Quercetin for COVID-19: real-time meta analysis of 11 studies

@CovidAnalysis, March 2024, Version 21
https://c19early.org/qmeta.html

Abstract

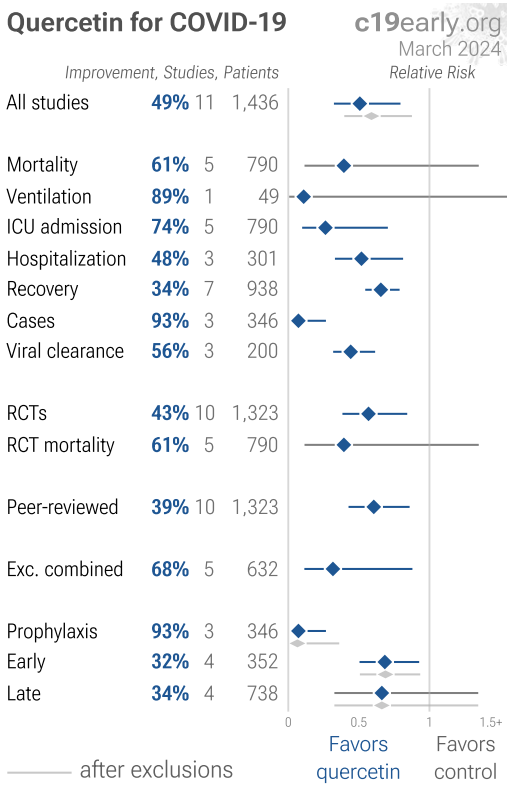
Statistically significant lower risk is seen for ICU admission, hospitalization, recovery, cases, and viral clearance. 10 studies from 8 independent teams in 7 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 49% [21-68%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies, better after excluding studies using combined treatment, and slightly worse for peer-reviewed studies.

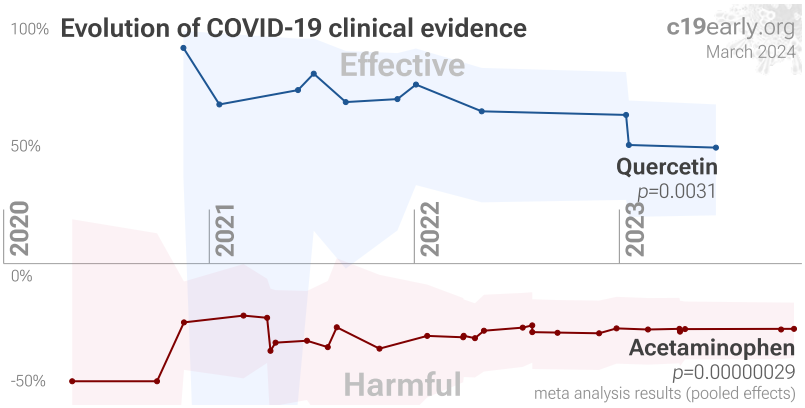
Results are robust — in exclusion sensitivity analysis 8 of 11 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

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 quercetin for mortality *Ziaei*, ICU admission *Cheema, Ziaei*, and hospitalization *Cheema, Ziaei*.



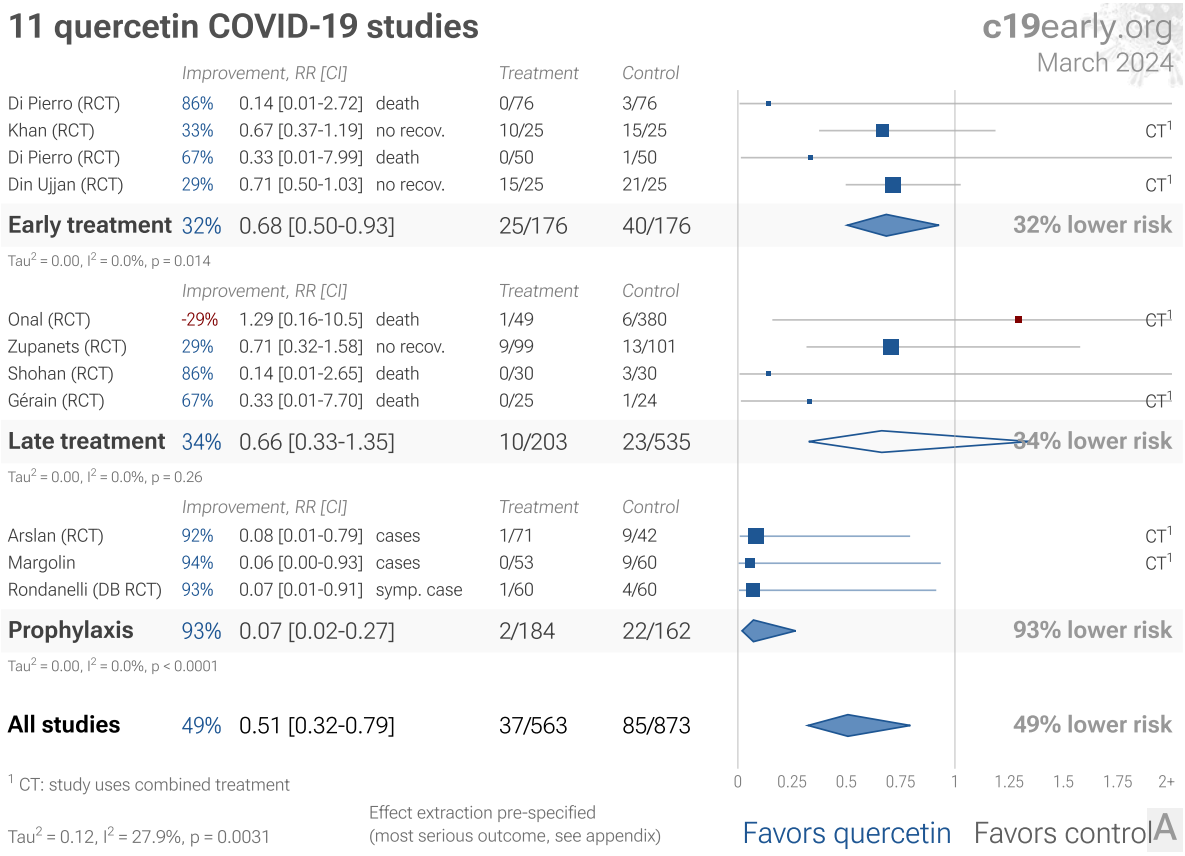
HIGHLIGHTS

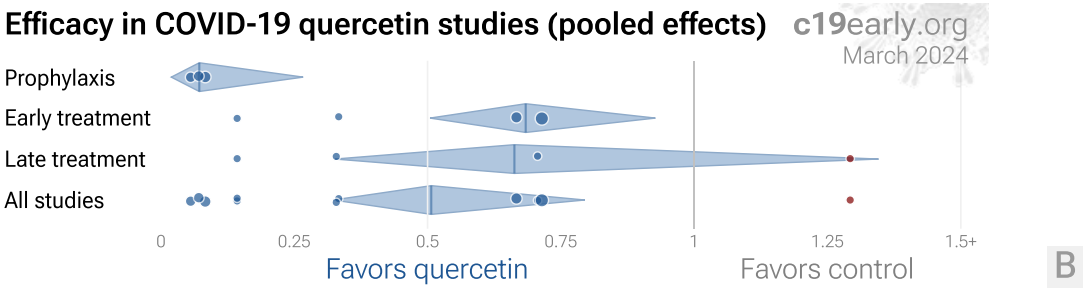
Quercetin reduces risk for COVID-19 with very high confidence for ICU admission, hospitalization, recovery, cases, viral clearance, and in pooled analysis, and very low confidence for mortality and ventilation. Studies typically use advanced formulations for greatly improved bioavailability.

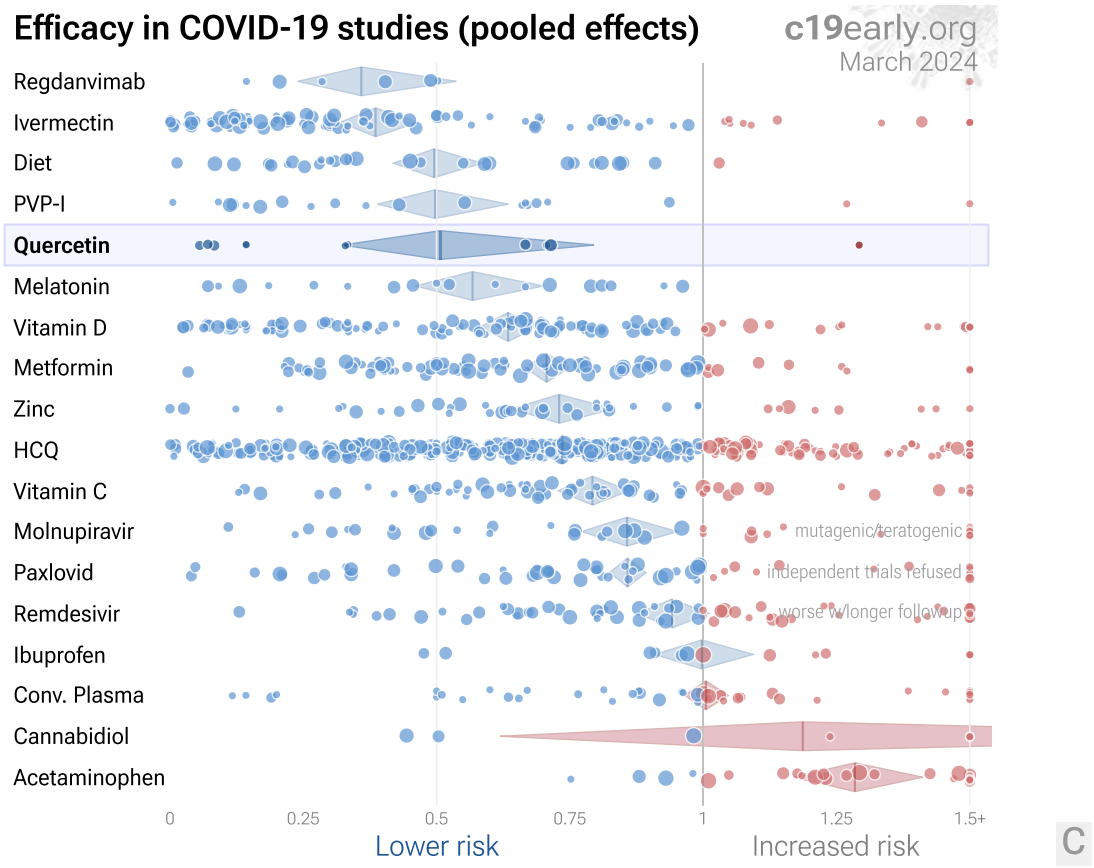
Quercetin was the 24th treatment shown effective with ≥3 clinical studies in July 2021, now known with $p = 0.0031$ from 11 studies.

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.







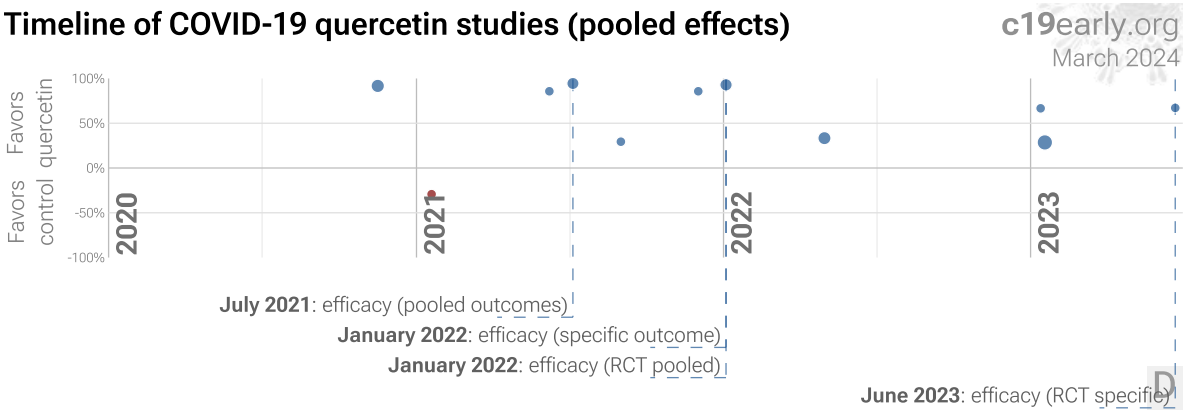


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the 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 quercetin 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 6.0 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 6.0 months, compared to using pooled outcomes. Efficacy based on specific outcomes in RCTs was delayed by 17.5 months, compared to using pooled outcomes in RCTs.

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, or minimization of side effects, with quercetin or metabolites via binding to the spike *Note B, Alavi, Azmi, Chandran, Kandeil, Mandal, Moschovou, Nguyen, Pan, Thapa, Şimşek*, M^{pro} *Note C, Akinwumi, Alanzi, Ibeh, Kandeil, Mandal, Moschovou, Nguyen, Qin, Rehman, Sekiou, Singh, Thapa, Wang, Zhang*, RNA-dependent RNA polymerase *Note D, Corbo*, PLpro *Note E, Ibeh, Zhang*, ACE2 *Note F, Chandran, Ibeh, Qin, Thapa, Şimşek, Alkafaas*, TMPRSS2 *Note G, Chandran*, helicase *Note H, Alanzi, Singh (B)*, endoribonuclease *Note I, Alavi*, cathepsin L *Note J, Ahmed*, Wnt-3 *Note K, Chandran*, FZD *Note L, Chandran*, LRP6 *Note M, Chandran*, ezrin *Note N, Chellasamy*, ADRP *Note O, Nguyen*, NRP1 *Note P, Şimşek*, PTGS2 *Note Q, Qin*, HSP90AA1 *Note R, Qin*, matrix metalloproteinase 9 *Note S, Sai Ramesh*, IL-6 *Note T, Yang (B), Yang (C)*, IL-10 *Note U, Yang (B)*, VEGFA *Note V, Yang (C)*, and RELA *Note W, Yang (C)* proteins. *In Vitro* studies demonstrate efficacy in Calu-3 *Note X, DiGuilio*, A549 *Note Y, Yang (B)*, HEK293-ACE2+ *Note Z, Singh (C)*, Huh-7 *Note AA, Pan*, Caco-2 *Note AB, Roy*, Vero E6 *Note AC, Kandeil, El-Megharbel, Roy*, mTEC *Note AD, Wu*, and RAW264.7 *Note AE, Wu* cells. Animal studies demonstrate efficacy in K18-hACE2 mice *Note AF, Aguado*, db/db mice *Note AG, Wu, Wu (B)*, BALB/c mice *Note AH, Shaker*, and rats *El-Megharbel (B)*. Quercetin reduced proinflammatory cytokines and protected lung and kidney tissue against LPS-induced damage in mice *Shaker*.

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

Treatment timing. Figure 2 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

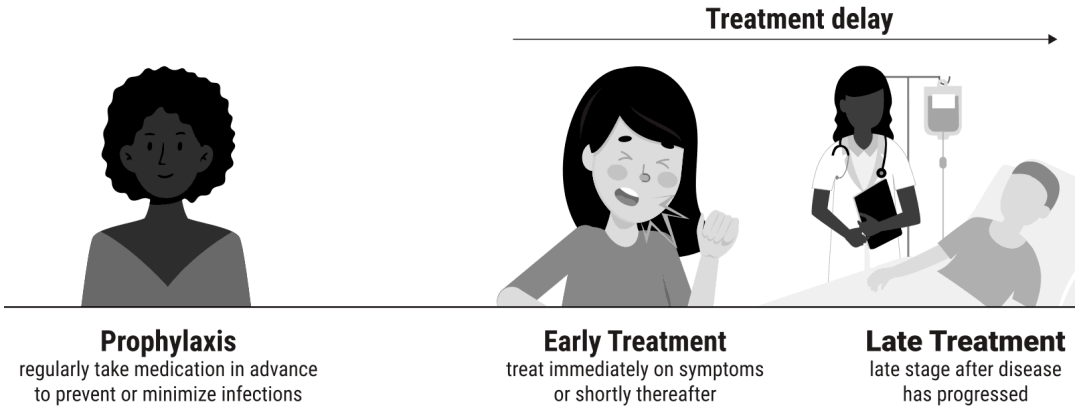


Figure 2. Treatment stages.

Preclinical Research

In Silico studies predict inhibition of SARS-CoV-2, or minimization of side effects, with quercetin or metabolites via binding to the spike Note B, Alavi, Azmi, Chandran, Kandeil, Mandal, Moschovou, Nguyen, Pan, Thapa, Şimşek, M^{pro} Note C, Akinwumi, Alanzi, Ibeh, Kandeil, Mandal, Moschovou, Nguyen, Qin, Rehman, Sekiou, Singh, Thapa, Wang, Zhang, RNA-dependent RNA polymerase Note D, Corbo, PLpro Note E, Ibeh, Zhang, ACE2 Note F, Chandran, Ibeh, Qin, Thapa, Şimşek, Alkafaas, TMPRSS2 Note G, Chandran, helicase Note H, Alanzi, Singh (B), endoribonuclease Note I, Alavi, cathepsin L Note J, Ahmed, Wnt-3 Note K, Chandran, FZD Note L, Chandran, LRP6 Note M, Chandran, ezrin Note N, Chellasamy, ADRP Note O, Nguyen, NRP1 Note P, Şimşek, PTGS2 Note Q, Qin, HSP90AA1 Note R, Qin, matrix metalloproteinase 9 Note S, Sai Ramesh, IL-6 Note T, Yang (B), Yang (C), IL-10 Note U, Yang (B), VEGFA Note V, Yang (C), and RELA Note W, Yang (C) proteins. *In Vitro* studies demonstrate efficacy in Calu-3 Note X, DiGuilio, A549 Note Y, Yang (B), HEK293-ACE2+ Note Z, Singh (C), Huh-7 Note AA, Pan, Caco-2 Note AB, Roy, Vero E6 Note AC, Kandeil, El-Megharbel, Roy, mTEC Note AD, Wu, and RAW264.7 Note AE, Wu cells. Animal studies demonstrate efficacy in K18-hACE2 mice Note AF, Aguado, db/db mice Note AG, Wu, Wu (B), BALB/c mice Note AH, Shaker, and rats El-Megharbel (B). Quercetin reduced proinflammatory cytokines and protected lung and kidney tissue against LPS-induced damage in mice Shaker.

28 *In Silico* studies support the efficacy of quercetin Ahmed, Akinwumi, Alanzi, Alavi, Alkafaas, Azmi (B), Chandran, Chellasamy, Corbo, El-Megharbel, Ibeh, Kandeil, Mandal, Moschovou, Nguyen, Pan, Qin, Rehman, Sai Ramesh, Sekiou (B), Singh, Singh (B), Thapa (B), Wang, Yang (B), Yang (C), Zhang, Şimşek.

14 *In Vitro* studies support the efficacy of quercetin Aguado, Bahun, DiGuilio, El-Megharbel, Goc, Kandeil, Munafò, Pan, Roy, Singh (C), Wu, Xu, Yang (B), Zhang (B).

5 *In Vivo* animal studies support the efficacy of quercetin Aguado, El-Megharbel, Shaker, Wu, Wu (B).

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.

Viral Lifecycle

SARS-CoV-2 infection and replication involves multiple steps as shown in Table 1. Each step can be disrupted by therapeutics. The timing of each step may vary significantly, and the cycle is continuous, with released virions attaching to new host cells. The efficacy of treatments depends on the delay from infection and the steps targeted. Preclinical research suggests that quercetin is most likely to interfere with early steps in the viral lifecycle, suggesting greater benefit for prophylaxis and very early treatment.

Step	Details	Approximate timing	Predicted benefit of quercetin
Viral attachment	Viral binding to specific receptors on host cell surface	Initial step	High: spike and ACE2 binding
Viral entry	Uptake of viral particle into host cell via mechanisms like endocytosis or membrane fusion	Within minutes to 1 hour	Moderate: spike binding
Viral uncoating and release	Disassembly of virion to release viral genome into host cell	1-2 hours	-
Genome replication and transcription	Production of viral mRNAs from the genome template and genome copies	2-4 hours	Moderate: RdRp binding
Translation and protein processing	Production of new viral proteins from the viral transcripts	4-8 hours	Moderate: M^{pro} and PLpro binding
Viral assembly and budding	Self-assembly of viral components and encapsidation of viral genome to form new viral particles, often utilizing host cell membrane	8-12 hours	-
Viral release	Escape of newly formed virions from the host cell to spread infection	12-24 hours	-

Table 1. Lifecycle of SARS-CoV-2 infection and replication.

Results

Table 2 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, with different exclusions, and for specific outcomes. Table 3 shows results by treatment stage. Figure 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, recovery, cases, viral clearance, peer reviewed studies, and all studies excluding combined treatment studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**49%** [21-68%] **	11	1,436	109
After exclusions	**41%** [12-60%] **	9	1,223	89
Peer-reviewed studies	**39%** [14-57%] **	10	1,323	102
Excluding combined treatment	**68%** [12-89%] *	5	632	66
Randomized Controlled Trials	**43%** [16-62%] **	10	1,323	104
Mortality	**61%** [-35-89%]	5	790	58
ICU admission	**74%** [29-90%] **	5	790	58
Hospitalization	**48%** [19-67%] **	3	301	40
Recovery	**34%** [21-45%] ****	7	938	66
Cases	**93%** [73-98%] ****	3	346	24
Viral	**56%** [38-68%] ****	3	200	26
RCT mortality	**61%** [-35-89%]	5	790	58
RCT hospitalization	**48%** [19-67%] **	3	301	40

Table 2. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, with different exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * p<0.05 ** p<0.01 *** p<0.001 **** p<0.0001.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	**32%** [7-50%] *	**34%** [-35-67%]	**93%** [73-98%] ****
After exclusions	**31%** [7-49%] *	**34%** [-35-67%]	**94%** [64-99%] **
Peer-reviewed studies	**32%** [7-50%] *	**34%** [-35-67%]	**94%** [64-99%] **
Excluding combined treatment	**79%** [-83-98%]	**40%** [-53-76%]	**93%** [9-99%] *
Randomized Controlled Trials	**32%** [7-50%] *	**34%** [-35-67%]	**92%** [66-98%] ***
Mortality	**79%** [-83-98%]	**47%** [-138-88%]	
ICU admission	**87%** [-5-98%]	**75%** [-10-94%]	
Hospitalization	**68%** [31-85%] **	**38%** [12-56%] **	
Recovery	**33%** [16-47%] ***	**37%** [13-54%] **	
Cases			**93%** [73-98%] ****
Viral	**56%** [38-68%] ****		
RCT mortality	**79%** [-83-98%]	**47%** [-138-88%]	
RCT hospitalization	**68%** [31-85%] **	**38%** [12-56%] **	

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.

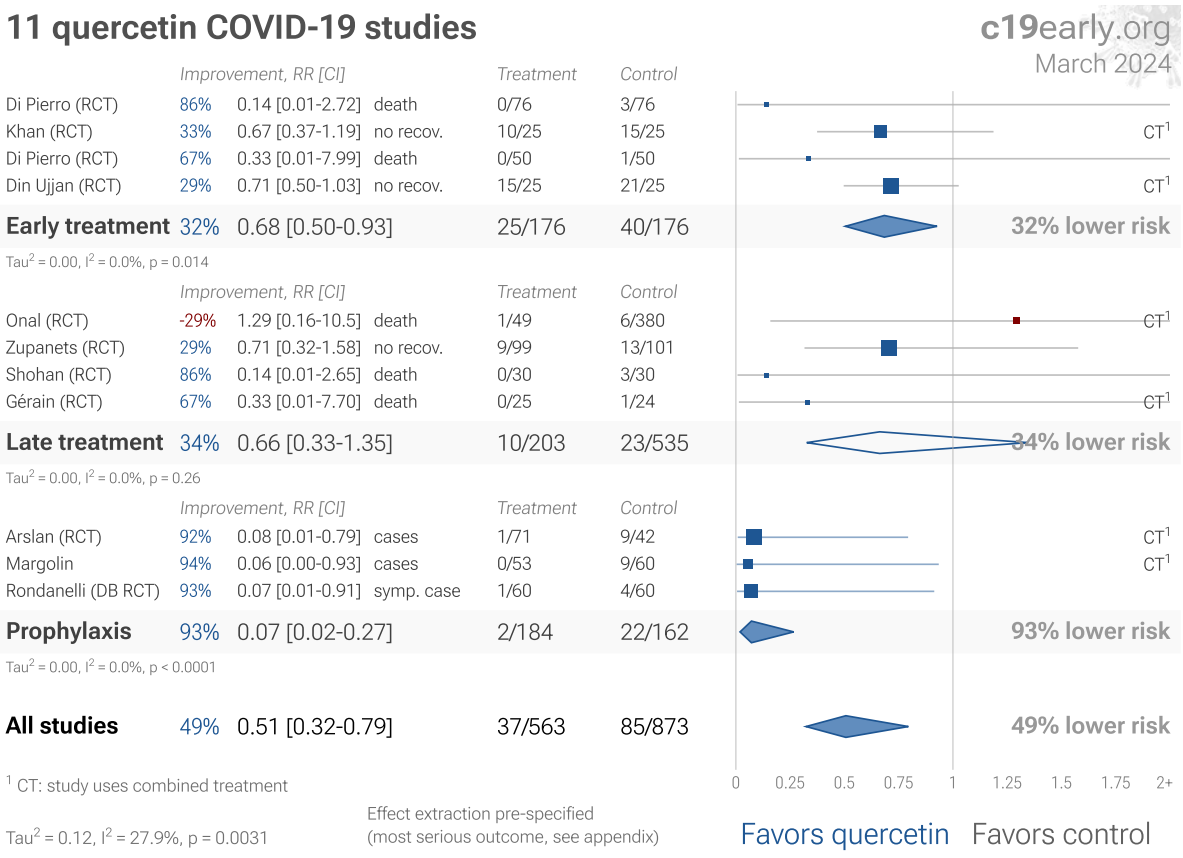


Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

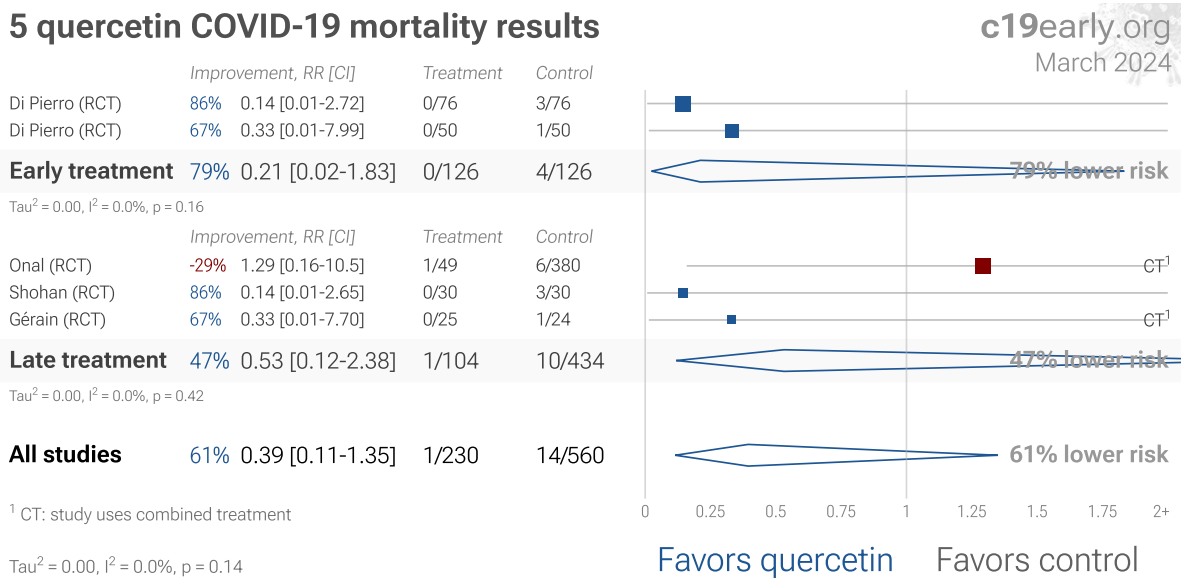


Figure 4. **Random effects meta-analysis for mortality results.**

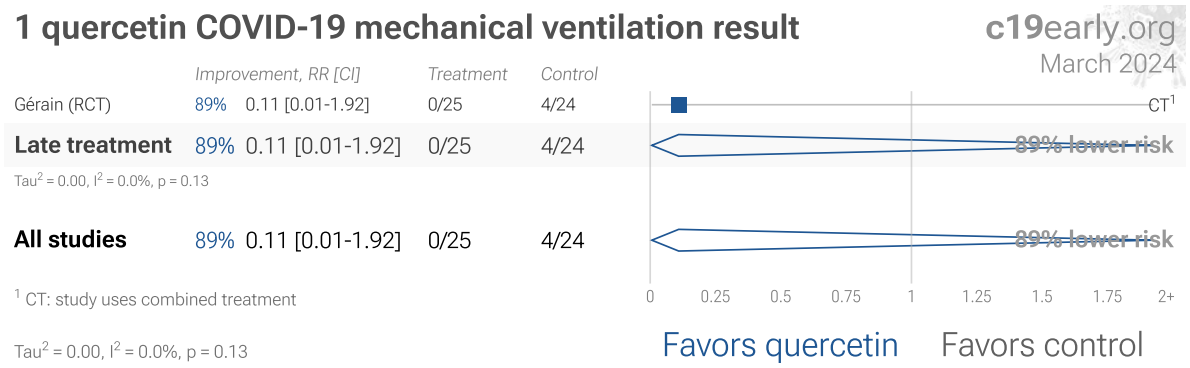


Figure 5. Random effects meta-analysis for ventilation.

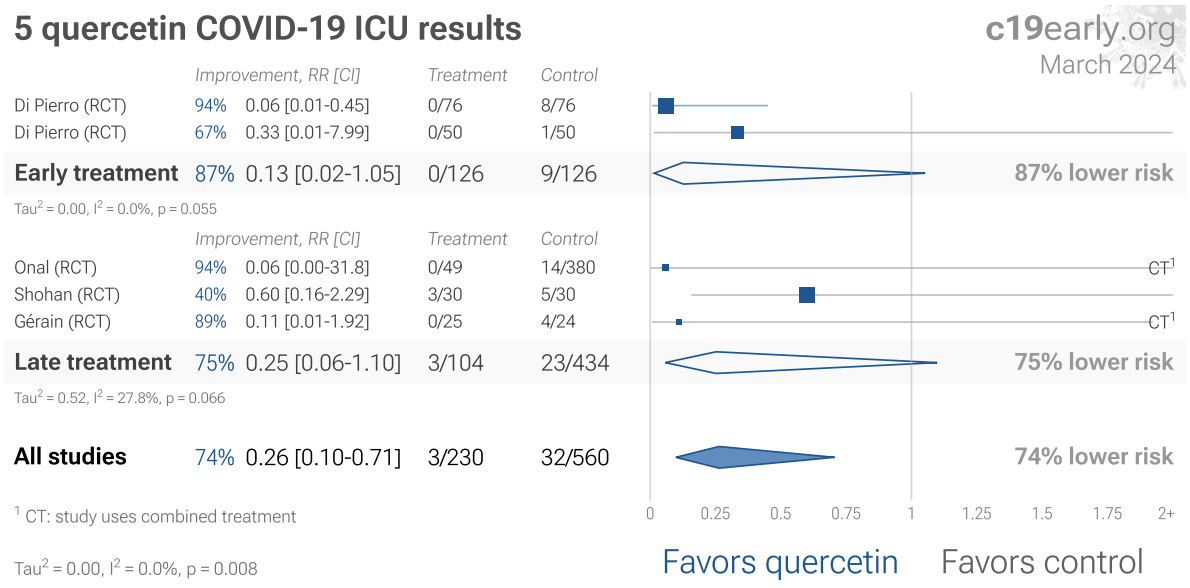


Figure 6. Random effects meta-analysis for ICU admission.

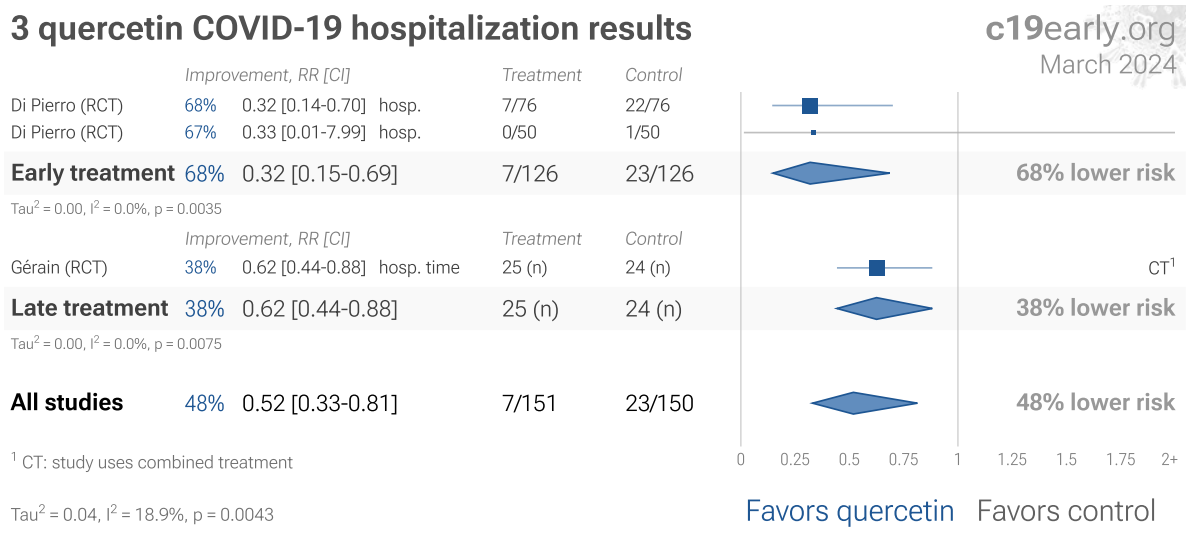


Figure 7. Random effects meta-analysis for hospitalization.

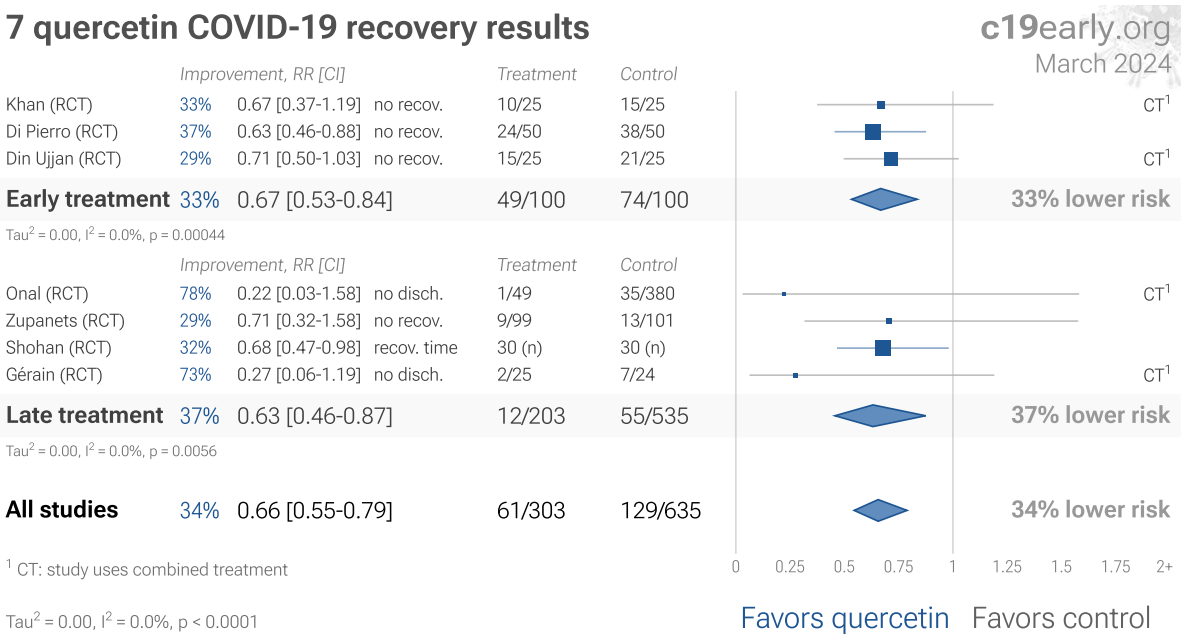


Figure 8. Random effects meta-analysis for recovery.

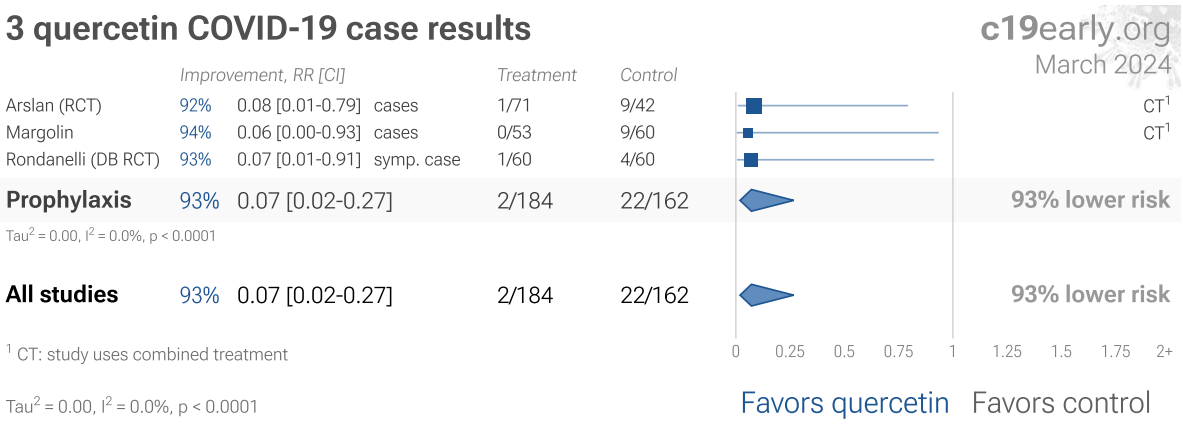


Figure 9. Random effects meta-analysis for cases.

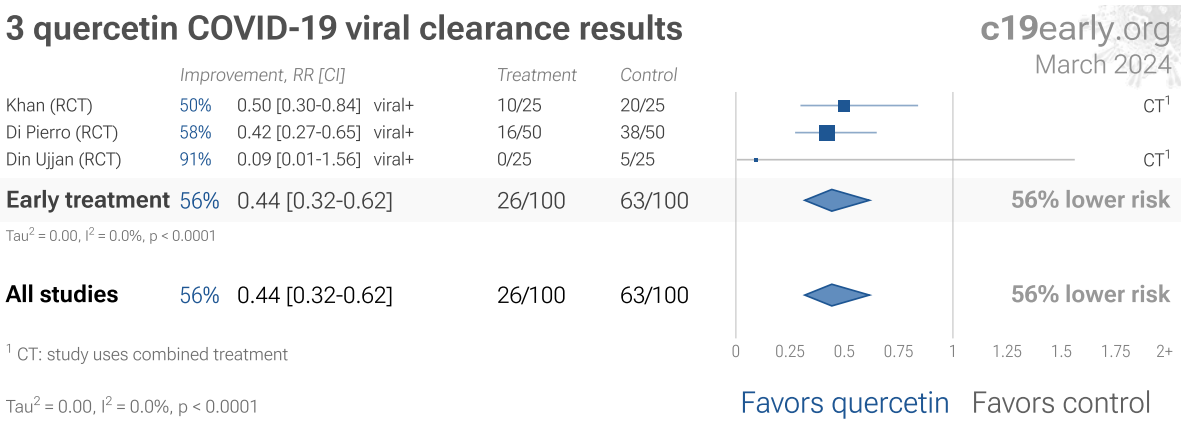


Figure 10. Random effects meta-analysis for viral clearance.

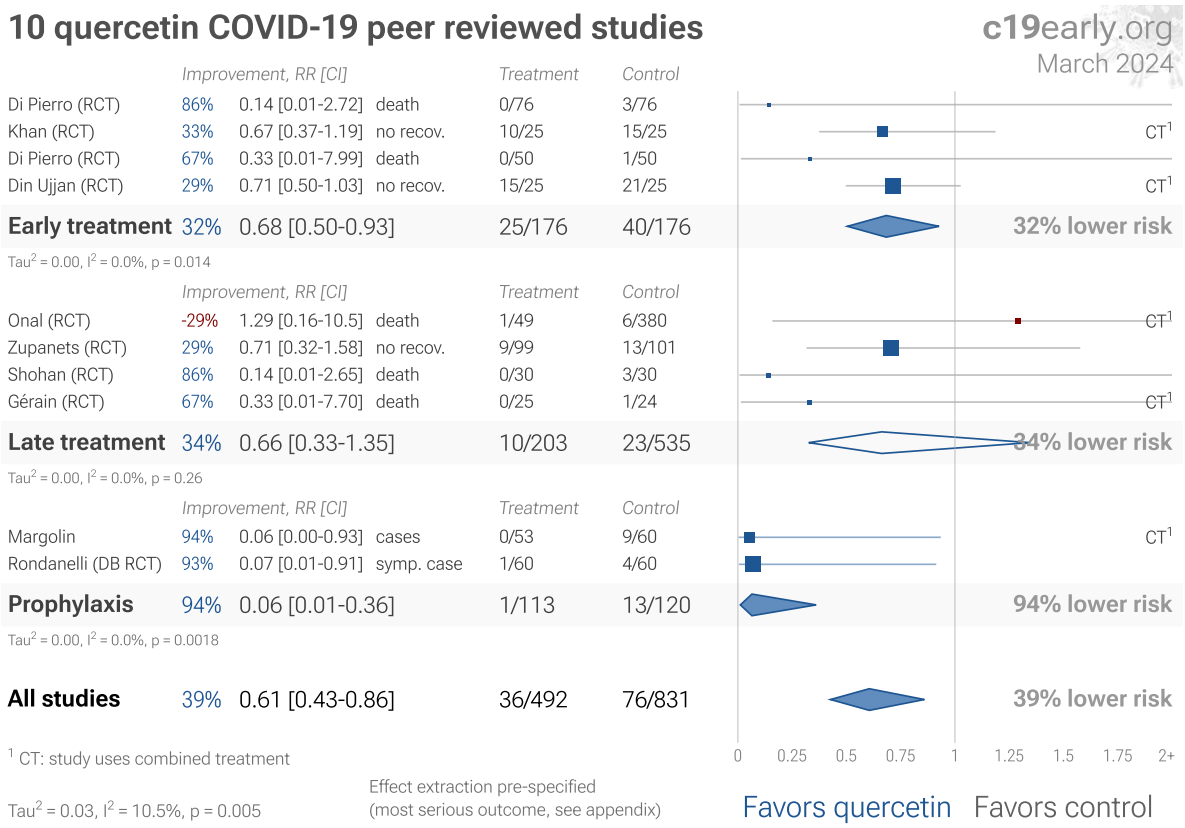


Figure 11. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with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

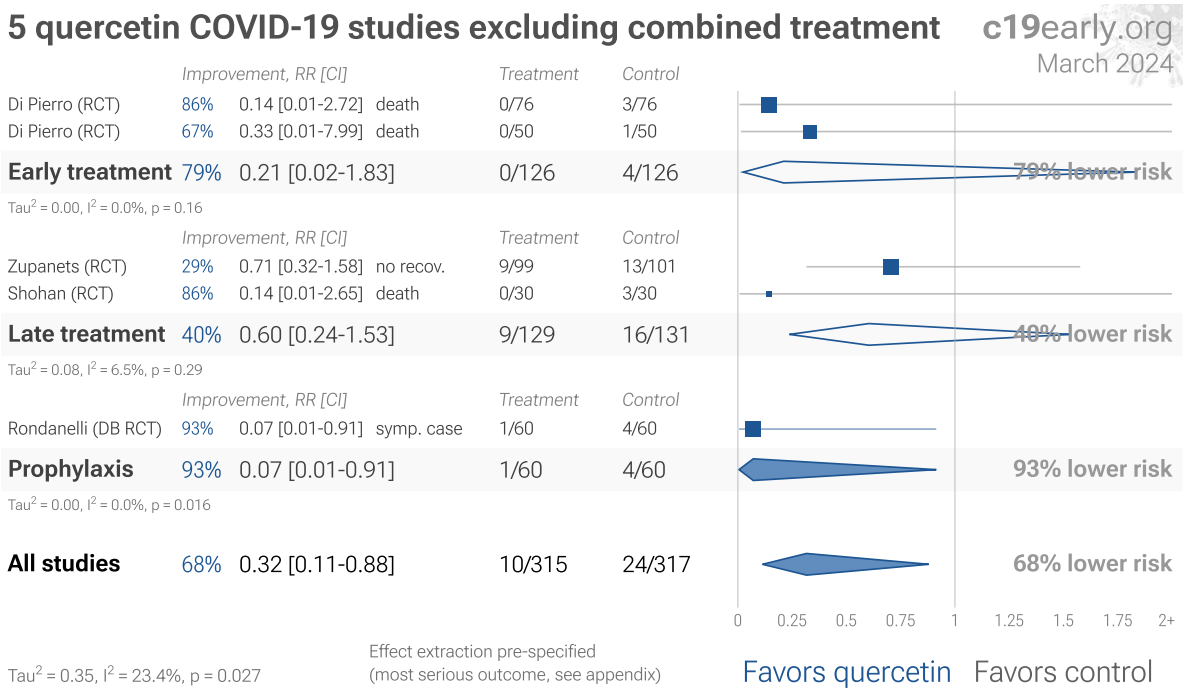


Figure 12. **Random effects meta-analysis for all studies excluding combined treatment studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

Randomized Controlled Trials (RCTs)

Figure 13 shows a comparison of results for RCTs and non-RCT studies. Figure 14, 15, and 16 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).

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

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.

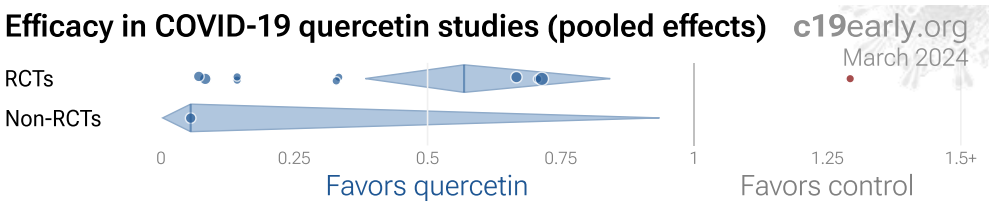


Figure 13. **Results for RCTs and non-RCT studies.**

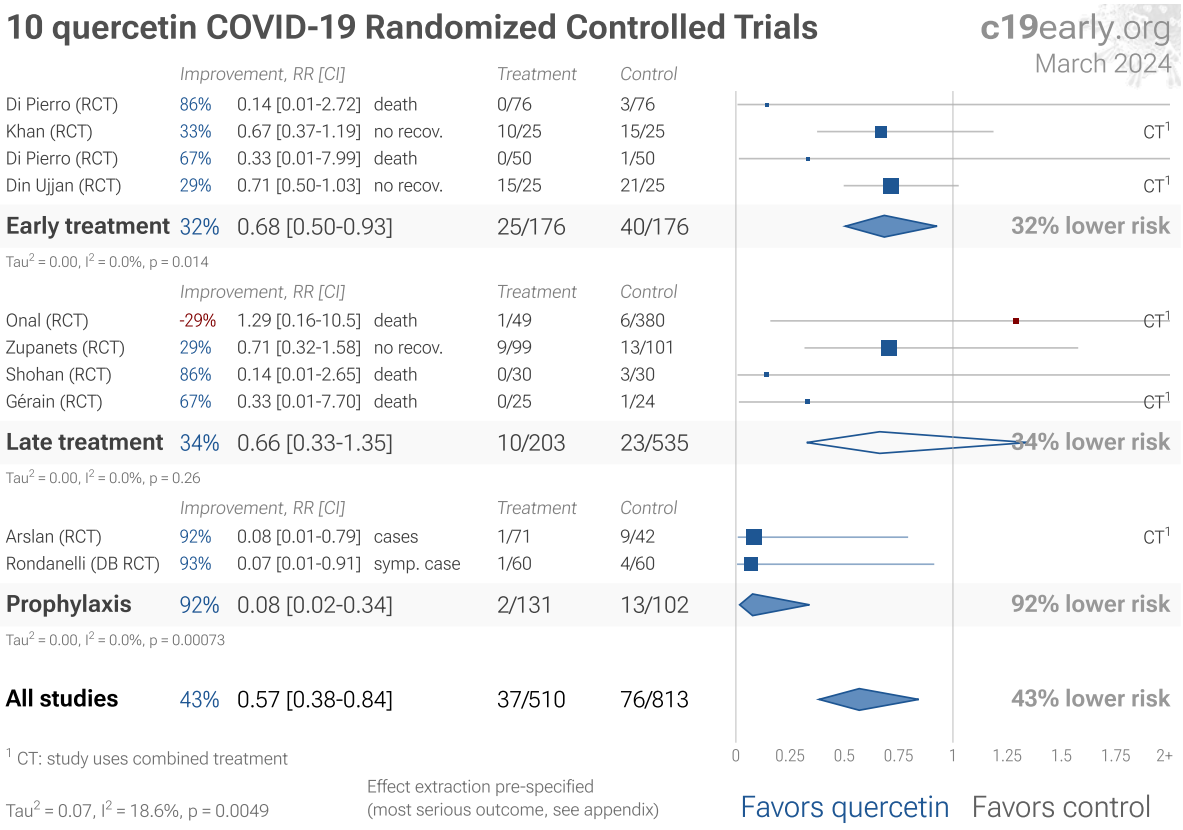


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

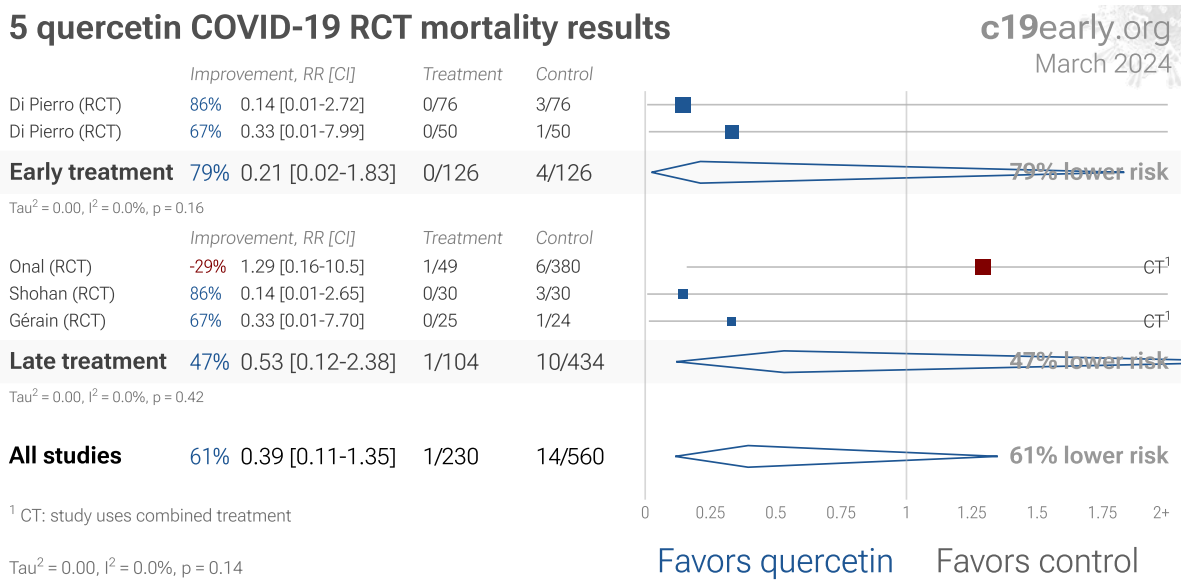


Figure 15. Random effects meta-analysis for RCT mortality results.

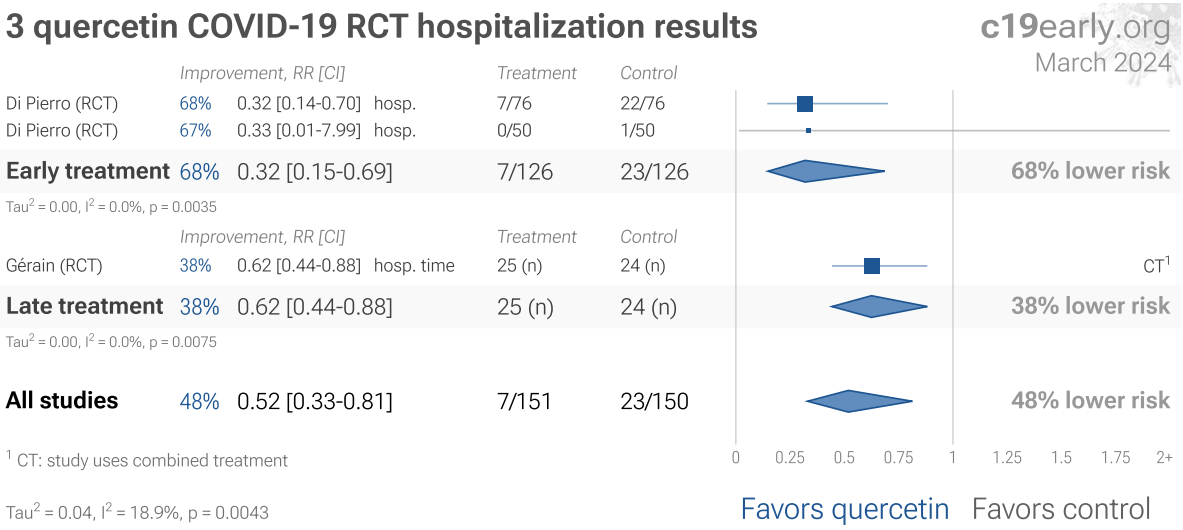


Figure 16. Random effects meta-analysis for RCT hospitalization results.

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 17 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Arslan, paper no longer available at the source, and the contact does not reply to queries.

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

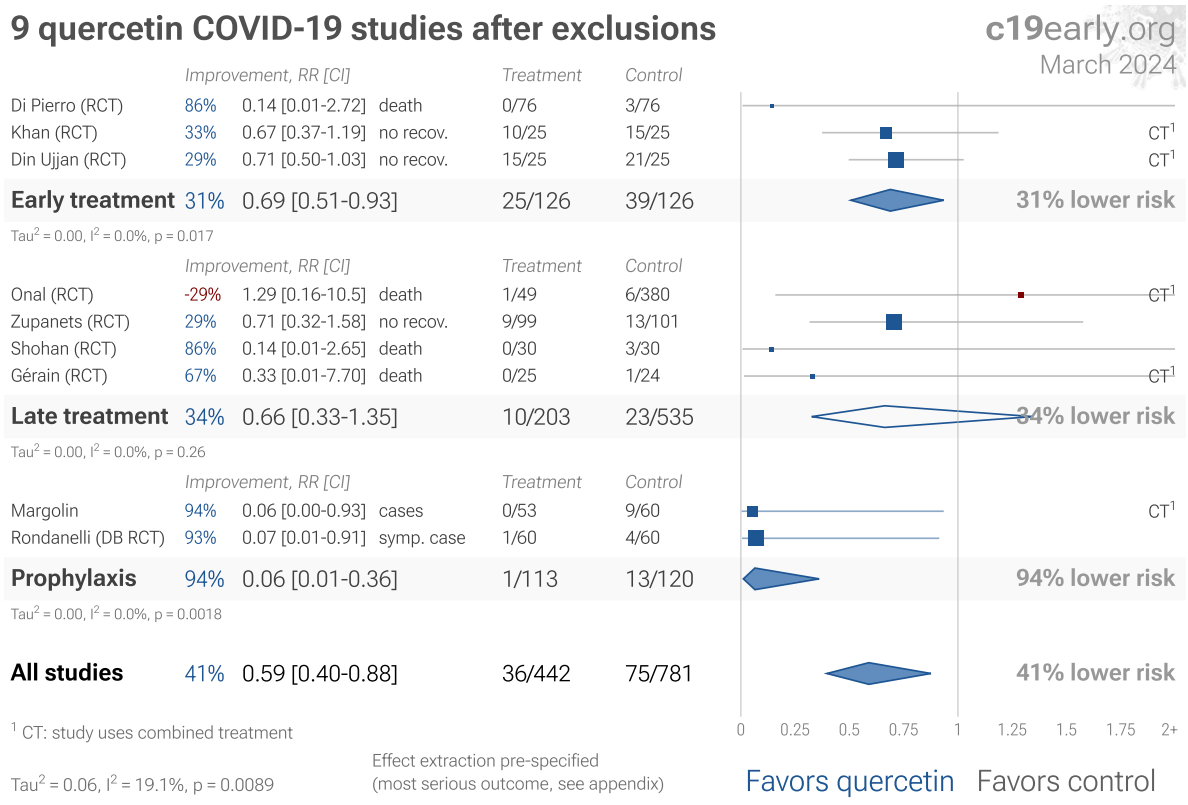


Figure 17. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details 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 18 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.

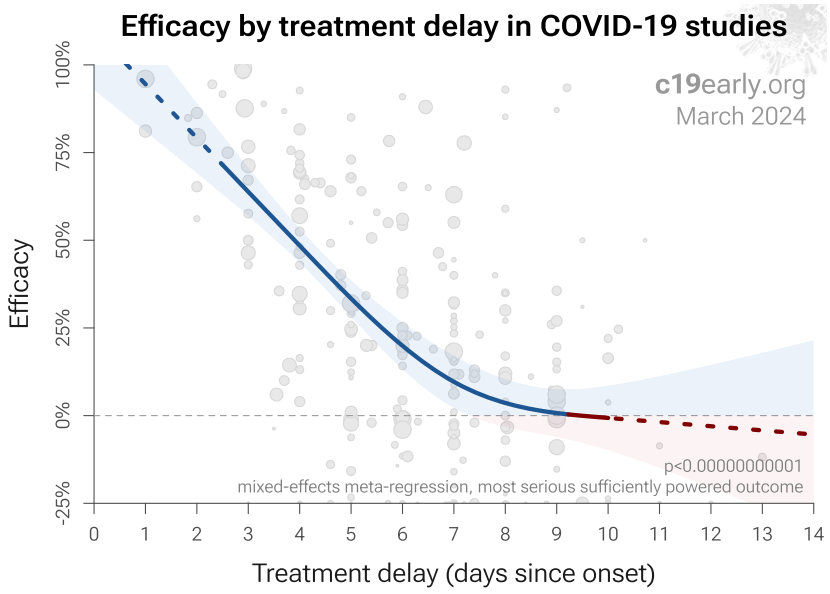


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 (B)* 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 19. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, 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.

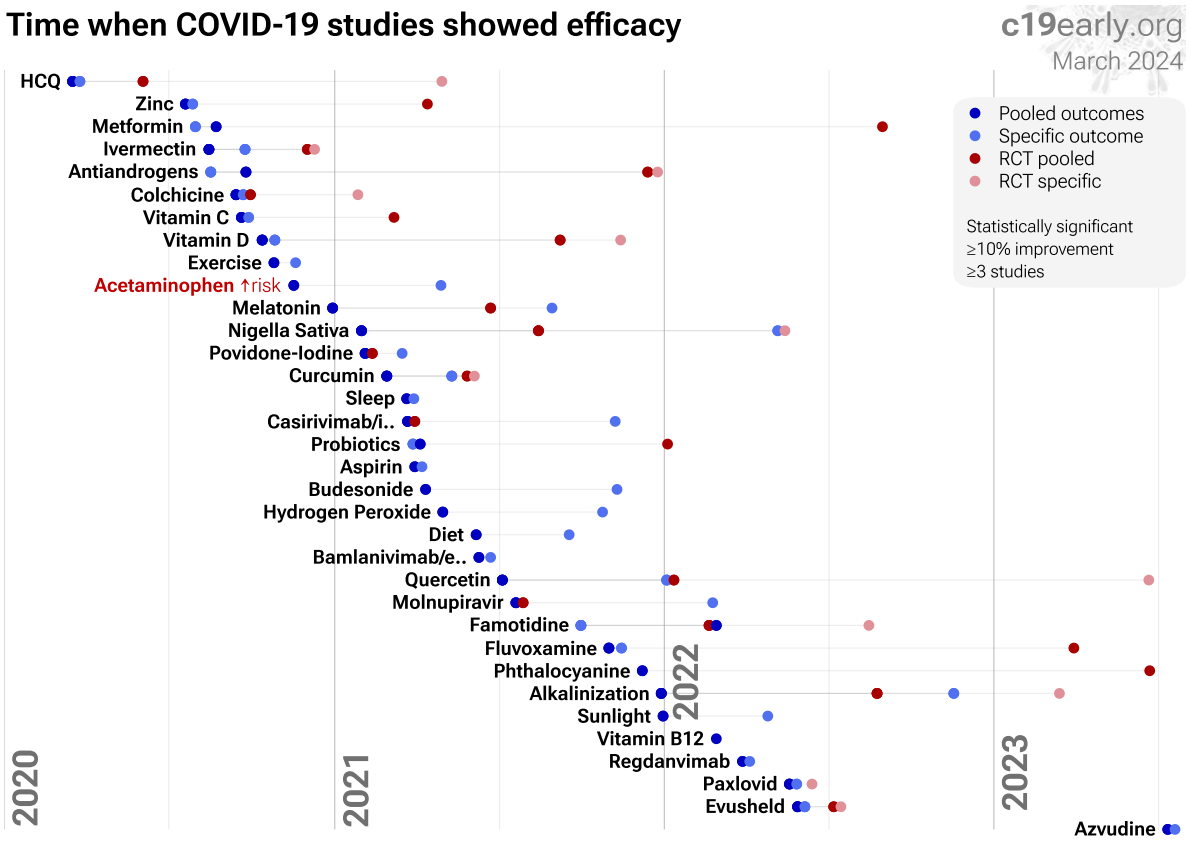


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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 quercetin, 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 20 shows a scatter plot of results for prospective and retrospective studies. 100% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 90% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 94% improvement, compared to 67% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.

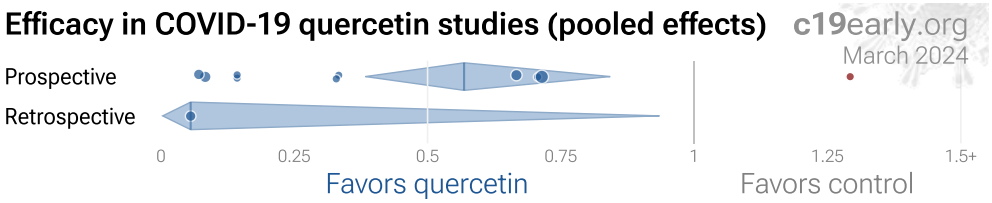


Figure 20. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 21 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.

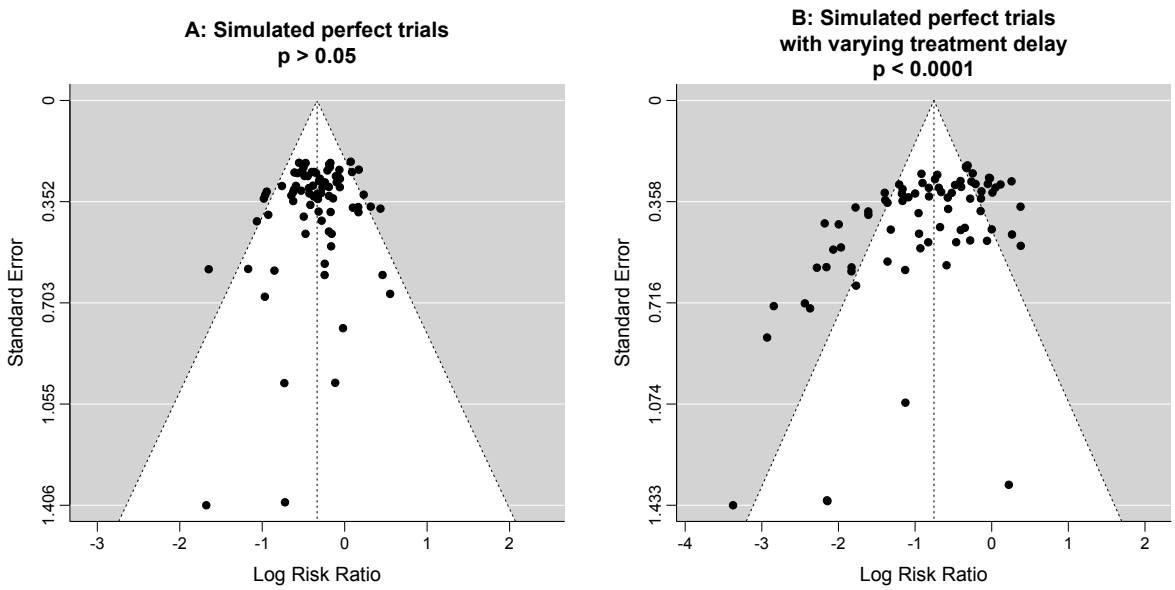


Figure 21. Example funnel plot analysis for simulated perfect trials.

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. Quercetin for COVID-19 lacks this because it is an inexpensive and widely available supplement. In contrast, most COVID-19 quercetin 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 quercetin 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. 6 of 11 studies combine treatments. The results of quercetin alone may differ. 5 of 10 RCTs use combined treatment. Other meta analyses show significant improvements with quercetin for mortality *Ziaei*, ICU admission *Cheema, Ziaei*, and hospitalization *Cheema, Ziaei*.

Reviews. Many reviews cover quercetin for COVID-19, presenting additional background on mechanisms, formulations, and related results, including *Agrawal, Biancatelli, Derosa, Dinda, Gasmi, Georgiou, Imran, Massimo Magro, Matías-Pérez, Mirza, Rizky, Shorobi*.

Conclusion

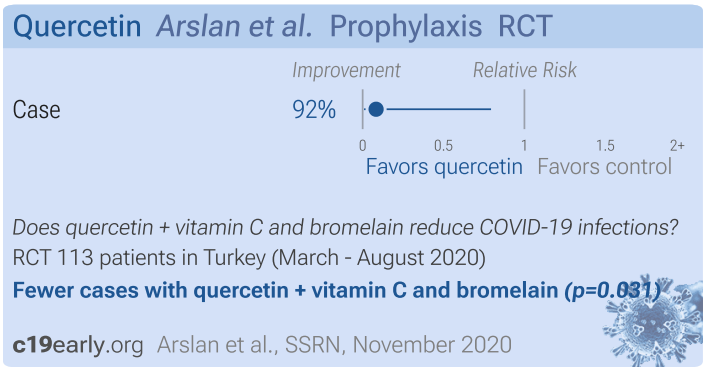
Studies to date show that quercetin is an effective treatment for COVID-19. Statistically significant lower risk is seen for ICU admission, hospitalization, recovery, cases, and viral clearance. 10 studies from 8 independent teams in 7 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 49% [21-68%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies, better after excluding studies using combined treatment, and slightly worse for peer-reviewed studies. Results are robust — in exclusion sensitivity analysis 8 of 11 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 quercetin for mortality *Ziaei*, ICU admission *Cheema, Ziaei*, and hospitalization *Cheema, Ziaei*.

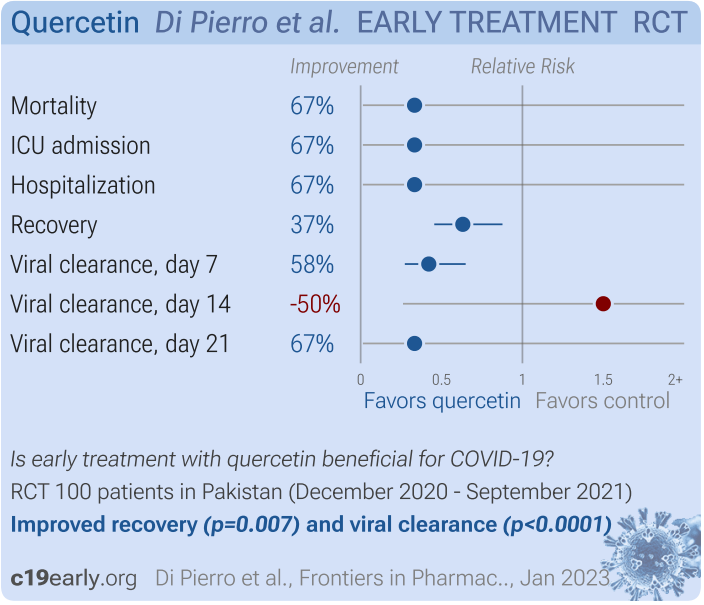
Study Notes

Arslan



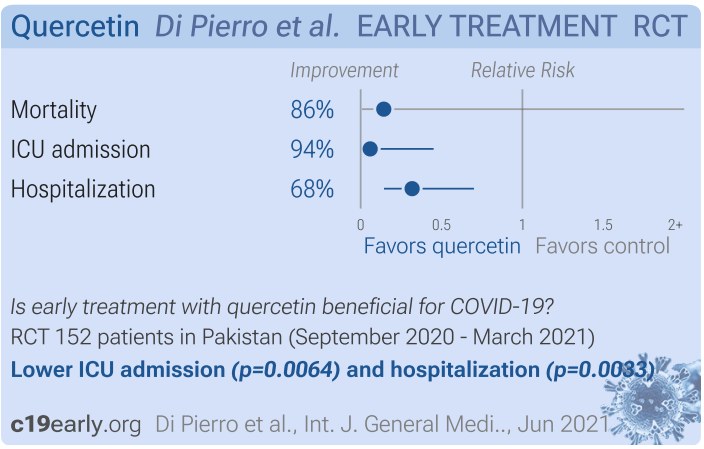
Arslan: Small prophylaxis RCT with 113 patients showing fewer cases with quercetin + vitamin C + bromelain prophylaxis. NCT04377789. Note that this paper disappeared from SSRN without explanation.

Di Pierro



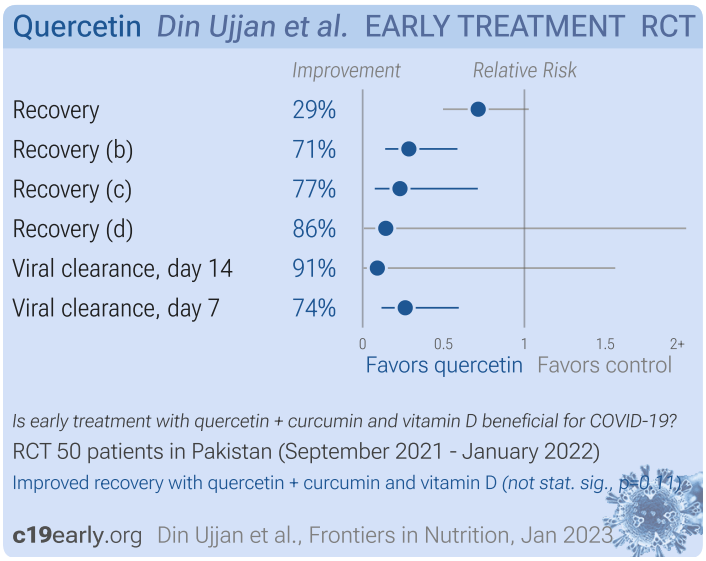
Di Pierro: RCT 100 outpatients in Pakistan, 50 treated with quercetin phytosome, showing faster viral clearance and improved recovery with treatment. Patients in the treatment group were significantly younger (41 vs. 54).

Di Pierro



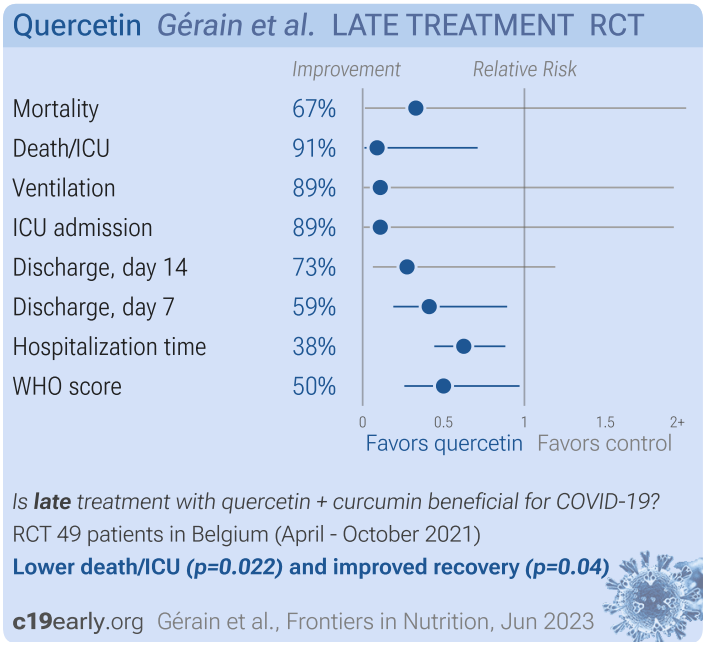
Di Pierro (B): RCT 152 outpatients in Pakistan, 76 treated with quercetin phytosome, showing lower mortality, ICU admission, and hospitalization with treatment.

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.

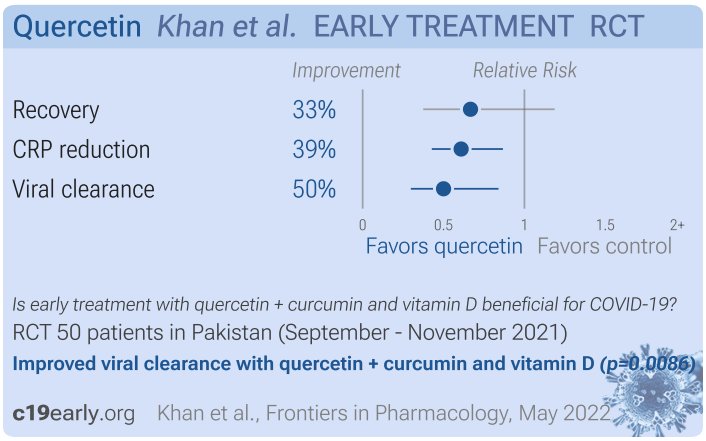
Gérain



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.

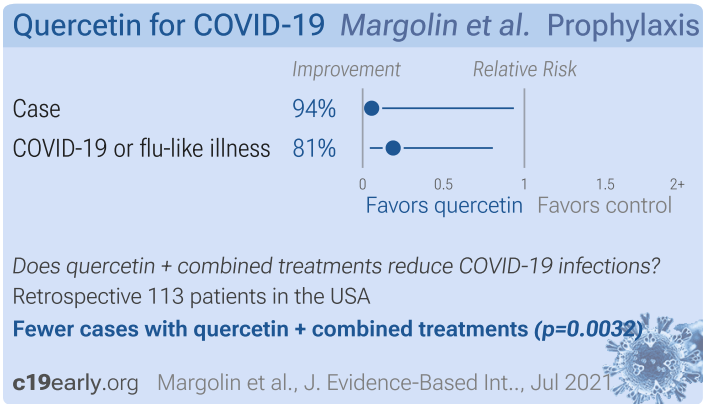
336mg curcumin, 520mg quercetin, and 18µg vitamin D3 daily for 14 days. The control arm received 20µg vitamin D3 daily. Baseline fever favored treatment while vaccination favored control.

Khan



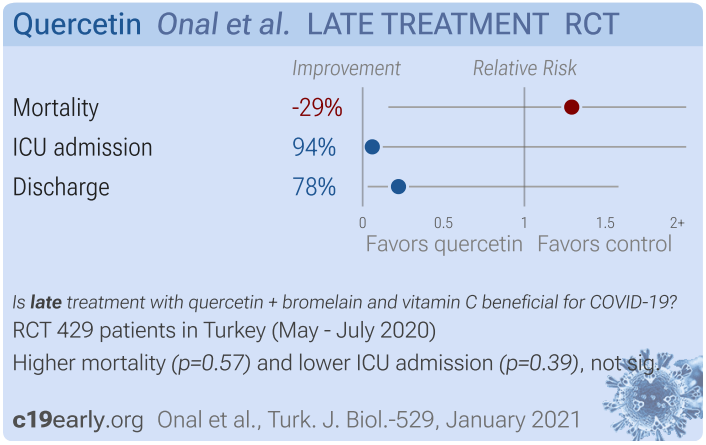
Khan: RCT 50 COVID+ outpatients in Pakistan, 25 treated with curcumin, quercetin, and vitamin D, showing significantly faster viral clearance, significantly improved CRP, and faster resolution of acute symptoms (p=0.154). 168mg curcumin, 260mg quercetin and 360IU cholecalciferol.

Margolin



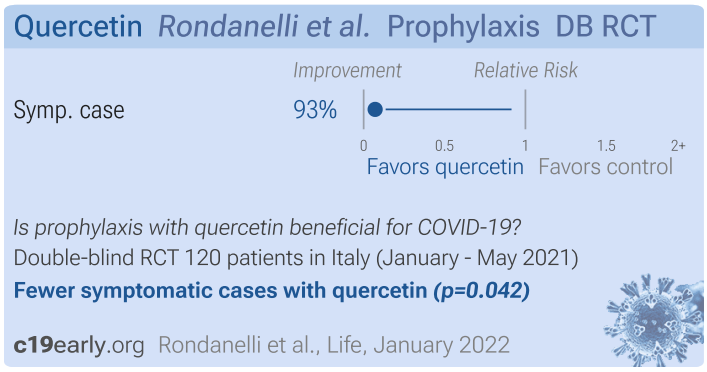
Margolin: Retrospective 113 outpatients, 53 (patient choice) treated with zinc, quercetin, vitamin C/D/E, l-lysine, and quina, showing lower cases with treatment. Results are subject to selection bias and limited information on the groups is provided. See *journals.sagepub.com*.

Onal



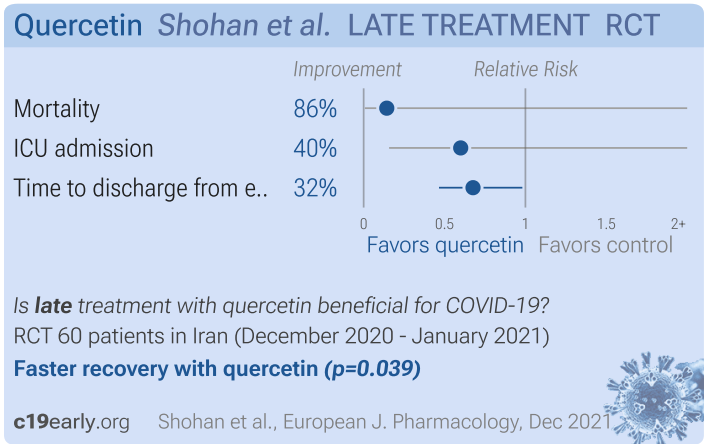
Onal: RCT 447 moderate-to-severe hospitalized patients in Turkey, 52 treated with quercetin, bromelain, and vitamin C, showing no statistically significant difference in clinical outcomes. NCT04377789.

Rondanelli



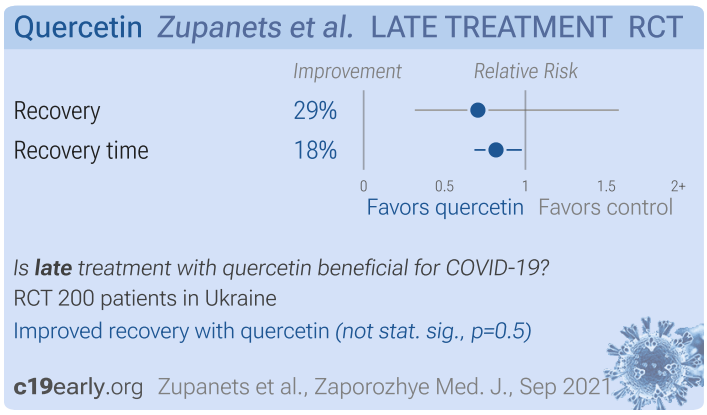
Rondanelli: RCT 120 healthcare workers, 60 treated with quercetin phytosome, showing lower risk of cases with treatment. Quercetin phytosome 250mg twice a day.

Shohan



Shohan: Small RCT with 60 severe hospitalized patients in Iran, 30 treated with quercetin, showing shorter time until discharge. All patients received remdesivir or favipiravir, and vitamin C, vitamin D, famotidine, zinc, dexamethasone, and magnesium (depending on serum levels). Quercetin 1000mg daily for 7 days. IRCT20200419047128N2.

Zupanets



Zupanets: RCT 200 patients in Ukraine, 99 treated with IV quercetin/polyvinylirolidone followed by oral quercetin/pectin, showing improved recovery with treatment.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are quercetin 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 quercetin 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 (C)*. 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/qmeta.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.

Di Pierro, 1/13/2023, Randomized Controlled Trial, Pakistan, peer-reviewed, mean age 47.6, 13 authors, study period December 2020 - September 2021, trial NCT04861298 (history), excluded in exclusion analyses: randomization resulted in significant baseline differences that were not adjusted for.	risk of death, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 50 (0.0%), control 1 of 50 (2.0%), NNT 50, 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, $p = 1.00$, treatment 0 of 50 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 50 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no recovery, 36.8% lower, RR 0.63, $p = 0.007$, treatment 24 of 50 (48.0%), control 38 of 50 (76.0%), NNT 3.6, day 7.
	risk of no viral clearance, 57.9% lower, RR 0.42, $p < 0.001$, treatment 16 of 50 (32.0%), control 38 of 50 (76.0%), NNT 2.3, mid-recovery, day 7.
	risk of no viral clearance, 50.0% higher, RR 1.50, $p = 1.00$, treatment 3 of 50 (6.0%), control 2 of 50 (4.0%), day 14.
	risk of no viral clearance, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 50 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 21.
Di Pierro (B), 6/8/2021, Randomized Controlled Trial, Pakistan, peer-reviewed, 19 authors, study period September 2020 - March 2021, trial NCT04578158 (history).	risk of death, 85.7% lower, RR 0.14, $p = 0.25$, treatment 0 of 76 (0.0%), control 3 of 76 (3.9%), NNT 25, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 94.1% lower, RR 0.06, $p = 0.006$, treatment 0 of 76 (0.0%), control 8 of 76 (10.5%), NNT 9.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 68.2% lower, RR 0.32, $p = 0.003$, treatment 7 of 76 (9.2%), control 22 of 76 (28.9%), NNT 5.1.
Din Ujjan, 1/18/2023, Randomized Controlled Trial, Pakistan, peer-reviewed, 6 authors, study period 21 September, 2021 - 21 January, 2022, this trial uses	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

multiple treatments in the treatment arm (combined with curcumin and vitamin D) - results of individual treatments may vary, trial NCT04603690 (history).	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 curcumin 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.

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.

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 curcumin) - 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.
Onal, 1/19/2021, Randomized Controlled Trial, Turkey, peer-reviewed, 10 authors, study period 7 May, 2020 - 8 July, 2020, this trial uses multiple treatments in the treatment arm (combined with bromelain and vitamin C) - results of individual treatments may vary, trial NCT04377789 (history).	risk of death, 29.3% higher, RR 1.29, *p* = 0.57, treatment 1 of 49 (2.0%), control 6 of 380 (1.6%).
	risk of ICU admission, 94.0% lower, RR 0.06, *p* = 0.39, treatment 0 of 49 (0.0%), control 14 of 380 (3.7%), NNT 27, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no hospital discharge, 77.8% lower, RR 0.22, *p* = 0.10, treatment 1 of 49 (2.0%), control 35 of 380 (9.2%), NNT 14.
Shohan, 12/2/2021, Randomized Controlled Trial, Iran, peer-reviewed, mean age 50.9 (treatment) 52.7 (control), 8 authors, study period December 2020 - January 2021, average treatment delay 7.8 days.	risk of death, 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).
	risk of ICU admission, 40.0% lower, RR 0.60, *p* = 0.71, treatment 3 of 30 (10.0%), control 5 of 30 (16.7%), NNT 15.
	time to discharge from end of intervention, 32.4% lower, relative time 0.68, *p* = 0.04, treatment 30, control 30.
Zupanets, 9/1/2021, Randomized Controlled Trial, Ukraine, peer-reviewed, 14 authors.	risk of no recovery, 29.4% lower, RR 0.71, *p* = 0.50, treatment 9 of 99 (9.1%), control 13 of 101 (12.9%), NNT 26.
	recovery time, 18.2% lower, relative time 0.82, *p* = 0.03, treatment 99, control 101.

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.

Arslan, 11/16/2020, Randomized Controlled Trial, Turkey, preprint, 7 authors, study period 20 March, 2020 - 31 August, 2020, this trial uses multiple treatments in the treatment arm (combined with vitamin C and bromelain) - results of individual treatments may vary, trial NCT04377789 (history), excluded in exclusion analyses: paper no longer available at the source, and the contact does not reply to queries.	risk of case, 91.7% lower, RR 0.08, p = 0.03, treatment 1 of 71 (1.4%), control 9 of 42 (21.4%), NNT 5.0, adjusted per study, inverted to make RR<1 favor treatment.
Margolin, 7/6/2021, retrospective, USA, peer-reviewed, 5 authors, this trial uses multiple treatments in the treatment arm (combined with zinc, vitamin C/D/E, l-lysine, and quina) - results of individual treatments may vary.	risk of case, 94.4% lower, RR 0.06, p = 0.003, treatment 0 of 53 (0.0%), control 9 of 60 (15.0%), NNT 6.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of COVID-19 or flu-like illness, 81.1% lower, RR 0.19, p = 0.01, treatment 2 of 53 (3.8%), control 12 of 60 (20.0%), NNT 6.2.
Rondanelli, 1/4/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Italy, peer-reviewed, 12 authors, study period 12 January, 2021 - 25 May, 2021, trial NCT05037240 (history).	risk of symptomatic case, 92.9% lower, HR 0.07, p = 0.04, treatment 1 of 60 (1.7%), control 4 of 60 (6.7%), adjusted per study, inverted to make HR<1 favor treatment, Cox proportional risk.

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 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.

d. 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.

e. The papain-like protease (PLpro) has multiple functions including cleaving viral polyproteins and suppressing the host immune response by deubiquitination and deISGylation of host proteins. Inhibiting PLpro may block viral replication and help restore normal immune responses.

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. 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.

h. The helicase, or nsp13, protein unwinds the double-stranded viral RNA, a crucial step in replication and transcription. Inhibition may prevent viral genome replication and the creation of new virus components.

i. The endoribonuclease, also known as NendoU or nsp15, cleaves specific sequences in viral RNA which may help the virus evade detection by the host immune system. Inhibition may hinder the virus's ability to mask itself from the immune system, facilitating a stronger immune response.

j. Cathepsin L is a host lysosomal cysteine protease that can prime the spike protein through an alternative pathway when TMPRSS2 is unavailable. Dual targeting of cathepsin L and TMPRSS2 may maximize disruption of alternative pathways for virus entry.

k. Wingless-related integration site (Wnt) ligand 3 is a host signaling molecule that activates the Wnt signaling pathway, which is important in development, cell growth, and tissue repair. Some studies suggest that SARS-CoV-2 infection may interfere with the Wnt signaling pathway, and that Wnt3a is involved in SARS-CoV-2 entry.

l. The frizzled (FZD) receptor is a host transmembrane receptor that binds Wnt ligands, initiating the Wnt signaling cascade. FZD serves as a co-receptor, along with ACE2, in some proposed mechanisms of SARS-CoV-2 infection. The virus may take advantage of this pathway as an alternative entry route.

m. Low-density lipoprotein receptor-related protein 6 is a cell surface co-receptor essential for Wnt signaling. LRP6 acts in tandem with FZD for signal transduction and has been discussed as a potential co-receptor for SARS-CoV-2 entry.

n. The ezrin protein links the cell membrane to the cytoskeleton (the cell's internal support structure) and plays a role in cell shape, movement, adhesion, and signaling. Drugs that occupy the same spot on ezrin where the viral spike protein would bind may hindering viral attachment, and drug binding could further stabilize ezrin, strengthening its potential natural capacity to impede viral fusion and entry.

o. The Adipocyte Differentiation-Related Protein (ADRP, also known as Perilipin 2 or PLIN2) is a lipid droplet protein regulating the storage and breakdown of fats in cells. SARS-CoV-2 may hijack the lipid handling machinery of host cells and ADRP may play a role in this process. Disrupting ADRP's interaction with the virus may hinder the virus's ability to use lipids for replication and assembly.

p. Neuropilin-1 (NRP1) is a cell surface receptor with roles in blood vessel development, nerve cell guidance, and immune responses. NRP1 may function as a co-receptor for SARS-CoV-2, facilitating viral entry into cells. Blocking NRP1 may disrupt an alternative route of viral entry.

q. Prostaglandin G/H synthase 2 (PTGS2, also known as COX-2) is an enzyme crucial for the production of inflammatory molecules called prostaglandins. PTGS2 plays a role in the inflammatory response that can become severe in COVID-19 and inhibitors (like some NSAIDs) may have benefits in dampening harmful inflammation, but note that prostaglandins have diverse physiological functions.

r. Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1) is a chaperone protein that helps other proteins fold correctly and maintains their stability. HSP90AA1 plays roles in cell signaling, survival, and immune responses. HSP90AA1 may interact with numerous viral proteins, but note that it has diverse physiological functions.

s. Matrix metalloproteinase 9 (MMP9), also called gelatinase B, is a zinc-dependent enzyme that breaks down collagen and other components of the extracellular matrix. MMP9 levels increase in severe COVID-19. Overactive MMP9 can damage lung tissue and worsen inflammation. Inhibition of MMP9 may prevent excessive tissue damage and help regulate the inflammatory response.

t. The interleukin-6 (IL-6) pro-inflammatory cytokine (signaling molecule) has a complex role in the immune response and may trigger and perpetuate inflammation. Elevated IL-6 levels are associated with severe COVID-19 cases and cytokine storm. Anti-IL-6 therapies may be beneficial in reducing excessive inflammation in severe COVID-19 cases.

u. The interleukin-10 (IL-10) anti-inflammatory cytokine helps regulate and dampen immune responses, preventing excessive inflammation. IL-10 levels can also be elevated in severe COVID-19. IL-10 could either help control harmful inflammation or potentially contribute to immune suppression.

v. Vascular Endothelial Growth Factor A (VEGFA) promotes the growth of new blood vessels (angiogenesis) and has roles in inflammation and immune responses. VEGFA may contribute to blood vessel leakiness and excessive inflammation associated with severe COVID-19.

w. RELA is a transcription factor subunit of NF-kB and is a key regulator of inflammation, driving pro-inflammatory gene expression. SARS-CoV-2 may hijack and modulate NF-kB pathways.

x. 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.

y. 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.

z. HEK293-ACE2+ is a human embryonic kidney cell line engineered for high ACE2 expression and SARS-CoV-2 susceptibility.

aa. Huh-7 cells were derived from a liver tumor (hepatoma).

ab. Caco-2 cells come from a colorectal adenocarcinoma (cancer). They are valued for their ability to form a polarized cell layer with properties similar to the intestinal lining.

ac. 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.

ad. mTEC is a mouse tubular epithelial cell line.

ae. RAW264.7 is a mouse macrophage cell line.

af. A mouse model expressing the human ACE2 receptor under the control of the K18 promoter.

ag. A mouse model of obesity and severe insulin resistance leading to type 2 diabetes due to a mutation in the leptin receptor gene that impairs satiety signaling.

ah. A mouse model commonly used in infectious disease and cancer research due to higher immune response and susceptibility to infection.

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