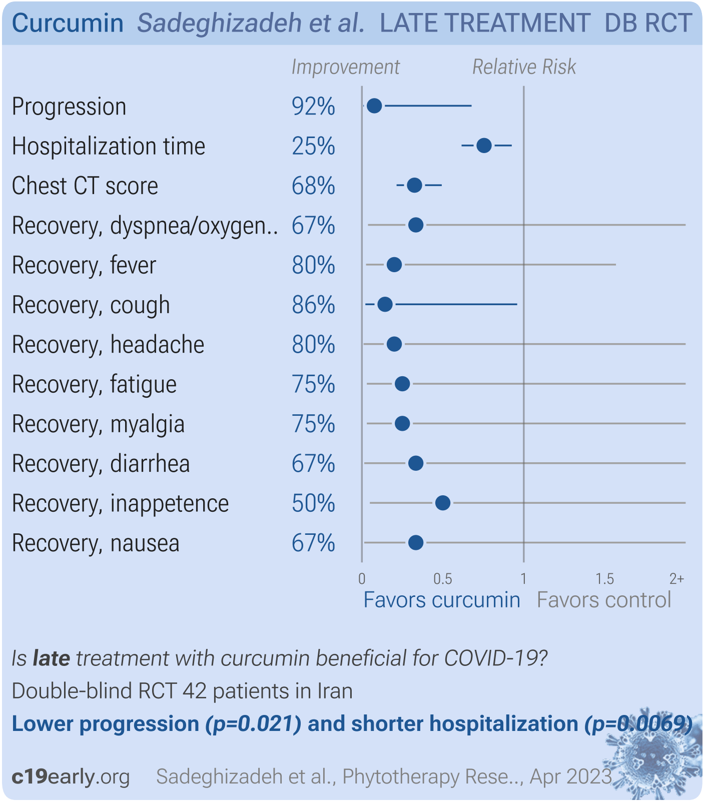
Pawar: RCT 140 patients, 70 treated with curcumin and piperine (for absorption), and 70 treated with probiotics, showing faster recovery, lower progression, and lower mortality with curcumin.

Saber-Moghaddam



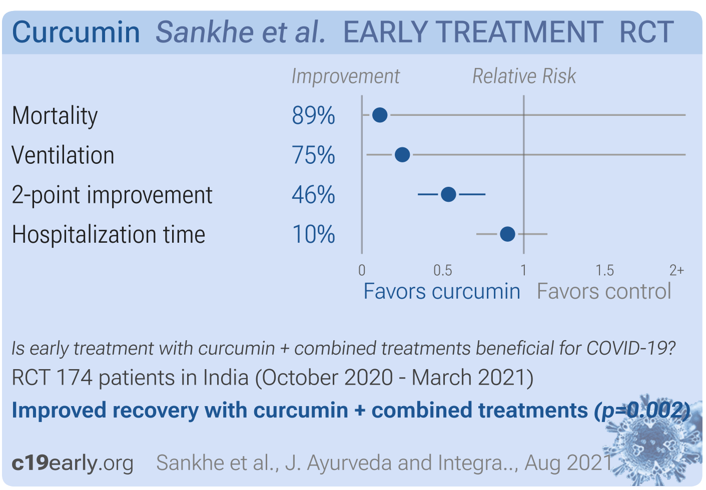
Saber-Moghaddam: Small prospective nonrandomized trial with 41 patients, 21 treated with curcumin, showing lower disease progression and faster recovery with treatment. IRCT20200408046990N1.

Sadeghizadeh



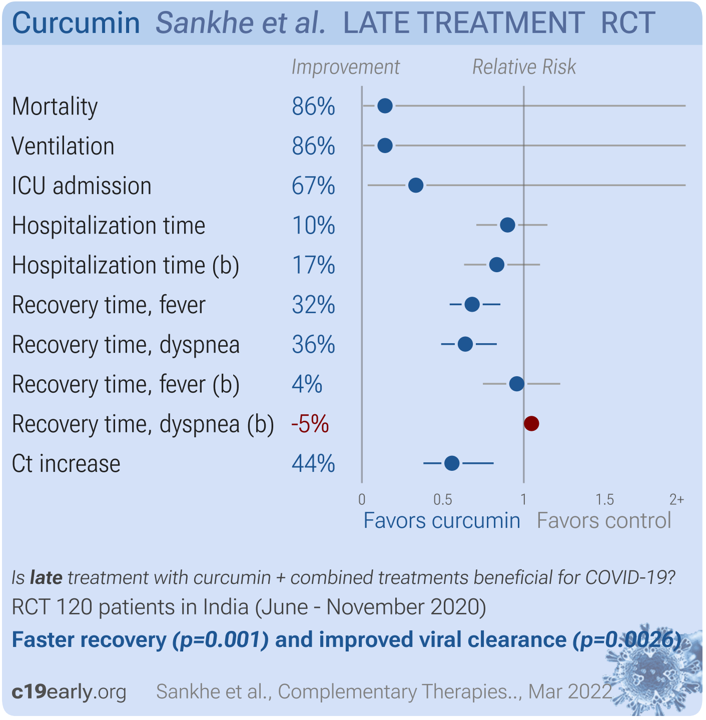
Sadeghizadeh: RCT 42 hospitalized moderate/severe COVID-19 patients in Iran, showing lower progression and improved recovery with nano-curcumin. Nano-curcumin 70mg bid for 14 days.

Sankhe



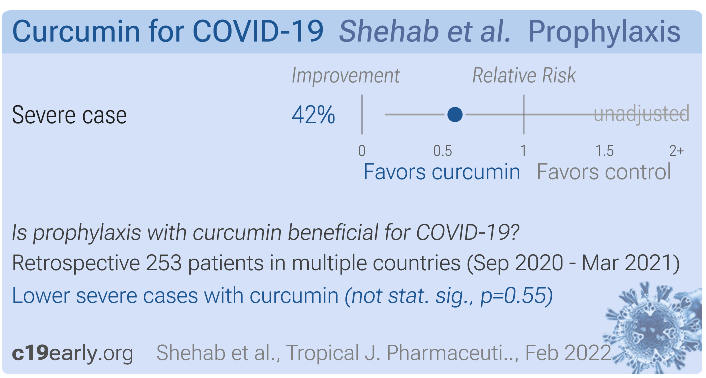
Sankhe: RCT 174 patients in India, 87 treated with AyurCoro-3 (turmeric, gomutra, potassium alum, khadisakhar, bos indicus milk, ghee), showing faster recovery with treatment. EC/NEW/INST/2019/245.

Sankhe



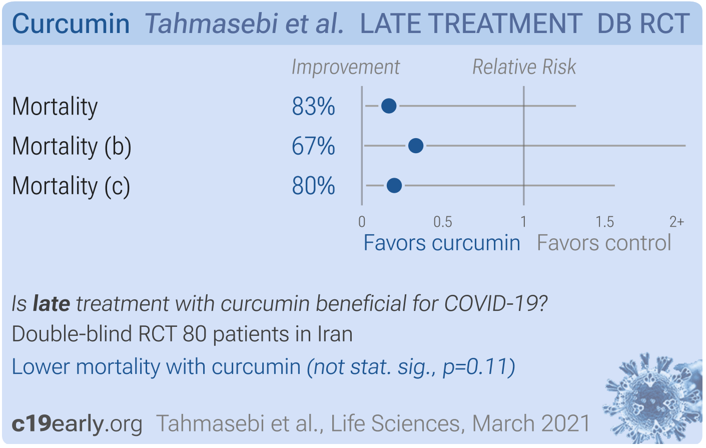
Sankhe (B): RCT with 60 hospitalized patients treated with Ayurcov and 60 control patients in India, showing improved viral clearance and faster symptom resolution in the mild/moderate group, but no significant differences in the severe group. Ayurcov contains curcuma longa, go ark, sphatika (alum), sita (rock candy), godugdham (bos indicus) milk, and goghritam (bos indicus ghee).

Shehab



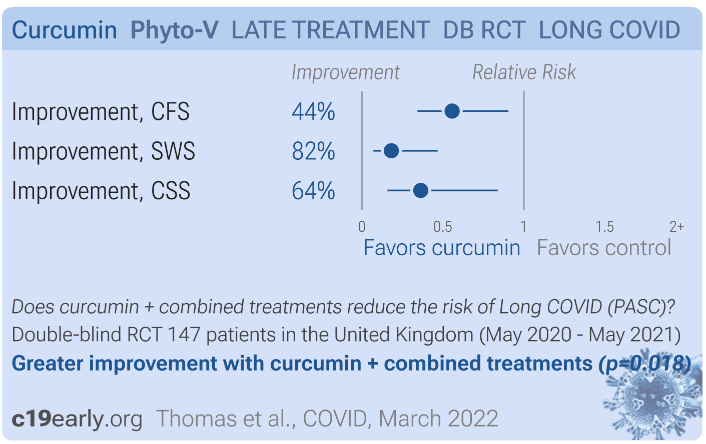
Shehab: Retrospective survey-based analysis of 349 COVID-19 patients, showing a lower risk of severe cases with vitamin D, zinc, turmeric, and honey prophylaxis in unadjusted analysis, without statistical significance. REC/UG/2020/03.

Tahmasebi



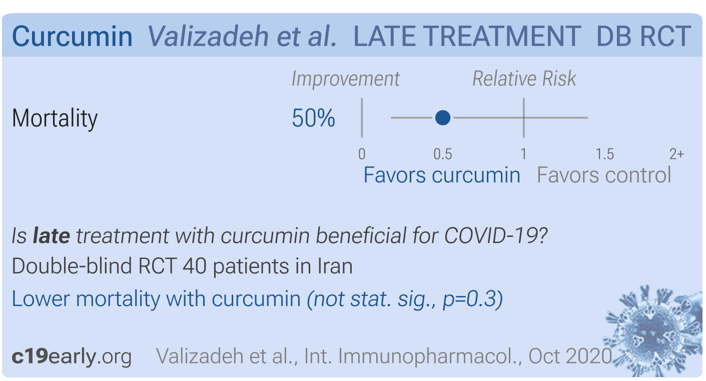
Tahmasebi: RCT 40 hospitalized, 40 ICU, and 40 control patients in Iran, showing lower mortality and improved regulatory T cell responses with nanocurcumin treatment (SinaCurcumin).

Thomas



Thomas: RCT 147 long COVID patients in the UK, 56 treated with a phytochemical-rich concentrated food capsule, showing improved recovery with treatment. Treatment included curcumin, bioflavonoids, chamomile, ellagic acid, and resveratrol.

Valizadeh



Valizadeh: Small RCT with 40 nano-curcumin patients and 40 control patients showing lower mortality with treatment. Authors conclude that nano-curcumin may be able to modulate the increased rate of inflammatory cytokines especially IL-1β and IL-6 mRNA expression and cytokine secretion in COVID-19 patients, which may improve clinical outcomes.

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 curcumin 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 curcumin 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 [Zhang (B)]. 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 [Sweeting]. 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 (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

Forest plots are computed using PythonMeta [Deng] 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 (4.1.2) using the metafor (3.0-2) and rms (6.2-0) 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 [McLean, Treanor].

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/tmeta.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.

Ahmadi, 6/19/2021, Double Blind Randomized Controlled Trial, Iran, peer-reviewed, 11 authors, study period April 2020 - July 2020.	risk of hospitalization, 85.7% lower, RR 0.14, *p* = 0.24, treatment 0 of 30 (0.0%), control 3 of 30 (10.0%), NNT 10.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	recovery time, 20.6% lower, relative time 0.79, *p* = 0.37, treatment 30, control 30.
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, 31.2% lower, RR 0.69, *p* = 0.10, treatment 30 of 144 (20.8%), control 207 of 594 (34.8%), NNT 7.1, adjusted per study, odds ratio converted to relative risk, multivariable.
Askari, 6/6/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 11 authors, study period November 2020 - April 2021, trial IRCT20121216011763N46.	risk of no recovery, 125.0% higher, RR 2.25, *p* = 0.58, treatment 3 of 8 (37.5%), control 1 of 6 (16.7%), dyspnea.
	risk of no recovery, 433.3% higher, RR 5.33, *p* = 0.19, treatment 2 of 6 (33.3%), control 0 of 7 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), ague.
	risk of no recovery, 72.9% lower, RR 0.27, *p* = 0.04, treatment 2 of 12 (16.7%), control 8 of 13 (61.5%), NNT 2.2, weakness.
	risk of no recovery, 40.0% lower, RR 0.60, *p* = 0.42, treatment 3 of 10 (30.0%), control 7 of 14 (50.0%), NNT 5.0, muscular pain.
	risk of no recovery, 38.5% lower, RR 0.62, *p* = 0.65, treatment 4 of 13 (30.8%), control 4 of 8 (50.0%), NNT 5.2, headache.
	risk of no recovery, 71.4% higher, RR 1.71, *p* = 1.00, treatment 2 of 7 (28.6%), control 1 of 6 (16.7%), sore throat.
	risk of no recovery, 12.5% lower, RR 0.88, *p* = 1.00, treatment 1 of 8 (12.5%), control 1 of 7 (14.3%), NNT 56, sputum cough.
	risk of no recovery, no change, RR 1.00, *p* = 1.00, treatment 3 of 13 (23.1%), control 3 of 13 (23.1%), dry cough.
Chitre, 11/23/2022, Double Blind Randomized Controlled Trial, placebo-controlled, India, peer-reviewed, 8 authors, study period September 2020 - April 2021, this trial uses multiple treatments in the treatment arm (combined with ashwagandha, boswellia, ginger) - results of individual treatments may vary, trial CTRI/2020/09/027817.	recovery time, 11.3% lower, relative time 0.89, *p* = 0.04, treatment 89, control 86.
	fever, 11.0% lower, RR 0.89, *p* = 0.03, treatment 70 of 89 (78.7%), control 76 of 86 (88.4%), NNT 10, day 4.

	congestion, 20.0% lower, RR 0.80, *p* = 0.05, treatment 89, control 86, mid-recovery, day 7.
	sore throat, 20.0% lower, RR 0.80, *p* = 0.09, treatment 89, control 86, mid-recovery, day 7.
	cough, 14.3% lower, RR 0.86, *p* = 0.14, treatment 89, control 86, mid-recovery, day 7.
	dyspnea, 15.4% lower, RR 0.85, *p* = 0.15, treatment 89, control 86, mid-recovery, day 7.
	pain, 8.3% lower, RR 0.92, *p* = 0.41, treatment 89, control 86, mid-recovery, day 7.
	fatigue, 16.7% lower, RR 0.83, *p* = 0.13, treatment 89, control 86, mid-recovery, day 7.
	headache, 16.7% lower, RR 0.83, *p* = 0.12, treatment 89, control 86, mid-recovery, day 7.
	chills, 18.2% lower, RR 0.82, *p* = 0.09, treatment 89, control 86, mid-recovery, day 7.
	diarrhea, 25.0% lower, RR 0.75, *p* = 0.08, treatment 89, control 86, mid-recovery, day 7.
	vomiting, 18.2% lower, RR 0.82, *p* = 0.07, treatment 89, control 86, mid-recovery, day 7.
	smell, 16.7% lower, RR 0.83, *p* = 0.06, treatment 89, control 86, mid-recovery, day 7.
	taste, 16.7% lower, RR 0.83, *p* = 0.14, treatment 89, control 86, mid-recovery, day 7.
Din Ujjan, 1/18/2023, Randomized Controlled Trial, Pakistan, peer-reviewed, 6 authors, study period 21 September, 2021 - 21 January, 2022, this trial uses multiple treatments in the treatment arm (combined with quercetin and vitamin D) - results of individual treatments may vary, trial NCT04603690 (history).	**risk of no recovery, 28.6% lower, RR 0.71, *p* = 0.11**, treatment 15 of 25 (60.0%), control 21 of 25 (84.0%), NNT 4.2, no symptoms, day 7.
	risk of no recovery, 71.4% lower, RR 0.29, *p* < 0.001, treatment 6 of 25 (24.0%), control 21 of 25 (84.0%), NNT 1.7, <= 1 symptom, day 7.
	risk of no recovery, 76.9% lower, RR 0.23, *p* = 0.005, treatment 3 of 25 (12.0%), control 13 of 25 (52.0%), NNT 2.5, <= 2 symptoms, day 7.
	risk of no recovery, 85.7% lower, RR 0.14, *p* = 0.23, treatment 0 of 25 (0.0%), control 3 of 25 (12.0%), NNT 8.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), <= 3 symptoms, day 7.
	risk of no viral clearance, 90.9% lower, RR 0.09, *p* = 0.05, treatment 0 of 25 (0.0%), control 5 of 25 (20.0%), NNT 5.0, relative risk is not 0 because of continuity correction due to zero

	events (with reciprocal of the contrasting arm), day 14.
	risk of no viral clearance, 73.7% lower, RR 0.26, $p < 0.001$, treatment 5 of 25 (20.0%), control 19 of 25 (76.0%), NNT 1.8, day 7.
Khan, 5/1/2022, Randomized Controlled Trial, Pakistan, peer-reviewed, 7 authors, study period 2 September, 2021 - 28 November, 2021, this trial uses multiple treatments in the treatment arm (combined with quercetin and vitamin D) - results of individual treatments may vary, trial NCT05130671 (history).	**risk of no recovery, 33.3% lower, RR 0.67, $p = 0.15$**, treatment 10 of 25 (40.0%), control 15 of 25 (60.0%), NNT 5.0.
	relative CRP reduction, 39.1% better, RR 0.61, $p = 0.006$, treatment 25, control 25.
	risk of no viral clearance, 50.0% lower, RR 0.50, $p = 0.009$, treatment 10 of 25 (40.0%), control 20 of 25 (80.0%), NNT 2.5.
Majeed, 10/11/2021, Double Blind Randomized Controlled Trial, India, peer-reviewed, 4 authors, study period September 2020 - November 2020, this trial uses multiple treatments in the treatment arm (combined with andrographolides, resveratrol, zinc, selenium, and piperine) - results of individual treatments may vary, trial CTRI/2020/09/027841.	**risk of mechanical ventilation, 66.2% lower, RR 0.34, $p = 1.00$**, treatment 0 of 45 (0.0%), control 1 of 47 (2.1%), NNT 47, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 79.7% lower, RR 0.20, $p = 0.49$, treatment 0 of 45 (0.0%), control 2 of 47 (4.3%), NNT 24, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	relative ordinal scale, 43.0% better, RR 0.57, $p = 0.004$, treatment 45, control 47, day 28.
	risk of no recovery, 24.6% lower, RR 0.75, $p = 0.08$, treatment 26 of 45 (57.8%), control 36 of 47 (76.6%), NNT 5.3, day 28.
	time to viral-, 5.8% lower, relative time 0.94, $p = 0.47$, treatment 45, control 47.
Pawar, 5/28/2021, Double Blind Randomized Controlled Trial, India, peer-reviewed, 8 authors, study period July 2020 - September 2020, this trial compares with another treatment - results may be better when compared to placebo, trial CTRI/2020/05/025482.	**risk of death, 81.8% lower, RR 0.18, $p = 0.02$**, treatment 2 of 70 (2.9%), control 11 of 70 (15.7%), NNT 7.8.
	risk of death, 60.0% lower, RR 0.40, $p = 0.39$, treatment 2 of 15 (13.3%), control 5 of 15 (33.3%), NNT 5.0, severe group.
	risk of death, 90.9% lower, RR 0.09, $p = 0.05$, treatment 0 of 25 (0.0%), control 5 of 25 (20.0%), NNT 5.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), moderate group.
	risk of death, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 30 (0.0%), control 1 of 30 (3.3%), NNT 30, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), mild group.
Saber-Moghaddam, 1/3/2021, prospective, Iran, peer-reviewed, 9 authors.	**risk of progression, 94.3% lower, RR 0.06, $p = 0.001$**, treatment 0 of 21 (0.0%), control 8 of 20 (40.0%), NNT 2.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no recovery, 38.4% lower, RR 0.62, $p = 0.04$, treatment 11 of 21 (52.4%), control 17 of 20 (85.0%), NNT 3.1.

	hospitalization time, 44.8% lower, relative time 0.55, $p < 0.001$, treatment 21, control 20.
Sankhe, 8/10/2021, Randomized Controlled Trial, India, peer-reviewed, 8 authors, study period October 2020 - March 2021, this trial uses multiple treatments in the treatment arm (combined with gomutra, potassium alum, khadisakhar, bos indicus milk, ghee) - results of individual treatments may vary.	risk of death, 88.9% lower, RR 0.11, $p = 0.12$, treatment 0 of 87 (0.0%), control 4 of 87 (4.6%), NNT 22, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 75.0% lower, RR 0.25, $p = 0.37$, treatment 1 of 87 (1.1%), control 4 of 87 (4.6%), NNT 29.
	risk of no 2-point improvement, 46.5% lower, RR 0.54, $p = 0.002$, treatment 29 of 87 (33.3%), control 60 of 87 (69.0%), NNT 2.8, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, day 7 mid-recovery.
	hospitalization time, 10.0% lower, relative time 0.90, $p = 0.40$, treatment 87, control 87.

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.

Abbaspour-Aghdam, 9/17/2022, Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 16 authors, trial IRCT20200324046851N1.	risk of death, 71.4% lower, RR 0.29, $p = 0.15$, treatment 2 of 30 (6.7%), control 7 of 30 (23.3%), NNT 6.0.
	risk of no recovery, 86.3% lower, RR 0.14, $p = 0.04$, treatment 1 of 28 (3.6%), control 6 of 23 (26.1%), NNT 4.4, dyspnea.
	risk of no recovery, 89.9% lower, RR 0.10, $p = 0.04$, treatment 0 of 28 (0.0%), control 4 of 23 (17.4%), NNT 5.8, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), fever >39.0.
	risk of no recovery, 38.4% lower, RR 0.62, $p = 0.17$, treatment 9 of 28 (32.1%), control 12 of 23 (52.2%), NNT 5.0, bilateral chest radiograph involvement.
	risk of no recovery, 58.9% lower, RR 0.41, $p = 0.27$, treatment 3 of 28 (10.7%), control 6 of 23 (26.1%), NNT 6.5, cough.
	risk of no recovery, 81.6% lower, RR 0.18, $p = 0.20$, treatment 0 of 28 (0.0%), control 2 of 23 (8.7%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), headache.
Ahmadi (B), 7/28/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 5 authors, study period December 2021 - March 2022, trial IRCT20211126053183N1.	risk of oxygen therapy, 58.0% lower, RR 0.42, $p = 0.06$, treatment 5 of 29 (17.2%), control 16 of 39 (41.0%), NNT 4.2.
	relative improvement in SpO_2, 67.2% better, RR 0.33, $p = 0.04$, treatment mean 3.32 (±3.84) n=29, control mean 1.09 (±4.71) n=39.

	risk of no recovery, 49.6% lower, RR 0.50, *p* = 0.33, treatment 3 of 29 (10.3%), control 8 of 39 (20.5%), NNT 9.8, chest pain.
	risk of no recovery, 34.5% higher, RR 1.34, *p* = 1.00, treatment 1 of 29 (3.4%), control 1 of 39 (2.6%), chills.
	risk of no recovery, 58.0% lower, RR 0.42, *p* = 0.06, treatment 5 of 29 (17.2%), control 16 of 39 (41.0%), NNT 4.2, cough.
	risk of no recovery, 77.7% lower, RR 0.22, *p* = 0.50, treatment 0 of 29 (0.0%), control 2 of 39 (5.1%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), sore throat.
	risk of no recovery, 63.8% lower, RR 0.36, *p* < 0.001, treatment 7 of 29 (24.1%), control 26 of 39 (66.7%), NNT 2.4, fatigue.
	risk of no recovery, 91.3% lower, RR 0.09, *p* = 0.03, treatment 0 of 29 (0.0%), control 6 of 39 (15.4%), NNT 6.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), myalgia.
	risk of no recovery, 8.9% higher, RR 1.09, *p* = 0.81, treatment 17 of 29 (58.6%), control 21 of 39 (53.8%), anosmia.
	risk of no recovery, 10.3% lower, RR 0.90, *p* = 1.00, treatment 8 of 29 (27.6%), control 12 of 39 (30.8%), NNT 31, ageusia.
	risk of no recovery, 10.3% lower, RR 0.90, *p* = 1.00, treatment 2 of 29 (6.9%), control 3 of 39 (7.7%), NNT 126, anorexia.
	risk of no recovery, 63.6% lower, RR 0.36, *p* = 1.00, treatment 0 of 29 (0.0%), control 1 of 39 (2.6%), NNT 39, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), diarrhea.
	risk of no recovery, 234.5% higher, RR 3.34, *p* = 0.43, treatment 1 of 29 (3.4%), control 0 of 39 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), nausea.
Asadirad, 1/17/2022, Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 7 authors, study period June 2020 - July 2020.	**risk of death, 25.9% lower, RR 0.74, *p* = 0.74**, treatment 5 of 27 (18.5%), control 6 of 24 (25.0%), NNT 15, excluding patients that stopped treatment due to progression - 3 for curcumin and 6 for control.
	risk of progression, 50.0% lower, RR 0.50, *p* = 0.47, treatment 3 of 30 (10.0%), control 6 of 30 (20.0%), NNT 10.0.
	risk of unresolved fever, 45.3% lower, RR 0.55, *p* = 0.09, treatment 8 of 27 (29.6%), control 13 of 24 (54.2%), NNT 4.1.
	risk of unresolved dyspnea, 28.9% lower, RR 0.71, *p* = 0.72, treatment 4 of 27 (14.8%), control 5 of 24 (20.8%), NNT 17.
	risk of unresolved cough, 40.7% lower, RR 0.59, *p* = 0.36, treatment 6 of 27 (22.2%), control 9 of 24 (37.5%), NNT 6.5.

	risk of O2 <92%, 36.5% lower, RR 0.63, *p* = 0.51, treatment 5 of 27 (18.5%), control 7 of 24 (29.2%), NNT 9.4.
	risk of O2 <97%, 20.0% lower, RR 0.80, *p* = 0.21, treatment 18 of 27 (66.7%), control 20 of 24 (83.3%), NNT 6.0.
Gérain, 6/22/2023, Randomized Controlled Trial, Belgium, peer-reviewed, 8 authors, study period 1 April, 2021 - 29 October, 2021, this trial uses multiple treatments in the treatment arm (combined with quercetin) - results of individual treatments may vary, trial NCT04844658 (history).	**risk of death, 67.1% lower, RR 0.33, *p* = 0.49**, treatment 0 of 25 (0.0%), control 1 of 24 (4.2%), NNT 24, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7.
	risk of death/ICU, 91.1% lower, RR 0.09, *p* = 0.02, treatment 0 of 25 (0.0%), control 5 of 24 (20.8%), NNT 4.8, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7.
	risk of mechanical ventilation, 89.1% lower, RR 0.11, *p* = 0.05, treatment 0 of 25 (0.0%), control 4 of 24 (16.7%), NNT 6.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7.
	risk of ICU admission, 89.1% lower, RR 0.11, *p* = 0.05, treatment 0 of 25 (0.0%), control 4 of 24 (16.7%), NNT 6.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7.
	risk of no hospital discharge, 72.6% lower, RR 0.27, *p* = 0.07, treatment 2 of 25 (8.0%), control 7 of 24 (29.2%), NNT 4.7, day 14.
	risk of no hospital discharge, 58.9% lower, RR 0.41, *p* = 0.02, treatment 6 of 25 (24.0%), control 14 of 24 (58.3%), NNT 2.9, day 7.
	hospitalization time, 37.5% lower, relative time 0.62, *p* = 0.008, treatment median 5.0 IQR 4.0 n=25, control median 8.0 IQR 6.0 n=24.
	relative WHO score, 50.0% better, RR 0.50, *p* = 0.04, treatment 22, control 24, day 7.
Hartono, 2/22/2022, Randomized Controlled Trial, Indonesia, peer-reviewed, 13 authors, study period May 2020 - September 2020, this trial uses multiple treatments in the treatment arm (combined with virgin coconut oil) - results of individual treatments may vary, excluded in exclusion analyses: randomization resulted in significant baseline differences that were not adjusted for.	**risk of no viral clearance, 53.3% lower, RR 0.47, *p* < 0.001**, treatment 14 of 30 (46.7%), control 30 of 30 (100.0%), NNT 1.9, day 10.
	risk of no viral clearance, 75.0% lower, RR 0.25, *p* = 0.002, treatment 4 of 30 (13.3%), control 16 of 30 (53.3%), NNT 2.5, day 14.
	risk of no viral clearance, 66.7% lower, RR 0.33, *p* = 1.00, treatment 0 of 30 (0.0%), control 1 of 30 (3.3%), NNT 30, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 21.
Hassaniazad, 9/19/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-	**relative improvement in SpO_2, 45.7% worse, RR 1.46, *p* = 0.90**, treatment 20, control 20.

reviewed, 12 authors.	
Hellou, 5/19/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Israel, peer-reviewed, 6 authors, study period 8 May, 2020 - 21 December, 2020, this trial uses multiple treatments in the treatment arm (combined with vitamin C, artemisinin, and frankincense) - results of individual treatments may vary, trial NCT04382040 (history).	**relative NEWS2 score, 76.7% better, RR 0.23, *p* = 0.04**, treatment mean 0.52 (±0.67) n=33, control mean 2.23 (±3.2) n=17, day 15.
	risk of oxygen therapy, 92.2% lower, RR 0.08, *p* = 0.01, treatment 0 of 33 (0.0%), control 4 of 17 (23.5%), NNT 4.2, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 15.
	oxygen time, 69.7% lower, relative time 0.30, *p* = 0.17, treatment mean 2.3 (±1.4) n=33, control mean 7.6 (±4.6) n=17.
	hospitalization time, 13.3% lower, relative time 0.87, *p* = 0.92, treatment mean 7.8 (±7.3) n=33, control mean 9.0 (±8.0) n=17.
	risk of no viral clearance, 9.8% lower, RR 0.90, *p* = 0.77, treatment 14 of 33 (42.4%), control 8 of 17 (47.1%), NNT 22, day 15.
Kartika, 1/28/2022, retrospective, Indonesia, preprint, 6 authors, study period January 2021 - June 2021.	**hospitalization time, 41.0% lower, relative time 0.59, *p* = 0.048**, treatment 139, control 107.
Sadeghizadeh, 4/29/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 12 authors, trial IRCT20170128032241N3.	**risk of progression, 92.3% lower, RR 0.08, *p* = 0.02**, treatment 0 of 21 (0.0%), control 6 of 21 (28.6%), NNT 3.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	hospitalization time, 24.5% lower, relative time 0.75, *p* = 0.007, treatment mean 7.7 (±2.3) n=21, control mean 10.2 (±3.3) n=21.
	relative chest CT score, 67.5% better, RR 0.33, *p* < 0.001, treatment mean 1.3 (±0.82) n=21, control mean 4.0 (±1.8) n=21, day 14.
	risk of no recovery, 66.7% lower, RR 0.33, *p* = 0.61, treatment 1 of 21 (4.8%), control 3 of 21 (14.3%), NNT 10, day 14, dyspnea/oxygen need.
	risk of no recovery, 80.0% lower, RR 0.20, *p* = 0.18, treatment 1 of 21 (4.8%), control 5 of 21 (23.8%), NNT 5.2, day 14, fever.
	risk of no recovery, 85.7% lower, RR 0.14, *p* = 0.04, treatment 1 of 21 (4.8%), control 7 of 21 (33.3%), NNT 3.5, day 14, cough.
	risk of no recovery, 80.0% lower, RR 0.20, *p* = 0.49, treatment 0 of 21 (0.0%), control 2 of 21 (9.5%), NNT 10, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14, headache.
	risk of no recovery, 75.0% lower, RR 0.25, *p* = 0.34, treatment 1 of 21 (4.8%), control 4 of 21 (19.0%), NNT 7.0, day 14, fatigue.
	risk of no recovery, 75.0% lower, RR 0.25, *p* = 0.34, treatment 1 of 21 (4.8%), control 4 of 21 (19.0%), NNT 7.0, day 14, myalgia.

	risk of no recovery, 66.7% lower, RR 0.33, *p* = 1.00, treatment 0 of 21 (0.0%), control 1 of 21 (4.8%), NNT 21, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14, diarrhea.
	risk of no recovery, 50.0% lower, RR 0.50, *p* = 1.00, treatment 1 of 21 (4.8%), control 2 of 21 (9.5%), NNT 21, day 14, inappetence.
	risk of no recovery, 66.7% lower, RR 0.33, *p* = 1.00, treatment 0 of 21 (0.0%), control 1 of 21 (4.8%), NNT 21, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14, nausea.
Sankhe (B), 3/25/2022, Single Blind Randomized Controlled Trial, India, peer-reviewed, 10 authors, study period June 2020 - November 2020, this trial uses multiple treatments in the treatment arm (combined with gomutra, potassium alum, khadisakhar, bos indicus milk, ghee) - results of individual treatments may vary.	**risk of death, 85.7% lower, RR 0.14, *p* = 0.24**, treatment 0 of 60 (0.0%), control 3 of 60 (5.0%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 85.7% lower, RR 0.14, *p* = 0.24, treatment 0 of 60 (0.0%), control 3 of 60 (5.0%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 66.7% lower, RR 0.33, *p* = 0.62, treatment 1 of 60 (1.7%), control 3 of 60 (5.0%), NNT 30.
	hospitalization time, 10.0% lower, relative time 0.90, *p* = 0.40, treatment 45, control 45, moderate group.
	hospitalization time, 16.7% lower, relative time 0.83, *p* = 0.20, treatment 15, control 15, severe group.
	recovery time, 31.9% lower, relative time 0.68, *p* < 0.001, treatment 45, control 45, moderate group, fever.
	recovery time, 36.1% lower, relative time 0.64, *p* < 0.001, treatment 45, control 45, moderate group, dyspnea.
	recovery time, 4.3% lower, relative time 0.96, *p* = 0.74, treatment 15, control 15, severe group, fever.
	recovery time, 4.8% higher, relative time 1.05, *p* = 0.10, treatment 15, control 15, severe group, dyspnea.
	relative Ct increase, 44.4% better, RR 0.56, *p* = 0.003, treatment mean 9.98 (±6.39) n=44, control mean 5.55 (±6.91) n=43, moderate group.
Tahmasebi, 3/28/2021, Double Blind Randomized Controlled Trial, Iran, peer-reviewed, 14 authors.	**risk of death, 83.3% lower, RR 0.17, *p* = 0.11**, treatment 1 of 40 (2.5%), control 6 of 40 (15.0%), NNT 8.0.
	risk of death, 66.7% lower, RR 0.33, *p* = 1.00, treatment 0 of 20 (0.0%), control 1 of 20 (5.0%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), non-ICU patients.

	risk of death, 80.0% lower, RR 0.20, *p* = 0.18, treatment 1 of 20 (5.0%), control 5 of 20 (25.0%), NNT 5.0, ICU patients.
Thomas, 3/22/2022, Double Blind Randomized Controlled Trial, placebo-controlled, United Kingdom, peer-reviewed, 7 authors, study period May 2020 - May 2021, this trial uses multiple treatments in the treatment arm (combined with bioflavonoids, chamomile, ellagic acid, resveratrol) - results of individual treatments may vary, Phyto-V trial.	**relative improvement, 44.3% better, RR 0.56, *p* = 0.02**, treatment mean 6.1 (±7.5) n=74, control mean 3.4 (±6.1) n=73, CFS.
	relative improvement, 81.8% better, RR 0.18, *p* < 0.001, treatment mean 6.6 (±10.5) n=74, control mean 1.2 (±7.4) n=73, SWS.
	relative improvement, 63.6% better, RR 0.36, *p* = 0.02, treatment mean 1.1 (±2.0) n=74, control mean 0.4 (±1.5) n=73, CSS.
Valizadeh, 10/20/2020, Double Blind Randomized Controlled Trial, Iran, peer-reviewed, 12 authors.	**risk of death, 50.0% lower, RR 0.50, *p* = 0.30**, treatment 4 of 20 (20.0%), control 8 of 20 (40.0%), NNT 5.0.

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.

Bejan, 2/28/2021, retrospective, USA, peer-reviewed, mean age 42.0, 6 authors.	**risk of hospitalization, 59.0% lower, OR 0.41, *p* = 0.048**, treatment 148, control 9,600, adjusted per study, RR approximated with OR.
Nimer, 6/10/2022, retrospective, Jordan, peer-reviewed, survey, mean age 40.2, 4 authors, study period March 2021 - July 2021.	**risk of hospitalization, 30.8% lower, RR 0.69, *p* = 0.08**, treatment 29 of 329 (8.8%), control 179 of 1,819 (9.8%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of severe case, 12.6% lower, RR 0.87, *p* = 0.47, treatment 40 of 329 (12.2%), control 211 of 1,819 (11.6%), adjusted per study, odds ratio converted to relative risk, multivariable.
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, 42.4% lower, RR 0.58, *p* = 0.55**, treatment 2 of 32 (6.2%), control 24 of 221 (10.9%), NNT 22, unadjusted, severe vs. mild cases.

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.

b. The trimeric spike (S) protein is a glycoprotein that mediates viral entry by binding to the host ACE2 receptor, is critical for SARS-CoV-2's ability to infect host cells, and is a target of neutralizing antibodies. Inhibition of the spike protein prevents viral attachment, halting infection at the earliest stage.

c. The receptor binding domain is a specific region of the spike protein that binds ACE2 and is a major target of neutralizing antibodies. Focusing on the precise binding site allows highly specific disruption of viral attachment with reduced potential for off-target effects.

d. The main protease or M^{pro}, also known as $3CL^{pro}$ or nsp5, is a cysteine protease that cleaves viral polyproteins into functional units needed for replication. Inhibiting M^{pro} disrupts the SARS-CoV-2 lifecycle within the host cell, preventing the creation of new copies.

e. RNA-dependent RNA polymerase (RdRp), also called nsp12, is the core enzyme of the viral replicase-transcriptase complex that copies the positive-sense viral RNA genome into negative-sense templates for progeny RNA synthesis. Inhibiting RdRp blocks viral genome replication and transcription.

f. The angiotensin converting enzyme 2 (ACE2) protein is a host cell transmembrane protein that serves as the cellular receptor for the SARS-CoV-2 spike protein. ACE2 is expressed on many cell types, including epithelial cells in the lungs, and allows the virus to enter and infect host cells. Inhibition may affect ACE2's physiological function in blood pressure control.

g. The nucleocapsid (N) protein binds and encapsulates the viral genome by coating the viral RNA. N enables formation and release of infectious virions and plays additional roles in viral replication and pathogenesis. N is also an immunodominant antigen used in diagnostic assays.

h. Non-structural protein 10 (nsp10) serves as an RNA chaperone and stabilizes conformations of nsp12 and nsp14 in the replicase-transcriptase complex, which synthesizes new viral RNAs. Nsp10 disruption may destabilize replicase-transcriptase complex activity.

i. Transmembrane protease serine 2 (TMPRSS2) is a host cell protease that primes the spike protein, facilitating cellular entry. TMPRSS2 activity helps enable cleavage of the spike protein required for membrane fusion and virus entry. Inhibition may especially protect respiratory epithelial cells, buy may have physiological effects.

j. Calu-3 is a human lung adenocarcinoma cell line with moderate ACE2 and TMPRSS2 expression and SARS-CoV-2 susceptibility. It provides a model of the human respiratory epithelium, but many not be ideal for modeling early stages of infection due to the moderate expression levels of ACE2 and TMPRSS2.

k. A549 is a human lung carcinoma cell line with low ACE2 expression and SARS-CoV-2 susceptibility. Viral entry/replication can be studied but the cells may not replicate all aspects of lung infection.

l. 293T is a human embryonic kidney cell line that can be engineered for high ACE2 expression and SARS-CoV-2 susceptibility. 293T cells are easily transfected and support high protein expression.

m. HEK293-hACE2 is a human embryonic kidney cell line with high ACE2 expression and SARS-CoV-2 susceptibility. Cells have been transfected with a plasmid to express the human ACE2 (hACE2) protein.

n. 293T/hACE2/TMPRSS2 is a human embryonic kidney cell line engineered for high ACE2 and TMPRSS2 expression, which mimics key aspects of human infection. 293T/hACE2/TMPRSS2 cells are very susceptible to SARS-CoV-2 infection.

o. Vero E6 is an African green monkey kidney cell line with low/no ACE2 expression and high SARS-CoV-2 susceptibility. The cell line is easy to maintain and supports robust viral replication, however the monkey origin may not accurately represent human responses.

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