Nigella Sativa for COVID-19: real-time meta analysis of 14 studies

@CovidAnalysis, March 2024, Version 23
https://c19early.org/nsmeta.html

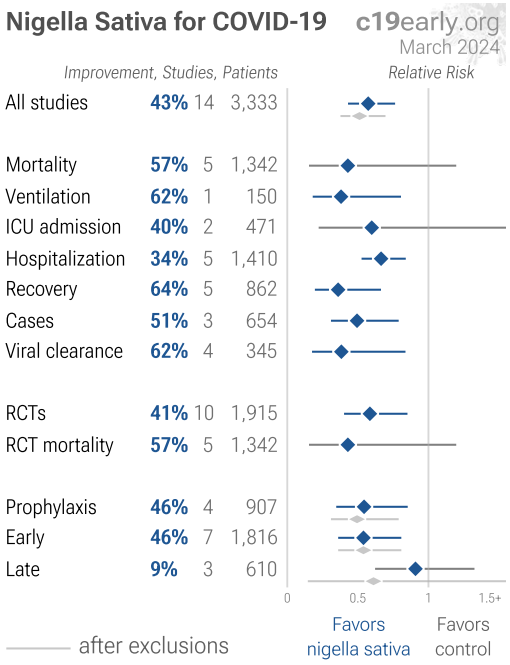
Abstract

Statistically significant lower risk is seen for ventilation, hospitalization, recovery, cases, and viral clearance. 11 studies from 10 independent teams in 8 countries show statistically significant improvements.

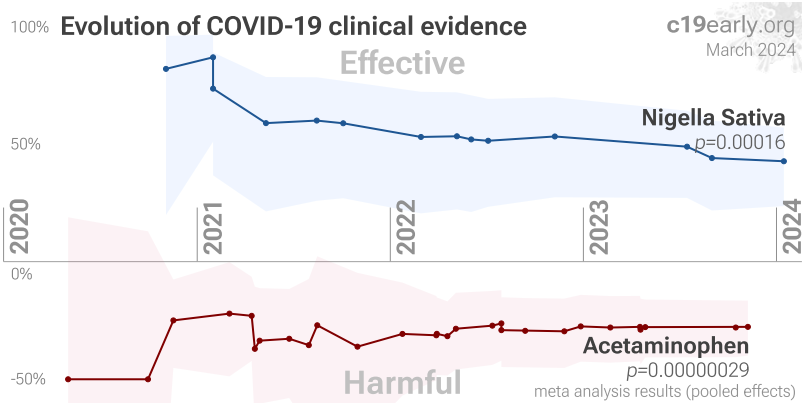
Meta analysis using the most serious outcome reported shows 43% [24-57%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies. Early treatment is more effective than late treatment.

Results are robust — in exclusion sensitivity analysis 11 of 14 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

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 nigella sativa for mortality *Kow, Umer* and viral clearance *Umer*.



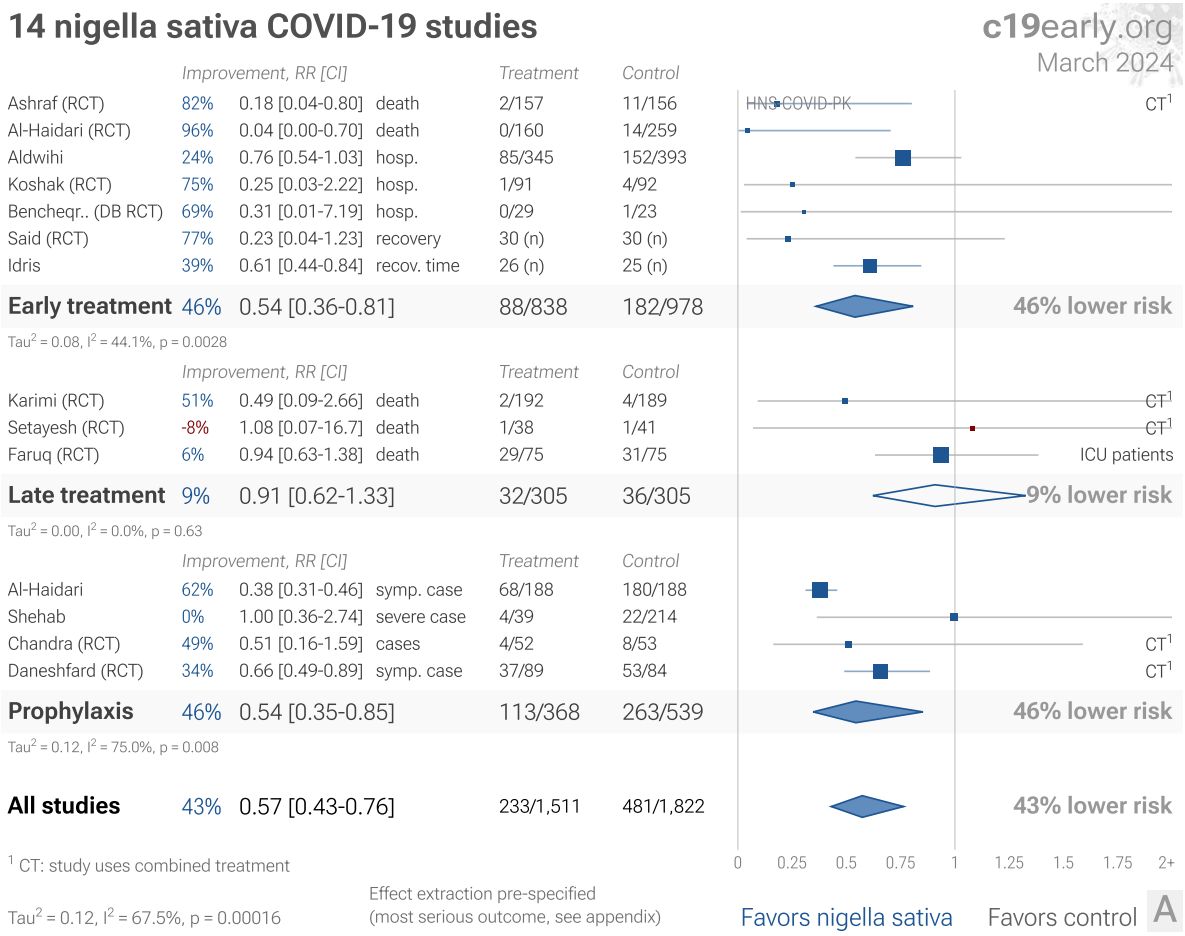
HIGHLIGHTS

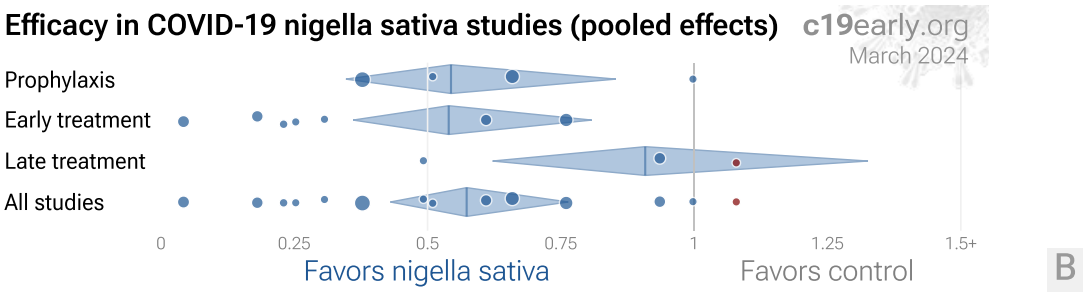
Studies to date suggest that Nigella Sativa reduces risk for COVID-19 with very high confidence for hospitalization, recovery, cases, and in pooled analysis, high confidence for viral clearance, and low confidence for mortality and ventilation.

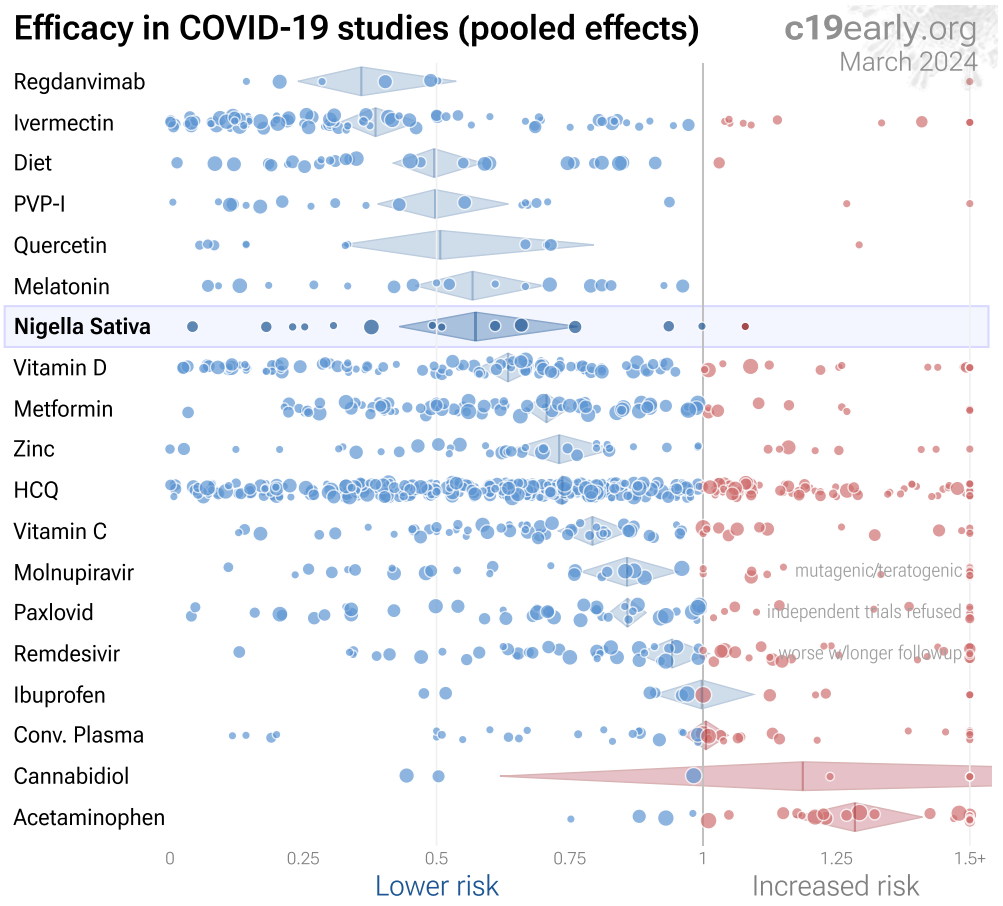
Nigella Sativa was the 11th treatment shown effective with ≥3 clinical studies in January 2021, now known with p = 0.00016 from 14 studies.

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.







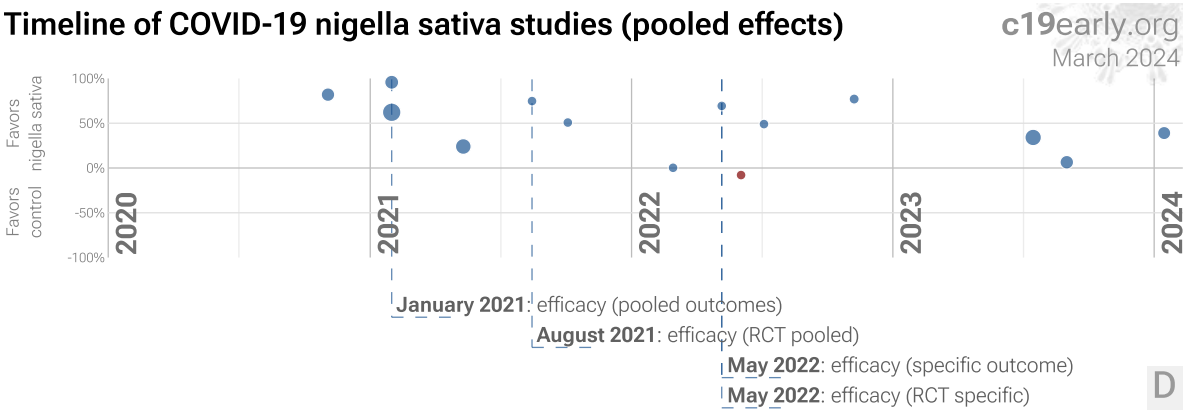


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the 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 nigella sativa 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 6.4 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 15.1 months, compared to using pooled outcomes. Efficacy based on specific outcomes in RCTs was delayed by 8.7 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.

Analysis. We analyze all significant controlled studies of nigella sativa 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, 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.

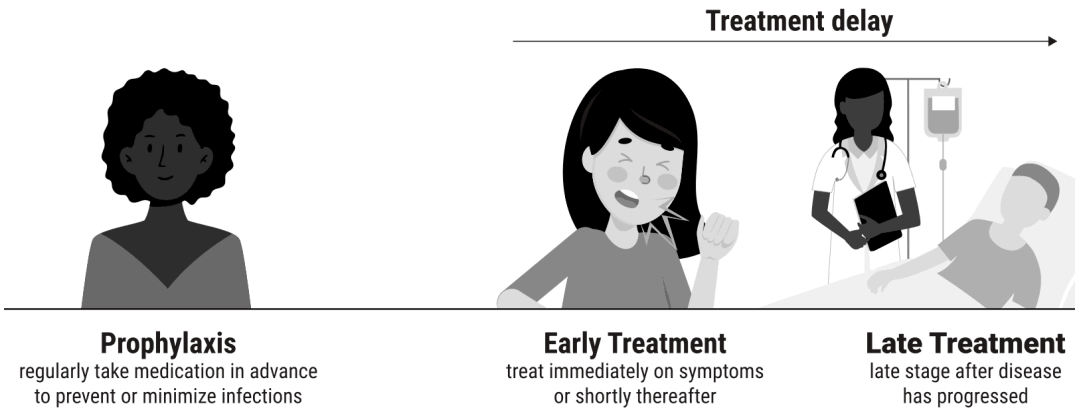


Figure 2. Treatment stages.

Preclinical Research

13 *In Silico* studies support the efficacy of nigella sativa [Ali, Alkafaas, Banerjee, Bouchentouf, Duru, Esharkawy, Hardianto, Khan, Maiti, Mir, Miraz, Rizvi, Sherwani].

3 *In Vitro* studies support the efficacy of nigella sativa [Esharkawy, Maen, Sherwani].

An *In Vivo* animal study supports the efficacy of nigella sativa [Maiti].

Thomas investigate a novel formulation of nigella sativa that may be more effective for COVID-19.

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

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3, 4, 5, 6, 7, 8, 9, and 10 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**43%** [24-57%] ***	14	3,333	174
After exclusions	**49%** [30-62%] ****	12	2,930	163
Randomized Controlled Trials	**41%** [15-60%] **	10	1,915	148
Mortality	**57%** [-20-85%]	5	1,342	80
ICU admission	**40%** [-61-78%]	2	471	41
Hospitalization	**34%** [16-47%] ***	5	1,410	87
Recovery	**64%** [34-80%] **	5	862	89
Cases	**51%** [21-69%] **	3	654	31
Viral	**62%** [16-82%] *	4	345	67
RCT mortality	**57%** [-20-85%]	5	1,342	80
RCT hospitalization	**53%** [8-76%] *	4	672	79

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

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	**46%** [19-64%] **	**9%** [-33-38%]	**46%** [15-65%] **
After exclusions	**46%** [19-64%] **	**39%** [-157-85%]	**51%** [21-69%] **
Randomized Controlled Trials	**82%** [55-93%] ***	**9%** [-33-38%]	**35%** [14-51%] **
Mortality	**87%** [51-96%] **	**9%** [-33-38%]	
ICU admission		**40%** [-61-78%]	
Hospitalization	**25%** [7-40%] **	**50%** [-15-78%]	
Recovery	**64%** [24-82%] **	**67%** [35-83%] **	
Cases			**51%** [21-69%] **
Viral	**62%** [16-82%] *		
RCT mortality	**87%** [51-96%] **	**9%** [-33-38%]	
RCT hospitalization	**73%** [-61-96%]	**50%** [-15-78%]	

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

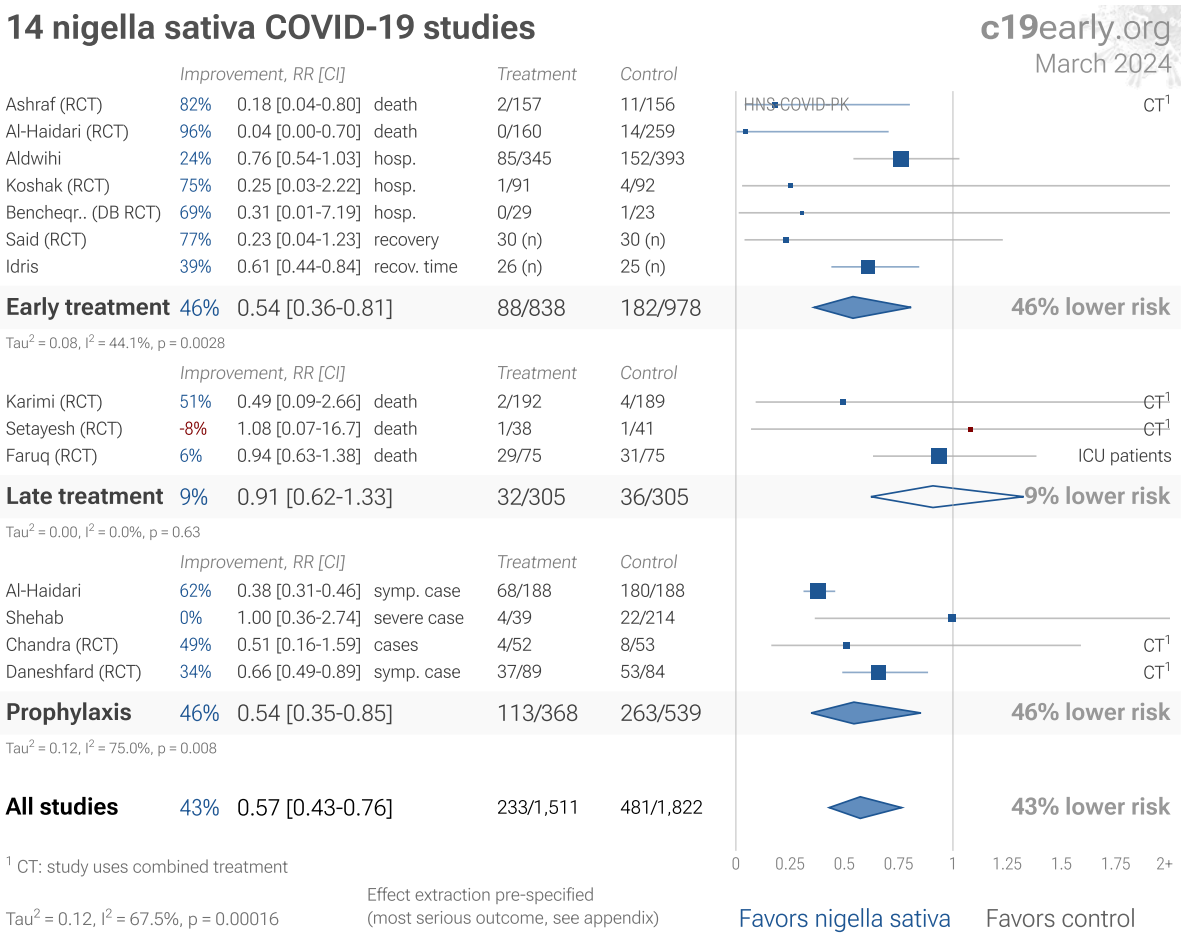


Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

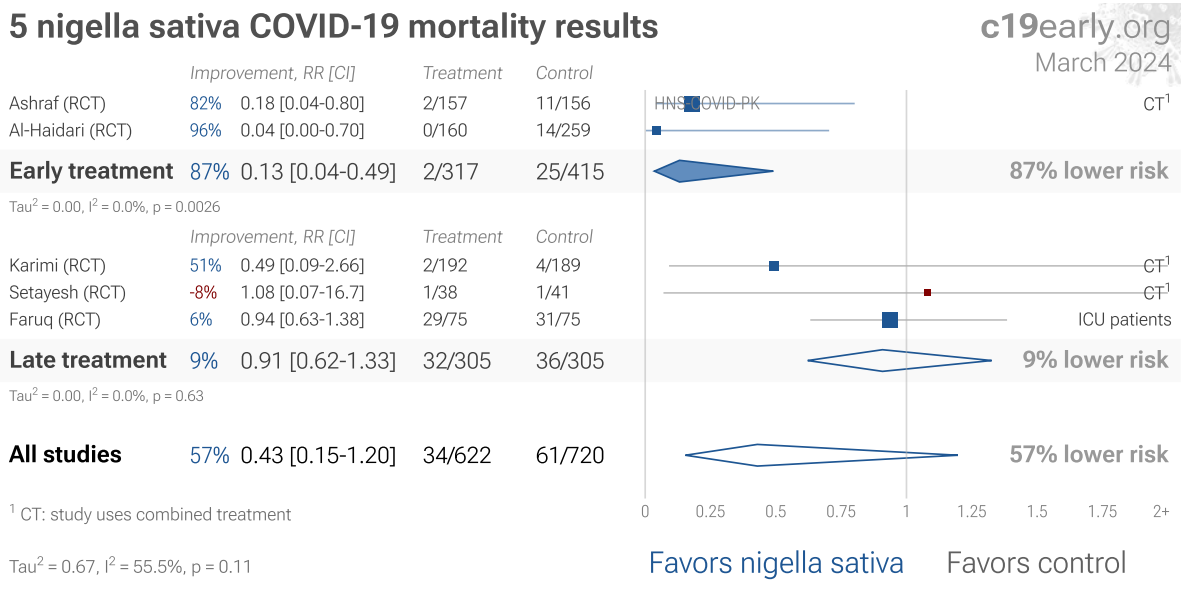


Figure 4. **Random effects meta-analysis for mortality results.**

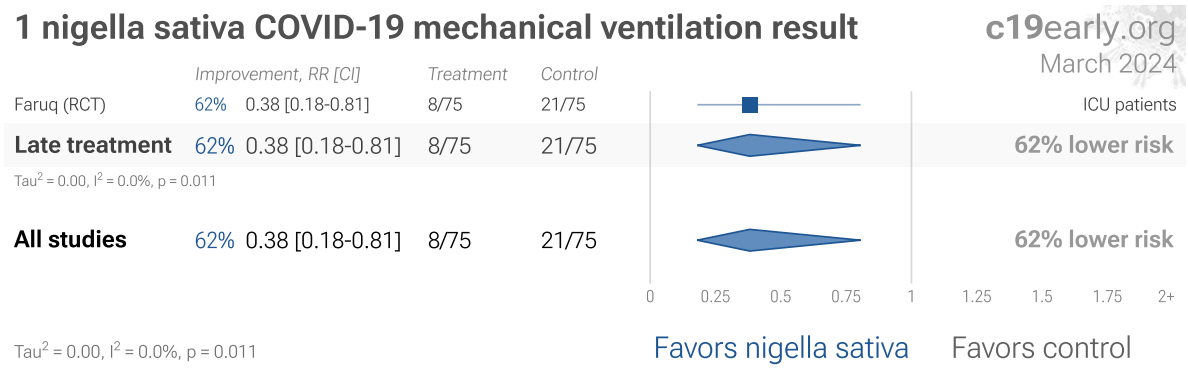


Figure 5. Random effects meta-analysis for ventilation.

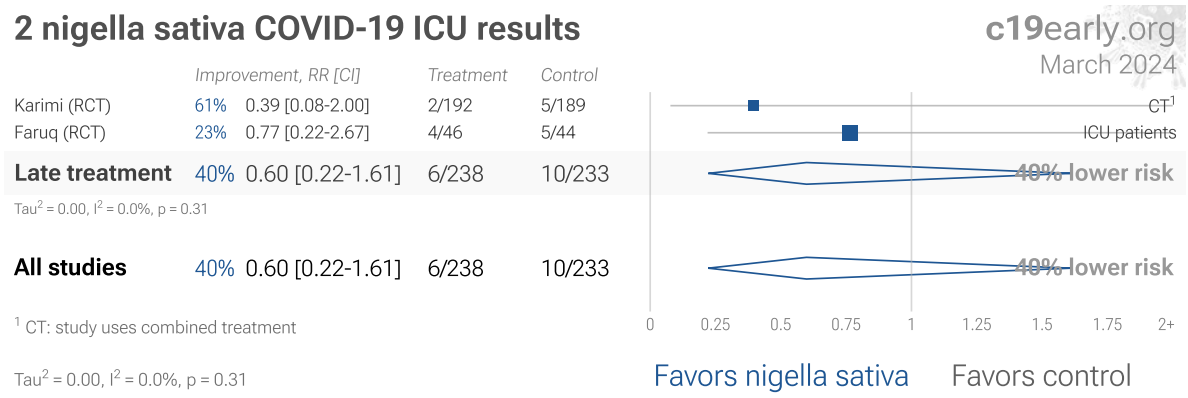


Figure 6. Random effects meta-analysis for ICU admission.

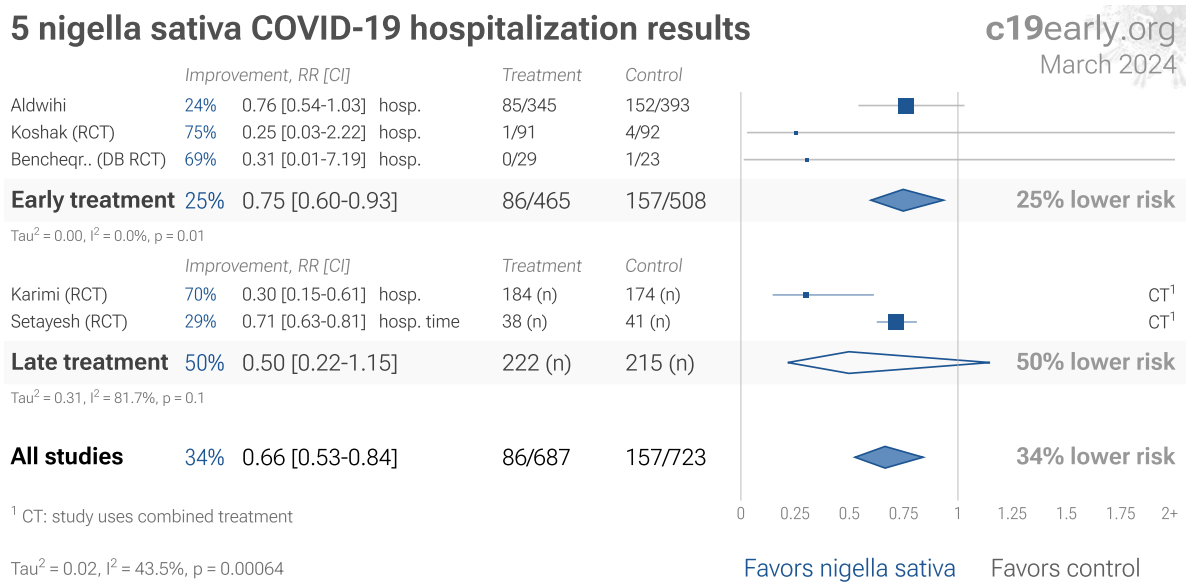


Figure 7. Random effects meta-analysis for hospitalization.

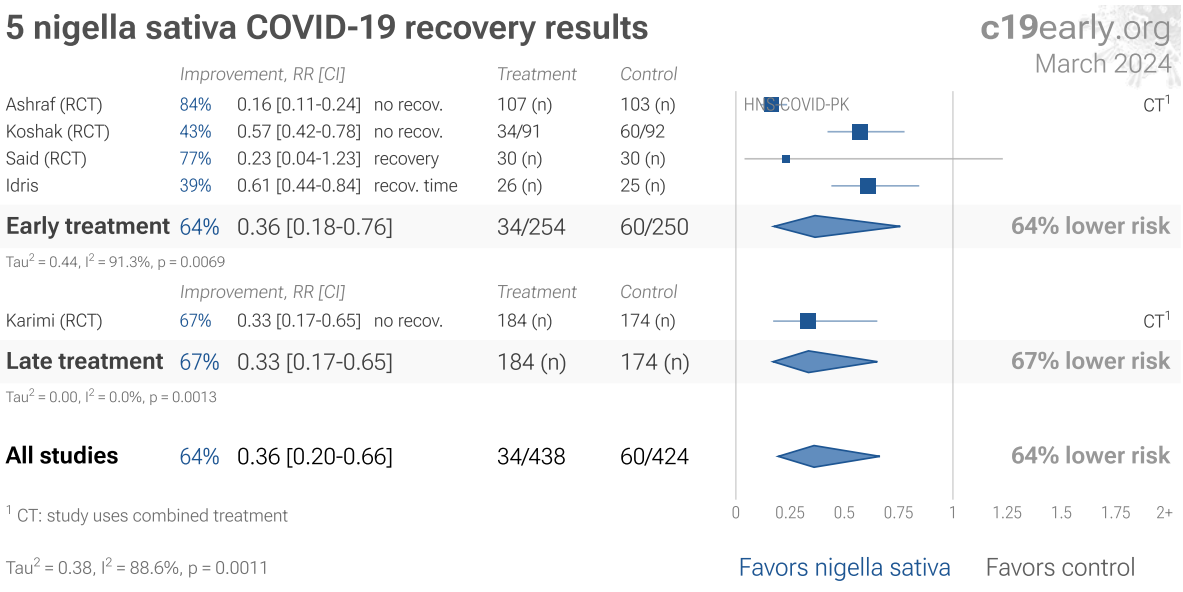


Figure 8. Random effects meta-analysis for recovery.

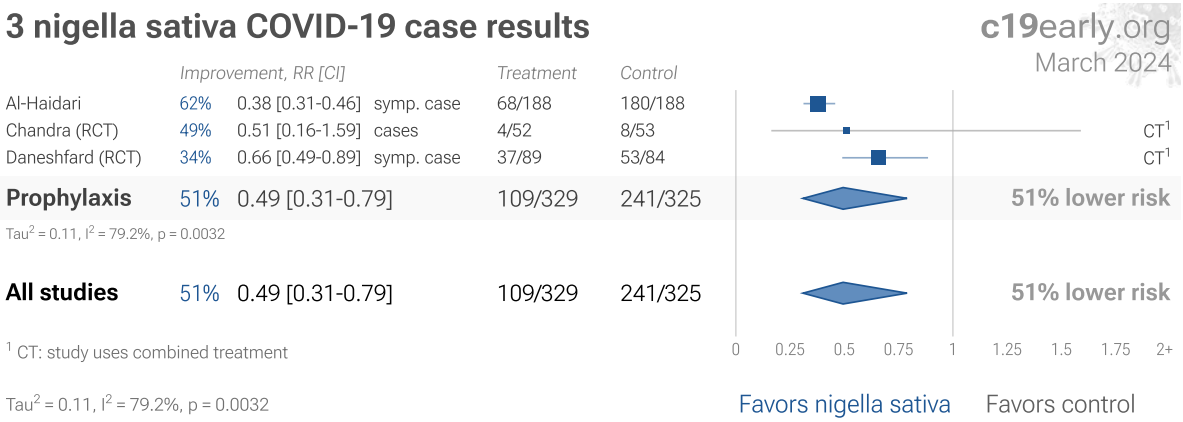


Figure 9. Random effects meta-analysis for cases.

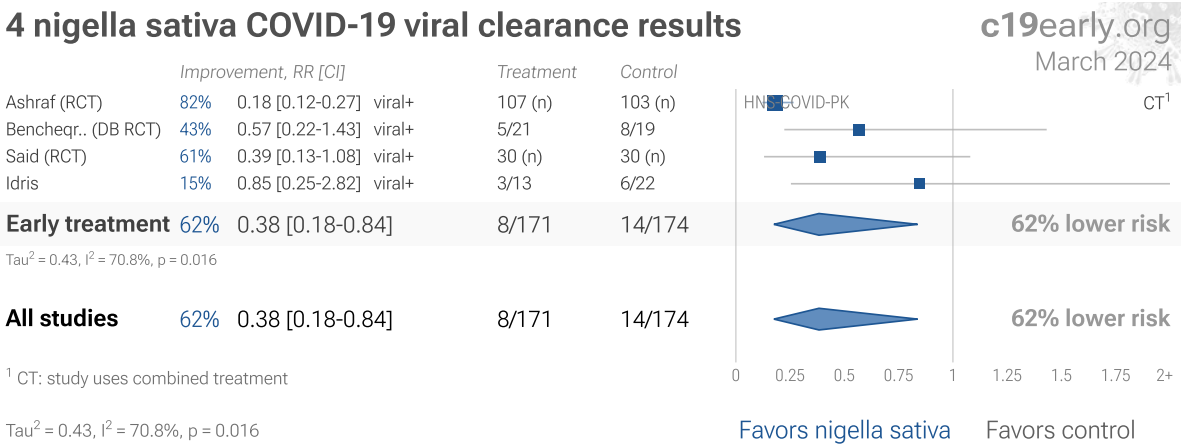


Figure 10. Random effects meta-analysis for viral clearance.

Randomized Controlled Trials (RCTs)

Figure 11 shows a comparison of results for RCTs and non-RCT studies. The median effect size for RCTs is 60% improvement, compared to 32% for other studies. Figure 12, 13, and 14 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

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.

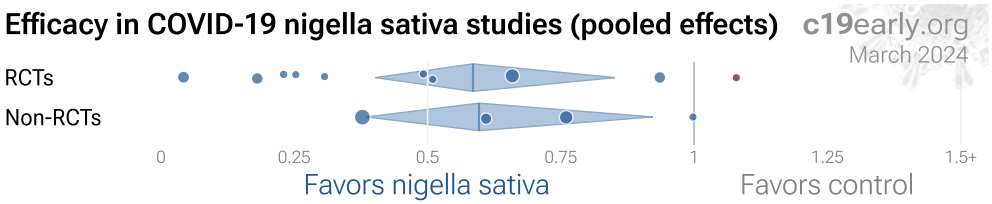


Figure 11. **Results for RCTs and non-RCT studies.**

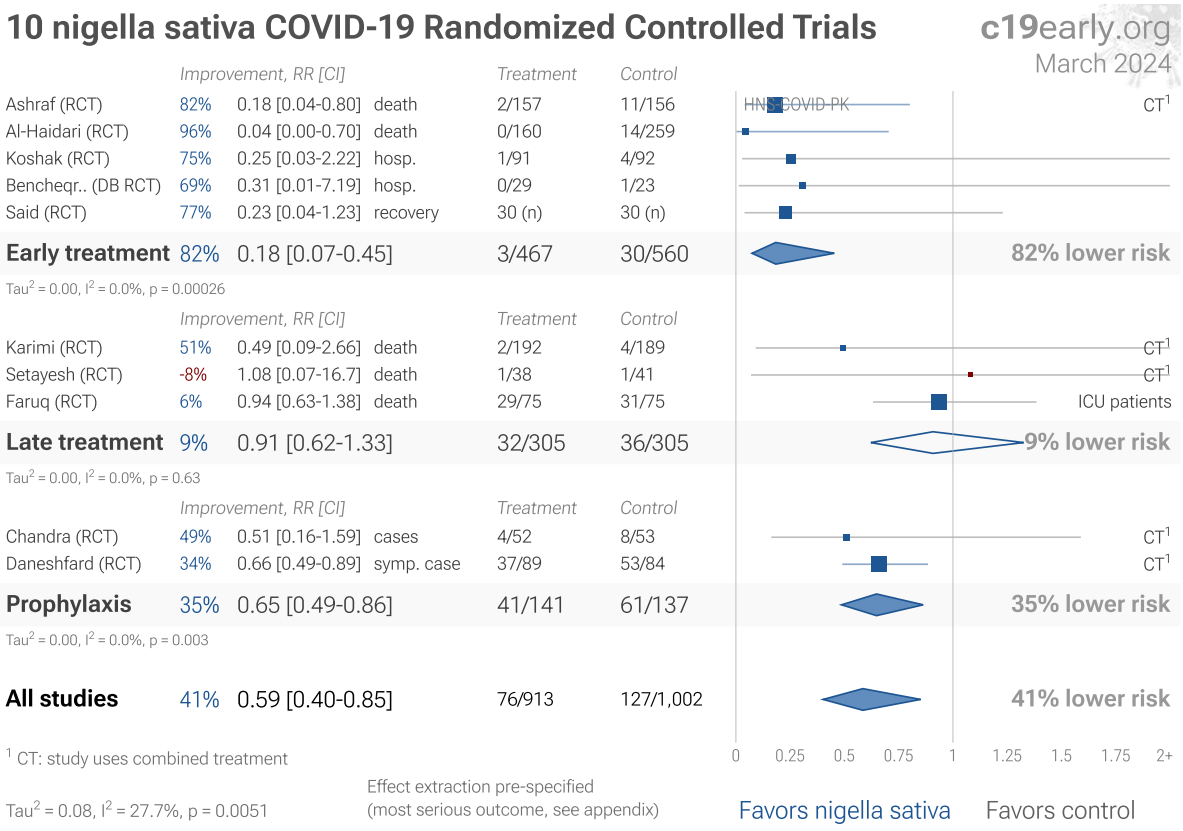


Figure 12. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

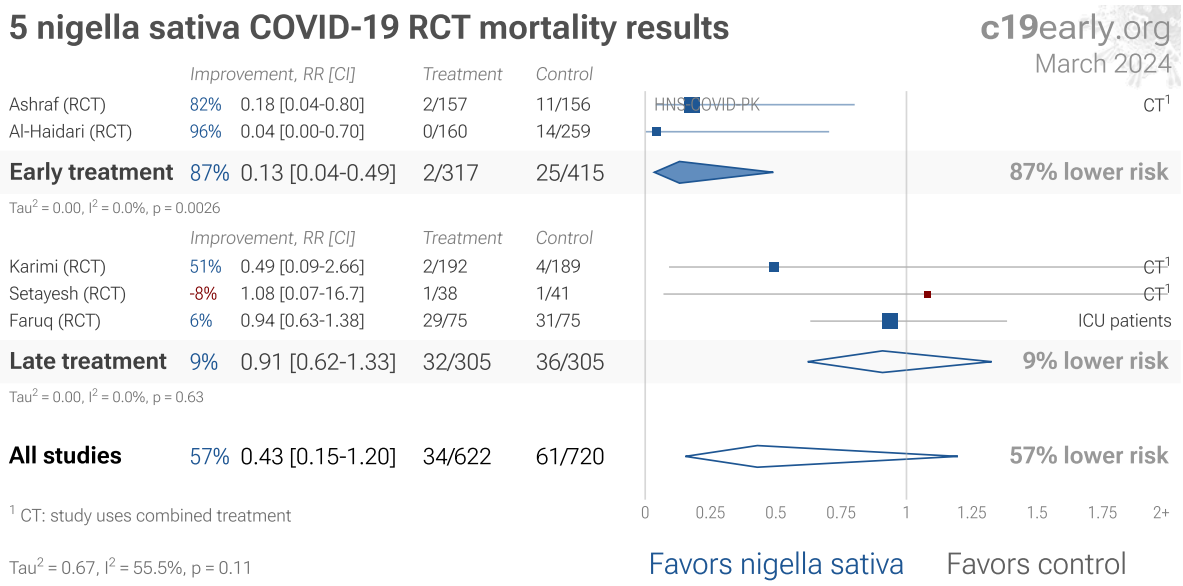


Figure 13. Random effects meta-analysis for RCT mortality results.

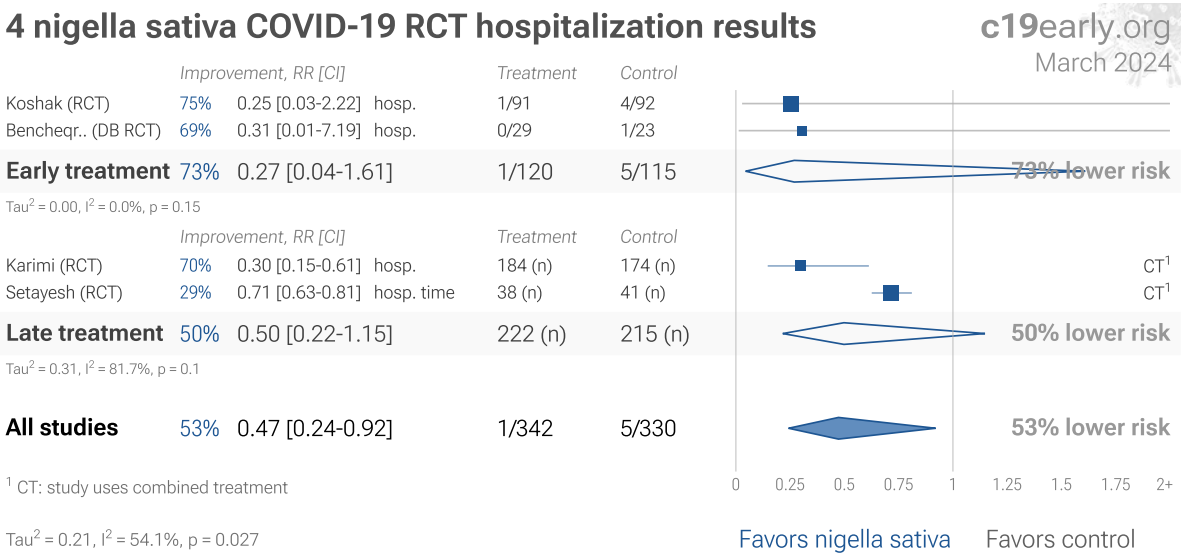


Figure 14. Random effects meta-analysis for RCT hospitalization results.

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

Faruq, potential data issue.

Shehab, unadjusted results with no group details.

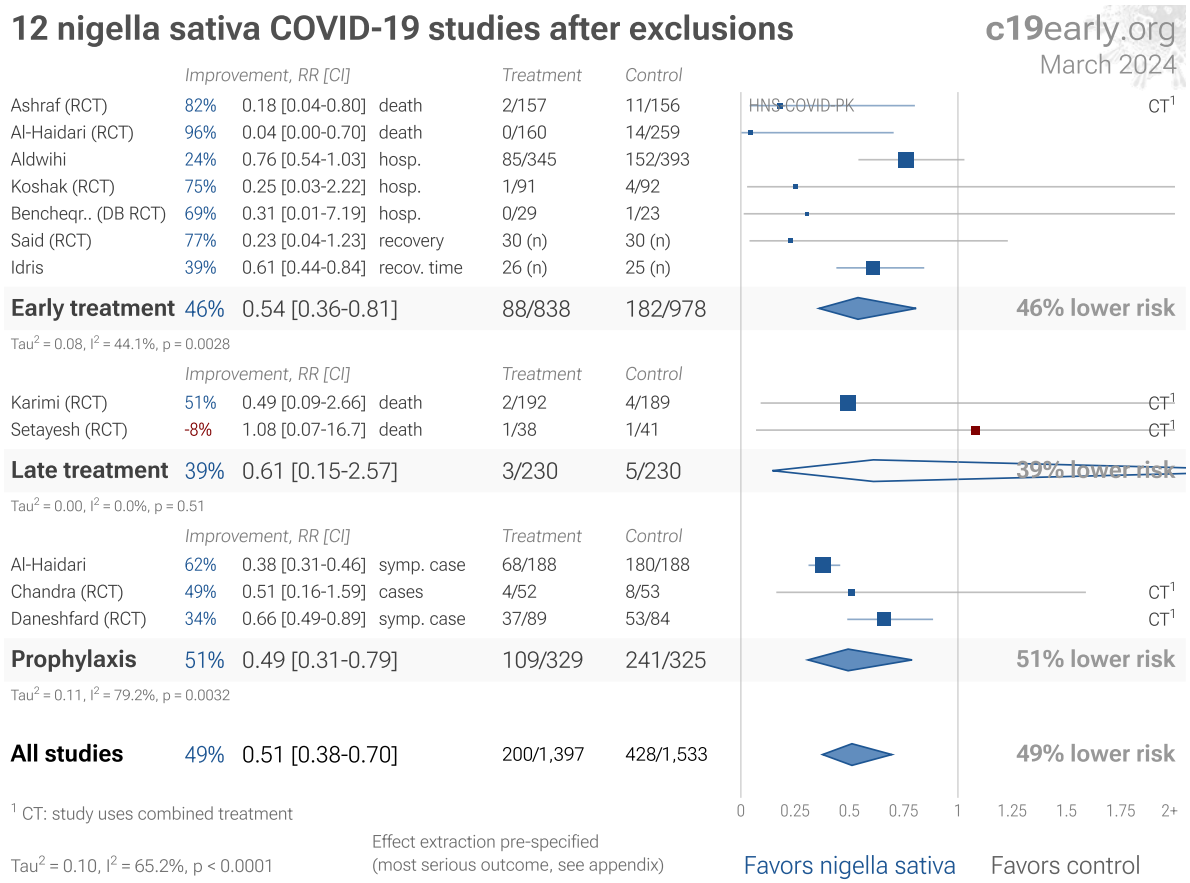


Figure 15. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details 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 3. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 16 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.

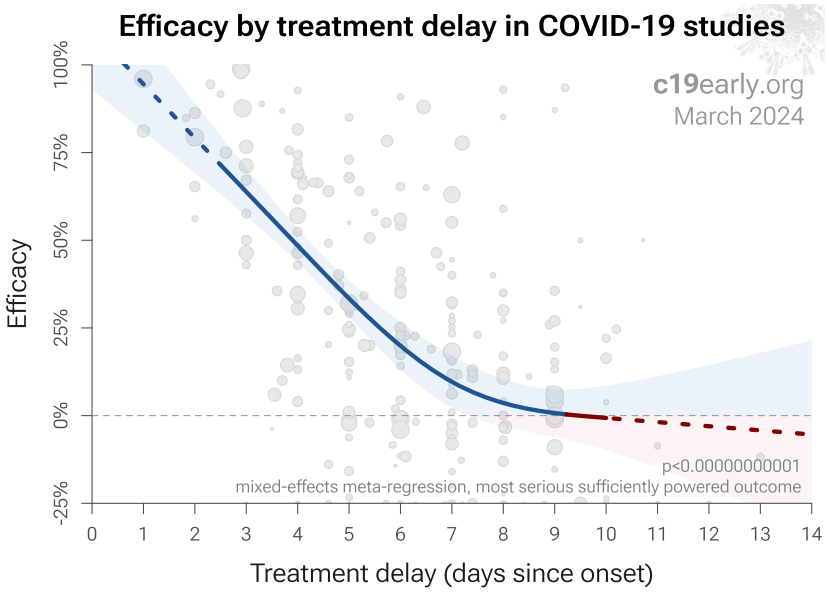


Figure 16. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 17. 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.

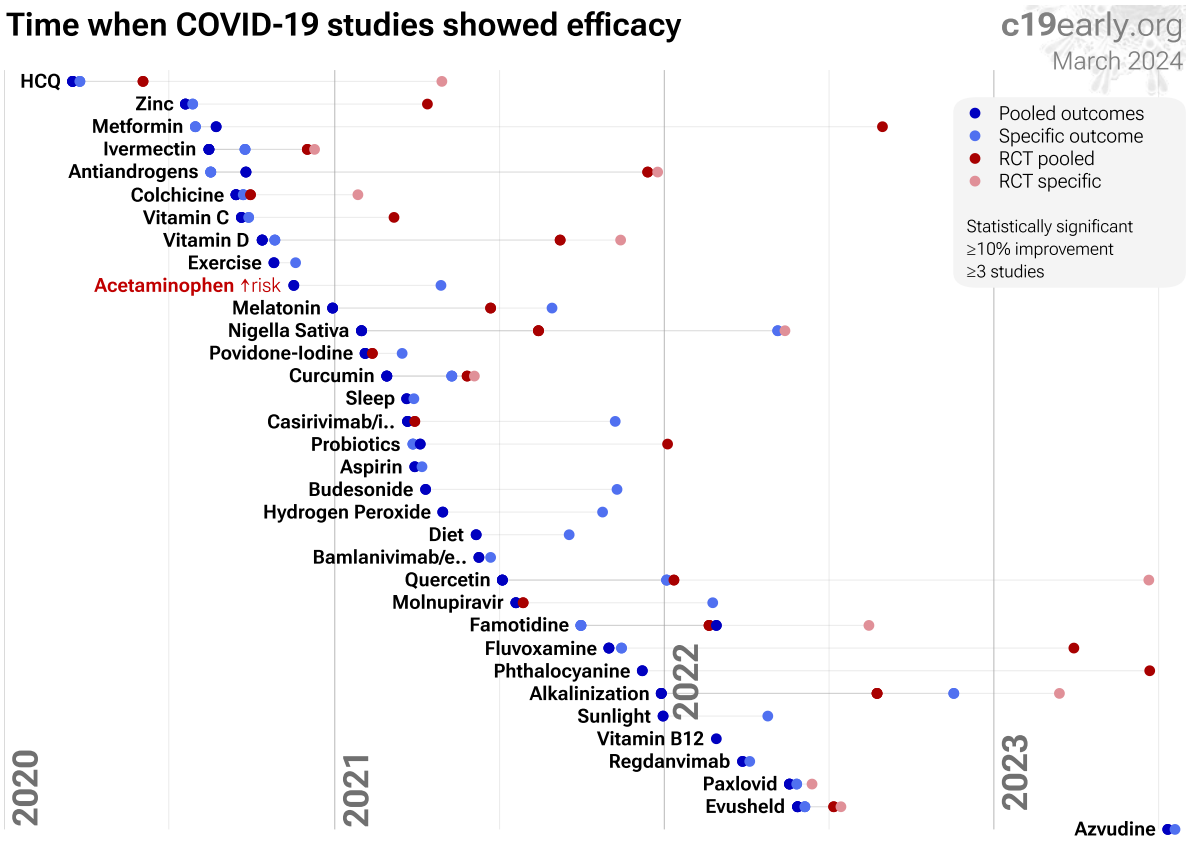


Figure 17. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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 nigella sativa, 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 18 shows a scatter plot of results for prospective and retrospective studies. 0% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 92% of prospective studies, consistent with a bias toward publishing negative results. The median effect size for retrospective studies is 12% improvement, compared to 57% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

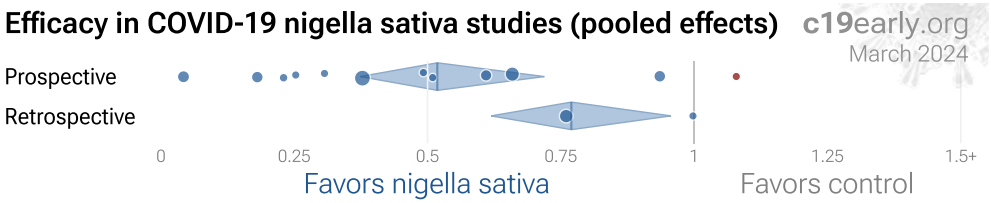


Figure 18. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 19 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.

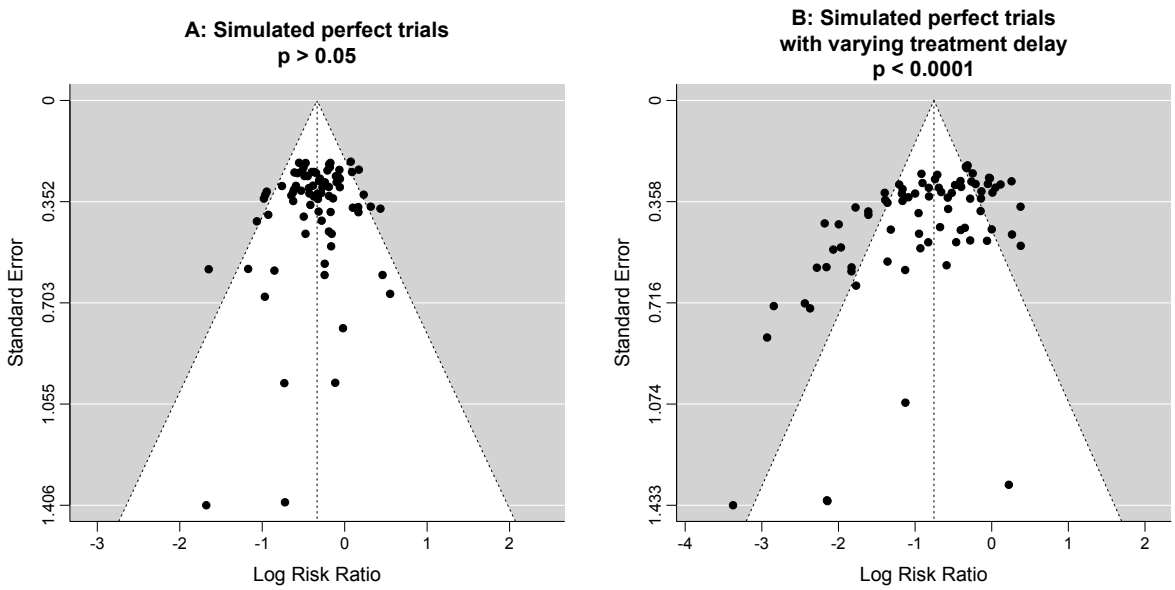


Figure 19. Example funnel plot analysis for simulated perfect trials.

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. Nigella Sativa for COVID-19 lacks this because it is an inexpensive and widely available supplement. In contrast, most COVID-19 nigella sativa 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 nigella sativa 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. 5 of 14 studies combine treatments. The results of nigella sativa alone may differ. 5 of 10 RCTs use combined treatment. Currently all studies are peer-reviewed. Other meta analyses show significant improvements with nigella sativa for mortality *Kow, Umer* and viral clearance *Umer*.

Reviews. Many reviews cover nigella sativa for COVID-19, presenting additional background on mechanisms and related results, including *Ahmad, Ahmad (B), Al-Gabri, Cyril, Kulyar, Shad*.

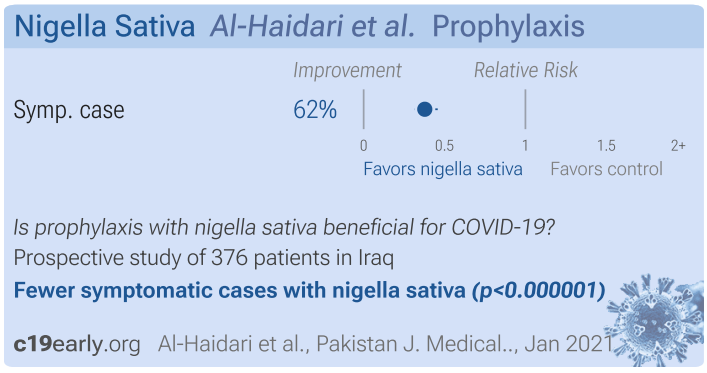
Conclusion

Studies to date suggest that nigella sativa is an effective treatment for COVID-19. Statistically significant lower risk is seen for ventilation, hospitalization, recovery, cases, and viral clearance. 11 studies from 10 independent teams in 8 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 43% [24-57%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies. Early treatment is more effective than late treatment. Results are robust — in exclusion sensitivity analysis 11 of 14 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Other meta analyses show significant improvements with nigella sativa for mortality *Kow, Umer* and viral clearance *Umer*.

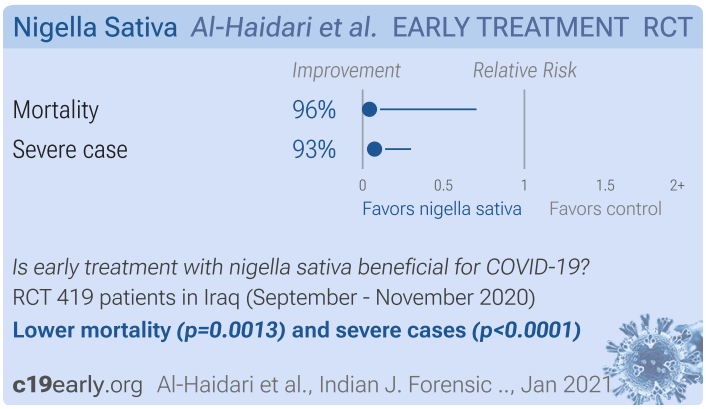
Study Notes

Al-Haidari



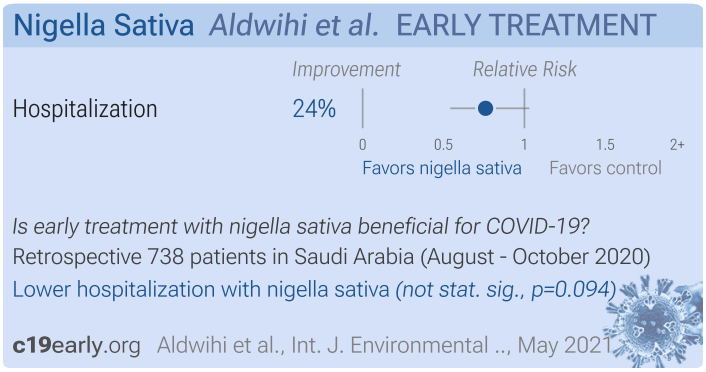
Al-Haidari (B): Prophylaxis study with 376 mostly high-risk patients, 188 treated with nigella sativa, showing significantly lower cases with treatment. Black seeds 40mg/kg orally once daily.

Al-Haidari



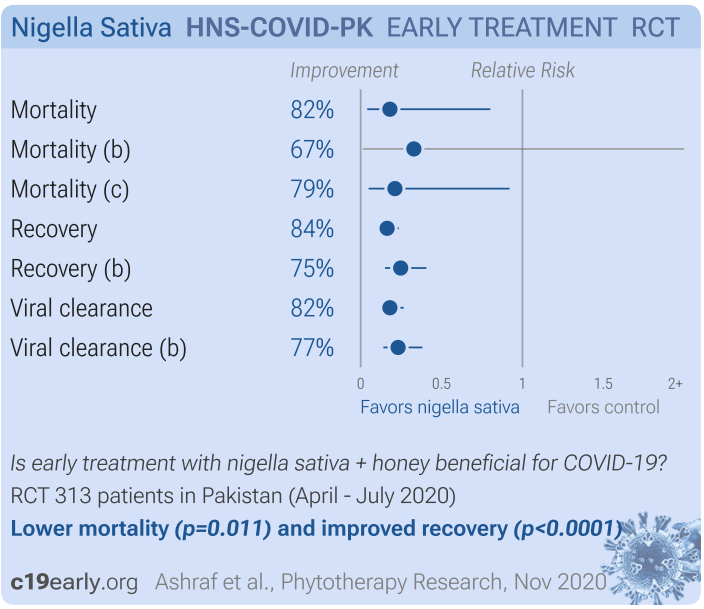
Al-Haidari: Open-label RCT with 419 patients in Iraq, 160 treated with Nigella Sativa, showing lower mortality and severe cases with treatment. Black seeds 40mg/kg orally once daily for 14 days.

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.

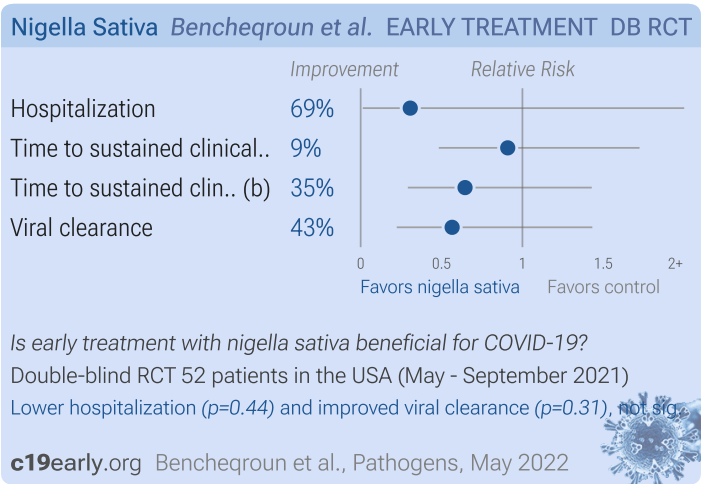
Ashraf



Ashraf: RCT with 157 patients treated with honey and nigella sativa, and 156 control patients, showing significantly faster recovery and viral clearance.

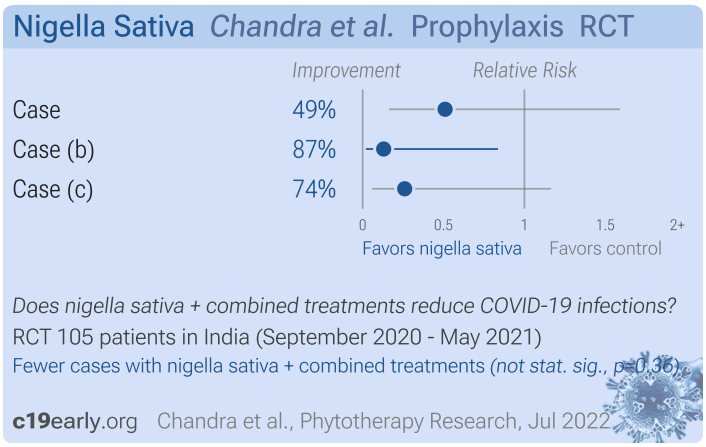
Honey (1gm/kg/day) plus encapsulated nigella sativa seeds (80mg/kg/day) orally in 2-3 divided doses daily for up to 13 days.

Bencheqroun



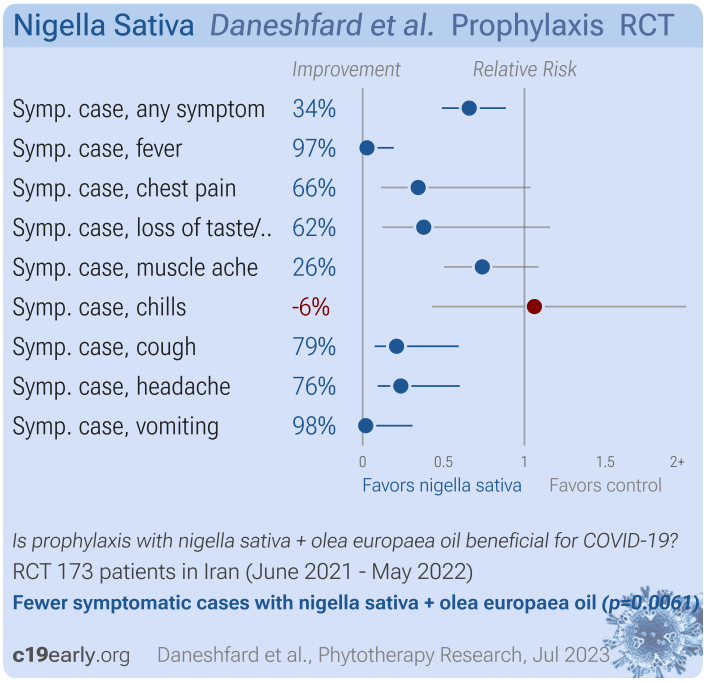
Bencheqroun: 52 patient RCT in the USA with nigella sativa component thymoquinone, showing improved recovery with treatment. There was a significantly faster decline in the total symptom burden, and a significant increase in CD8+ and helper CD4+ central memory T lymphocytes. The treatment group contained 5 more vaccinated patients and 7 more overweight patients. Authors also present in vitro results showing an inhibitory effect with five SARS-CoV-2 variants including omicron.

Chandra



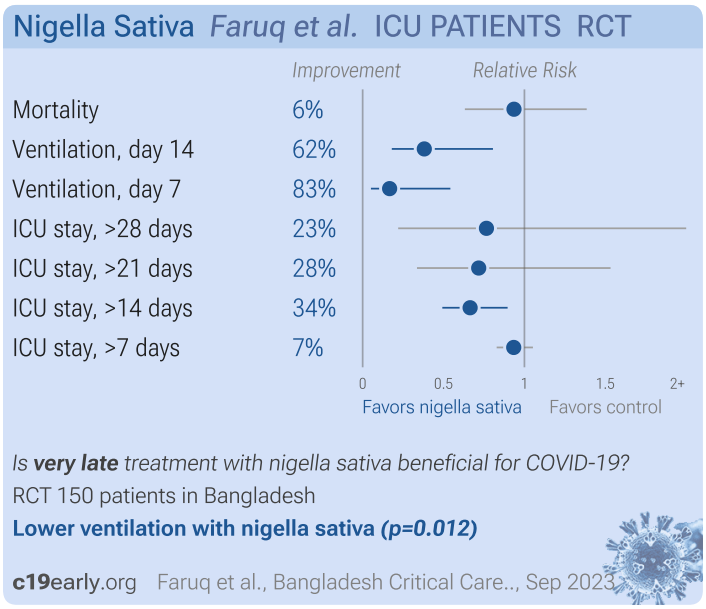
Chandra: RCT 251 high-risk individuals in India, mostly with direct contact with COVID-19 positive patients, testing polyherbal formulations Infuza, which includes nigella sativa, and Kulzam. Both formulations showed lower risk, without statisical significance, while the best results were from the combination of both.

Daneshfard



Daneshfard: RCT 173 family members of COVID-19 patients, showing lower incidence of COVID-19 symptoms with nasal drops containing nigella sativa oil and olea europaea oil. One drop in each nostril twice daily for 7 days.

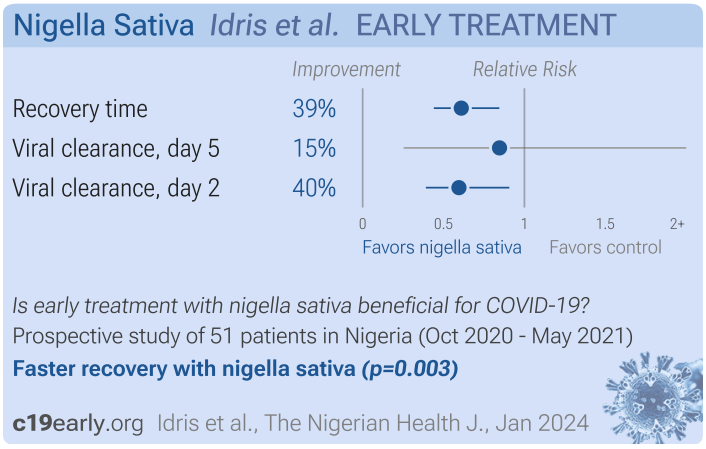
Faruq



Faruq: Open label randomized trial of 150 ICU patients in Bangladesh, showing shorter ICU stay and lower requirements for increased oxygen support including mechanical ventilation with nigella sativa treatment, but no significant difference in mortality.

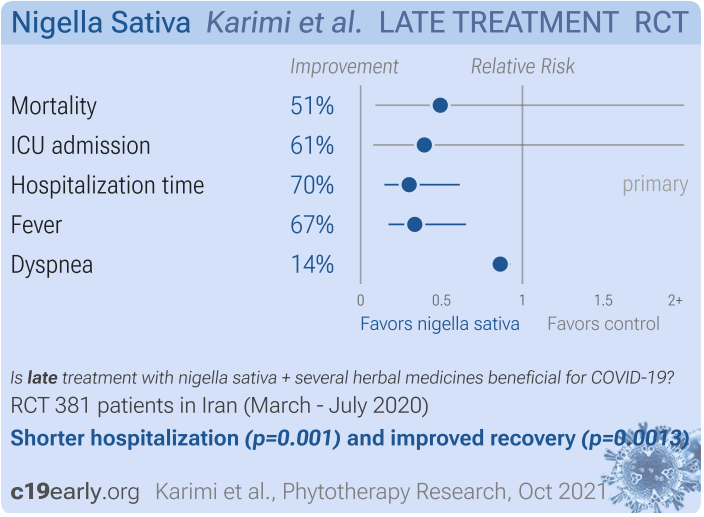
The large baseline difference in convalescent plasma usage suggests an error or randomization problem.

Idris



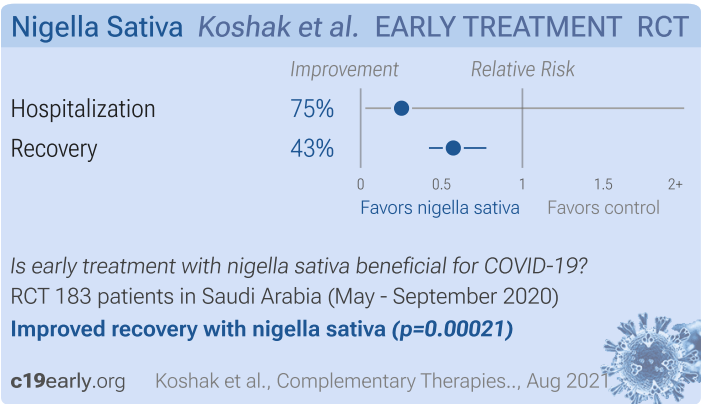
Idris: Prospective study of 51 mild COVID-19 cases in Nigeria, showing faster recovery and improved viral clearance with nigella sativa oil (NSO) treatment. NSO patients received 5mL twice daily in addition to usual care (zinc, vitamin C and a multivitamin).

Karimi



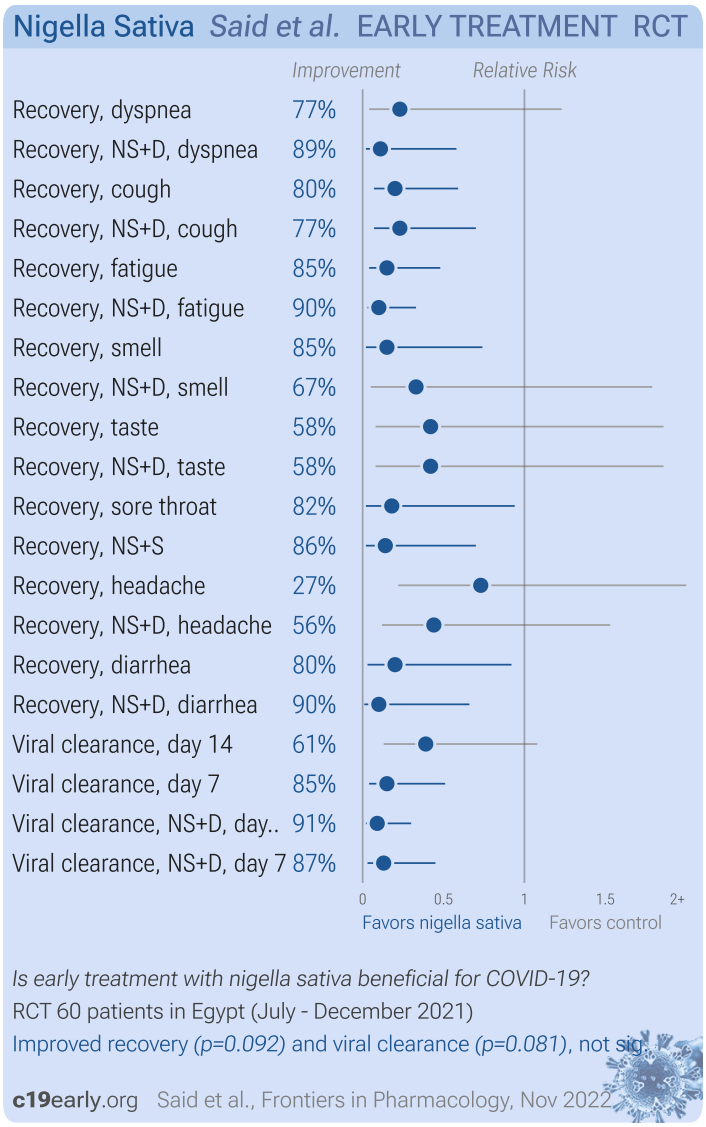
Karimi: RCT 358 hospitalized patients in Iran, 184 receiving treatment with a combination of nigella sativa and several other herbal medicines, showing shorter hospitalization time and improved recovery with treatment. IR.TUMS.VCR.REC.1399.024.

Koshak



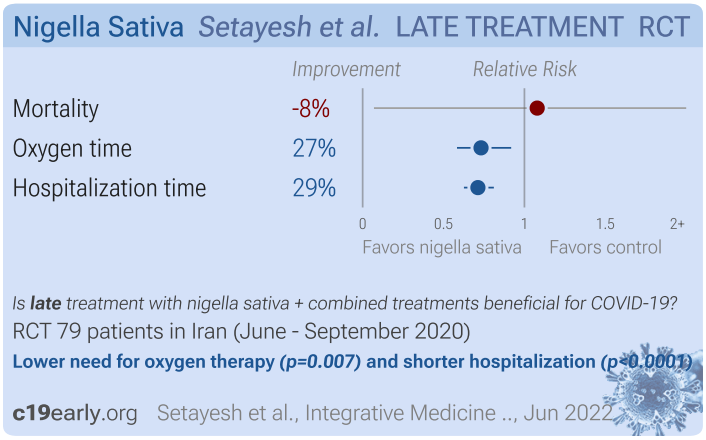
Koshak: RCT 183 mild COVID-19 outpatients in Saudi Arabia, 91 treated with Nigella Sativa, showing lower hospitalization and faster recovery with treatment. 500mg Nigella Sativa oil (MARNYS Cuminmar) twice daily for 10 days. NCT04401202.

Said



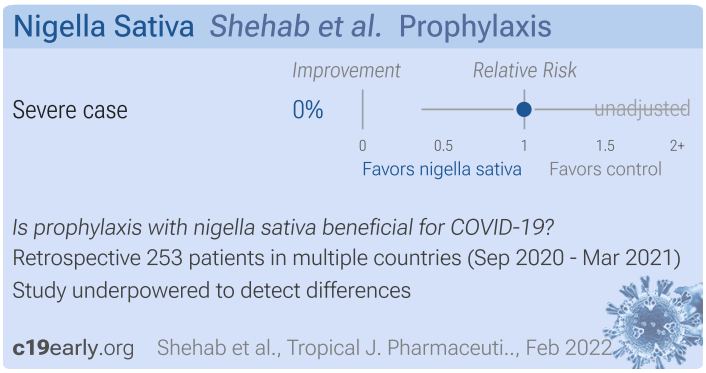
Said (B): 120 patient RCT comparing vitamin D, nigella sativa, and combined vitamin D+nigella sativa, showing improved symptom recovery and viral clearance with both vitamin D and nigella sativa, and further improvements with the combination of both. All patients received vitamin C, zinc, and lactoferrin.

Setayesh



Setayesh: Small RCT 41 patients treated with nigella sativa, glycyrrhiza glabra, punica granatum, and rheum palmatum, and 41 control patients, showing shorter hospitalization with treatment.

Shehab



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

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 nigella sativa 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 nigella sativa 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*. 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/nsmeta.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.

Al-Haidari, 1/31/2021, Randomized Controlled Trial, Iraq, peer-reviewed, 3 authors, study period 5 September, 2020 - 15 November, 2020.	risk of death, 95.8% lower, RR 0.04, $p = 0.001$, treatment 0 of 160 (0.0%), control 14 of 259 (5.4%), NNT 18, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of severe case, 92.6% lower, RR 0.07, $p < 0.001$, treatment 2 of 160 (1.2%), control 44 of 259 (17.0%), NNT 6.4.
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, 24.0% lower, RR 0.76, $p = 0.09$, treatment 85 of 345 (24.6%), control 152 of 393 (38.7%), NNT 7.1, adjusted per study, odds ratio converted to relative risk, multivariable.
Ashraf, 11/3/2020, Randomized Controlled Trial, placebo-controlled, Pakistan, peer-reviewed, 29 authors, study period 30 April, 2020 - 29 July, 2020, this trial uses multiple treatments in the treatment arm (combined with honey) - results of individual treatments may vary, trial NCT04347382 (history) (HNS-COVID-PK).	risk of death, 81.9% lower, RR 0.18, $p = 0.01$, treatment 2 of 157 (1.3%), control 11 of 156 (7.1%), NNT 17, all cases.
	risk of death, 67.1% lower, RR 0.33, $p = 0.49$, treatment 0 of 107 (0.0%), control 1 of 103 (1.0%), NNT 103, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), moderate cases.
	risk of death, 78.8% lower, RR 0.21, $p = 0.03$, treatment 2 of 50 (4.0%), control 10 of 53 (18.9%), NNT 6.7, severe cases.

	risk of no recovery, 83.6% lower, HR 0.16, $p < 0.001$, treatment 107, control 103, inverted to make HR<1 favor treatment, moderate cases.
	risk of no recovery, 75.2% lower, HR 0.25, $p < 0.001$, treatment 50, control 53, inverted to make HR<1 favor treatment, severe cases.
	risk of no viral clearance, 81.9% lower, HR 0.18, $p < 0.001$, treatment 107, control 103, inverted to make HR<1 favor treatment, moderate cases.
	risk of no viral clearance, 76.9% lower, HR 0.23, $p < 0.001$, treatment 50, control 53, inverted to make HR<1 favor treatment, severe cases.
Bencheqroun, 5/7/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, mean age 45.0, 25 authors, study period 27 May, 2021 - 27 September, 2021.	risk of hospitalization, 69.3% lower, RR 0.31, $p = 0.44$, treatment 0 of 29 (0.0%), control 1 of 23 (4.3%), NNT 23, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	time to sustained clinical response, 9.1% lower, HR 0.91, $p = 0.78$, treatment 28, control 23, inverted to make HR<1 favor treatment, Kaplan–Meier.
	time to sustained clinical response, 35.5% lower, HR 0.65, $p = 0.25$, treatment 28, control 23, inverted to make HR<1 favor treatment, Kaplan–Meier, high-risk patients.
	risk of no viral clearance, 43.5% lower, RR 0.57, $p = 0.31$, treatment 5 of 21 (23.8%), control 8 of 19 (42.1%), NNT 5.5, day 14.
Idris, 1/15/2024, prospective, Nigeria, peer-reviewed, mean age 30.8, 8 authors, study period 27 October, 2020 - 20 May, 2021.	recovery time, 39.0% lower, relative time 0.61, $p = 0.003$, treatment mean 4.5 (±1.51) n=26, control mean 7.38 (±2.2) n=25.
	risk of no viral clearance, 15.4% lower, RR 0.85, $p = 1.00$, treatment 3 of 13 (23.1%), control 6 of 22 (27.3%), NNT 24, day 5.
	risk of no viral clearance, 40.5% lower, RR 0.60, $p = 0.02$, treatment 13 of 26 (50.0%), control 21 of 25 (84.0%), NNT 2.9, day 2.
Koshak, 8/15/2021, Randomized Controlled Trial, Saudi Arabia, peer-reviewed, 10 authors, study period 1 May, 2020 - 30 September, 2020, trial NCT04401202 (history).	risk of hospitalization, 74.7% lower, RR 0.25, $p = 0.37$, treatment 1 of 91 (1.1%), control 4 of 92 (4.3%), NNT 31.
	risk of no recovery, 42.7% lower, RR 0.57, $p < 0.001$, treatment 34 of 91 (37.4%), control 60 of 92 (65.2%), NNT 3.6.
Said (B), 11/8/2022, Randomized Controlled Trial, Egypt, peer-reviewed, 5 authors, study period 21 July, 2021 - 30 December, 2021, trial NCT04981743 (history).	risk of no recovery, 77.0% lower, OR 0.23, $p = 0.09$, treatment 30, control 30, adjusted per study, multivariable, dyspnea, RR approximated with OR.

risk of no recovery, 89.0% lower, OR 0.11, $p = 0.01$, treatment 30, control 30, adjusted per study, vitamin D and nigella sativa, multivariable, dyspnea, RR approximated with OR.
risk of no recovery, 80.0% lower, OR 0.20, $p = 0.003$, treatment 30, control 30, adjusted per study, multivariable, cough, RR approximated with OR.
risk of no recovery, 77.0% lower, OR 0.23, $p = 0.01$, treatment 30, control 30, adjusted per study, vitamin D and nigella sativa, multivariable, cough, RR approximated with OR.
risk of no recovery, 85.0% lower, OR 0.15, $p = 0.003$, treatment 30, control 30, adjusted per study, multivariable, fatigue, RR approximated with OR.
risk of no recovery, 90.0% lower, OR 0.10, $p < 0.001$, treatment 30, control 30, adjusted per study, vitamin D and nigella sativa, multivariable, fatigue, RR approximated with OR.
risk of no recovery, 85.0% lower, OR 0.15, $p = 0.04$, treatment 30, control 30, adjusted per study, multivariable, smell, RR approximated with OR.
risk of no recovery, 67.0% lower, OR 0.33, $p = 0.23$, treatment 30, control 30, adjusted per study, vitamin D and nigella sativa, multivariable, smell, RR approximated with OR.
risk of no recovery, 58.0% lower, OR 0.42, $p = 0.28$, treatment 30, control 30, adjusted per study, multivariable, taste, RR approximated with OR.
risk of no recovery, 58.0% lower, OR 0.42, $p = 0.28$, treatment 30, control 30, adjusted per study, vitamin D and nigella sativa, multivariable, taste, RR approximated with OR.
risk of no recovery, 82.0% lower, OR 0.18, $p = 0.05$, treatment 30, control 30, sore throat, RR approximated with OR.
risk of no recovery, 86.0% lower, OR 0.14, $p = 0.03$, treatment 30, control 30, adjusted per study, vitamin D and nigella sativa, multivariable, sore throat, RR approximated with OR.
risk of no recovery, 27.0% lower, OR 0.73, $p = 0.62$, treatment 30, control 30, headache, RR approximated with OR.
risk of no recovery, 56.0% lower, OR 0.44, $p = 0.21$, treatment 30, control 30, adjusted per study, vitamin D and nigella sativa, multivariable, headache, RR approximated with OR.
risk of no recovery, 80.0% lower, OR 0.20, $p = 0.05$, treatment 30, control 30, diarrhea, RR approximated with OR.
risk of no recovery, 90.0% lower, OR 0.10, $p = 0.03$, treatment 30, control 30, adjusted per study, vitamin D and nigella sativa, multivariable, diarrhea, RR approximated with OR.

	risk of no viral clearance, 61.0% lower, OR 0.39, $p = 0.08$, treatment 30, control 30, day 14, RR approximated with OR.
	risk of no viral clearance, 85.0% lower, OR 0.15, $p = 0.004$, treatment 30, control 30, day 7, RR approximated with OR.
	risk of no viral clearance, 91.0% lower, OR 0.09, $p < 0.001$, treatment 30, control 30, vitamin D and nigella sativa, day 14, RR approximated with OR.
	risk of no viral clearance, 87.0% lower, OR 0.13, $p = 0.003$, treatment 30, control 30, vitamin D and nigella sativa, day 7, RR approximated with OR.

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.

Faruq, 9/1/2023, Randomized Controlled Trial, Bangladesh, peer-reviewed, 4 authors, excluded in exclusion analyses: potential data issue.	risk of death, 6.5% lower, RR 0.94, $p = 0.87$, treatment 29 of 75 (38.7%), control 31 of 75 (41.3%), NNT 37.
	risk of mechanical ventilation, 61.9% lower, RR 0.38, $p = 0.01$, treatment 8 of 75 (10.7%), control 21 of 75 (28.0%), NNT 5.8, day 14.
	risk of mechanical ventilation, 83.3% lower, RR 0.17, $p < 0.001$, treatment 3 of 75 (4.0%), control 18 of 75 (24.0%), NNT 5.0, day 7.
	ICU stay, 23.5% lower, RR 0.77, $p = 0.74$, treatment 4 of 46 (8.7%), control 5 of 44 (11.4%), NNT 37, >28 days.
	ICU stay, 28.3% lower, RR 0.72, $p = 0.46$, treatment 9 of 46 (19.6%), control 12 of 44 (27.3%), NNT 13, >21 days.
	ICU stay, 33.6% lower, RR 0.66, $p = 0.007$, treatment 25 of 46 (54.3%), control 36 of 44 (81.8%), NNT 3.6, >14 days.
	ICU stay, 6.6% lower, RR 0.93, $p = 0.43$, treatment 41 of 46 (89.1%), control 42 of 44 (95.5%), NNT 16, >7 days.
Karimi, 10/4/2021, Randomized Controlled Trial, Iran, peer-reviewed, 37 authors, study period March 2020 - July 2020, this trial uses multiple treatments in the treatment arm (combined with several herbal medicines) - results of individual treatments may vary.	risk of death, 50.8% lower, RR 0.49, $p = 0.45$, treatment 2 of 192 (1.0%), control 4 of 189 (2.1%), NNT 93.
	risk of ICU admission, 60.6% lower, RR 0.39, $p = 0.28$, treatment 2 of 192 (1.0%), control 5 of 189 (2.6%), NNT 62.
	hospitalization time, 70.0% lower, HR 0.30, $p < 0.001$, treatment 184, control 174, Cox proportional hazards, primary outcome.
	fever, 66.5% lower, OR 0.33, $p = 0.001$, treatment 184, control 174, inverted to make OR<1 favor treatment, RR approximated

	with OR.
	dyspnea, 13.7% lower, OR 0.86, $p < 0.001$, treatment 184, control 174, inverted to make OR<1 favor treatment, RR approximated with OR.
Setayesh, 6/3/2022, Randomized Controlled Trial, Iran, peer-reviewed, mean age 59.1, 7 authors, study period June 2020 - September 2020, this trial uses multiple treatments in the treatment arm (combined with glycyrrhiza glabra, punica granatum, and rheum palmatum) - results of individual treatments may vary, trial IRCT20200330046899N1.	risk of death, 7.9% higher, RR 1.08, $p = 1.00$, treatment 1 of 38 (2.6%), control 1 of 41 (2.4%).
	oxygen time, 26.8% lower, relative time 0.73, $p = 0.007$, treatment mean 3.0 (±1.6) n=38, control mean 4.1 (±1.9) n=41.
	hospitalization time, 28.7% lower, relative time 0.71, $p < 0.001$, treatment mean 5.7 (±1.9) n=38, control mean 8.0 (±1.8) n=41.

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.

Al-Haidari (B), 1/31/2021, prospective, Iraq, peer-reviewed, 3 authors.	risk of symptomatic case, 62.2% lower, RR 0.38, $p < 0.001$, treatment 68 of 188 (36.2%), control 180 of 188 (95.7%), NNT 1.7.
Chandra, 7/5/2022, Randomized Controlled Trial, India, peer-reviewed, 12 authors, study period 18 September, 2020 - 21 May, 2021, this trial uses multiple treatments in the treatment arm (combined with Infuza polyherbal formulation) - results of individual treatments may vary, trial CTRI/2020/08/027222.	risk of case, 49.0% lower, RR 0.51, $p = 0.36$, treatment 4 of 52 (7.7%), control 8 of 53 (15.1%), NNT 14, Infuza.
	risk of case, 87.0% lower, RR 0.13, $p = 0.03$, treatment 1 of 51 (2.0%), control 8 of 53 (15.1%), NNT 7.6, Infuza and Kulzam.
	risk of case, 74.0% lower, RR 0.26, $p = 0.09$, treatment 2 of 51 (3.9%), control 8 of 53 (15.1%), NNT 9.0, Kulzam.
Daneshfard, 7/16/2023, Randomized Controlled Trial, Iran, peer-reviewed, mean age 39.5 (treatment) 34.0 (control), 16 authors, study period 16 June, 2021 - 22 May, 2022, this trial uses multiple treatments in the treatment arm (combined with olea europaea oil) - results of individual treatments may vary, trial IRCT20210515051305N1.	risk of symptomatic case, 34.1% lower, RR 0.66, $p = 0.006$, treatment 37 of 89 (41.6%), control 53 of 84 (63.1%), NNT 4.6, any symptom.
	risk of symptomatic case, 97.3% lower, RR 0.03, $p < 0.001$, treatment 1 of 89 (1.1%), control 35 of 84 (41.7%), NNT 2.5, fever.
	risk of symptomatic case, 65.7% lower, RR 0.34, $p = 0.06$, treatment 4 of 89 (4.5%), control 11 of 84 (13.1%), NNT 12, chest pain.
	risk of symptomatic case, 62.2% lower, RR 0.38, $p = 0.10$, treatment 4 of 89 (4.5%), control 10 of 84 (11.9%), NNT 13, loss of taste/smell.
	risk of symptomatic case, 26.0% lower, RR 0.74, $p = 0.16$, treatment 29 of 89 (32.6%), control 37 of 84 (44.0%), NNT 8.7, muscle ache.
	risk of symptomatic case, 6.2% higher, RR 1.06, $p = 1.00$,

	treatment 9 of 89 (10.1%), control 8 of 84 (9.5%), chills.
	risk of symptomatic case, 79.0% lower, RR 0.21, $p = 0.001$, treatment 4 of 89 (4.5%), control 18 of 84 (21.4%), NNT 5.9, cough.
	risk of symptomatic case, 76.4% lower, RR 0.24, $p < 0.001$, treatment 5 of 89 (5.6%), control 20 of 84 (23.8%), NNT 5.5, headache.
	risk of symptomatic case, 98.1% lower, RR 0.02, $p < 0.001$, treatment 0 of 89 (0.0%), control 25 of 84 (29.8%), NNT 3.4, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), vomiting.
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, 0.2% lower, RR 1.00, $p = 1.00$, treatment 4 of 39 (10.3%), control 22 of 214 (10.3%), NNT 4173, 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.

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