

Spironolactone for COVID-19: real-time meta analysis of 12 studies

@CovidAnalysis, March 2024, Version 13

<https://c19early.org/spmeta.html>

Abstract

Statistically significant lower risk is seen for mortality, progression, and recovery. 11 studies from 10 independent teams in 8 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 31% [15-44%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies and slightly worse for peer-reviewed studies. Early treatment is more effective than late treatment.

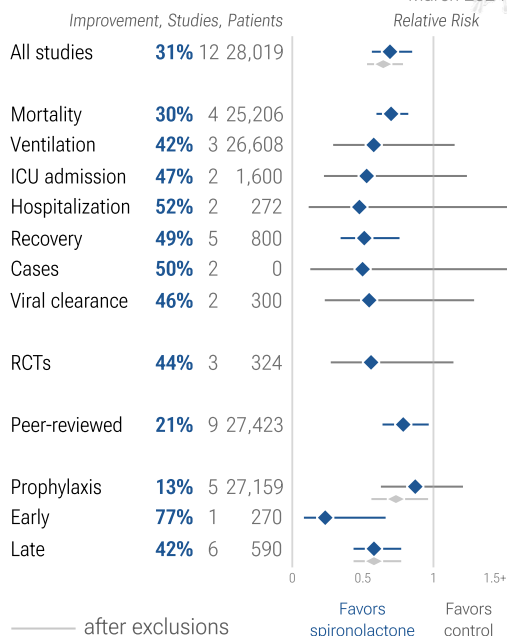
Results are robust — in exclusion sensitivity analysis 4 of 12 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

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.

All data to reproduce this paper and sources are in the appendix.

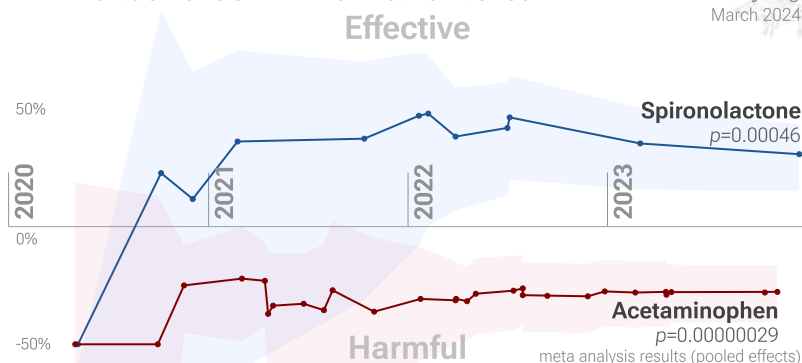
Spironolactone for COVID-19

c19early.org
March 2024



Evolution of COVID-19 clinical evidence

c19early.org
March 2024



HIGHLIGHTS

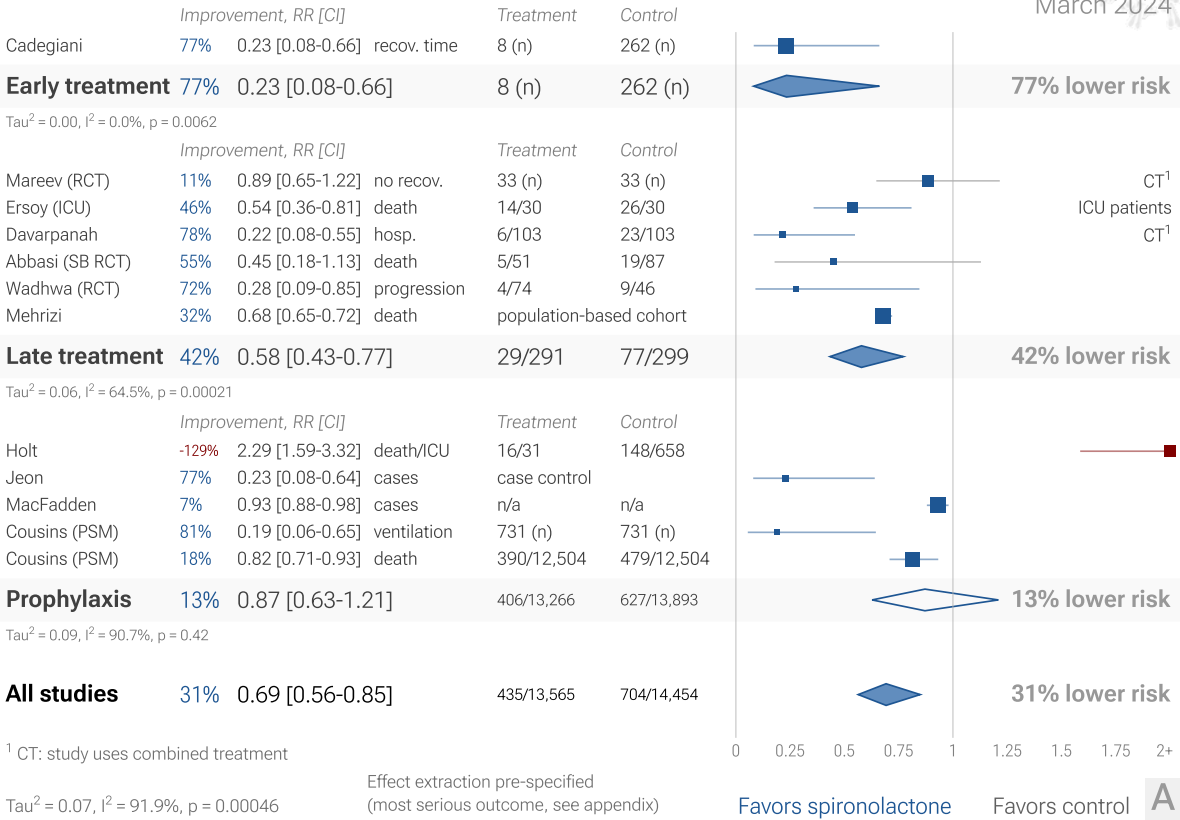
Spironolactone reduces risk for COVID-19 with very high confidence for mortality, recovery, and in pooled analysis, low confidence for ventilation and progression, and very low confidence for ICU admission and viral clearance.

Spironolactone was the 33rd treatment shown effective with ≥ 3 clinical studies in February 2022, now known with $p = 0.00046$ from 12 studies.

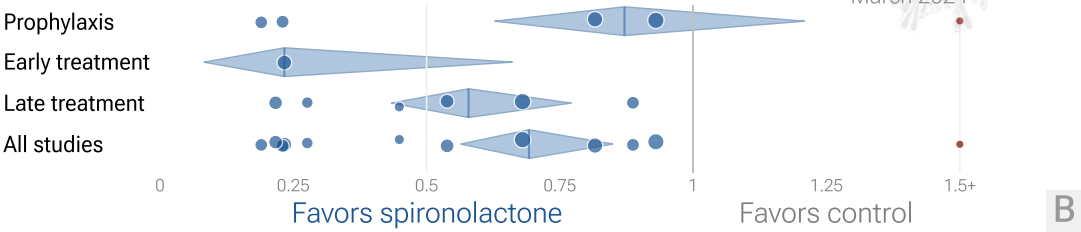
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

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

12 spironolactone COVID-19 studies

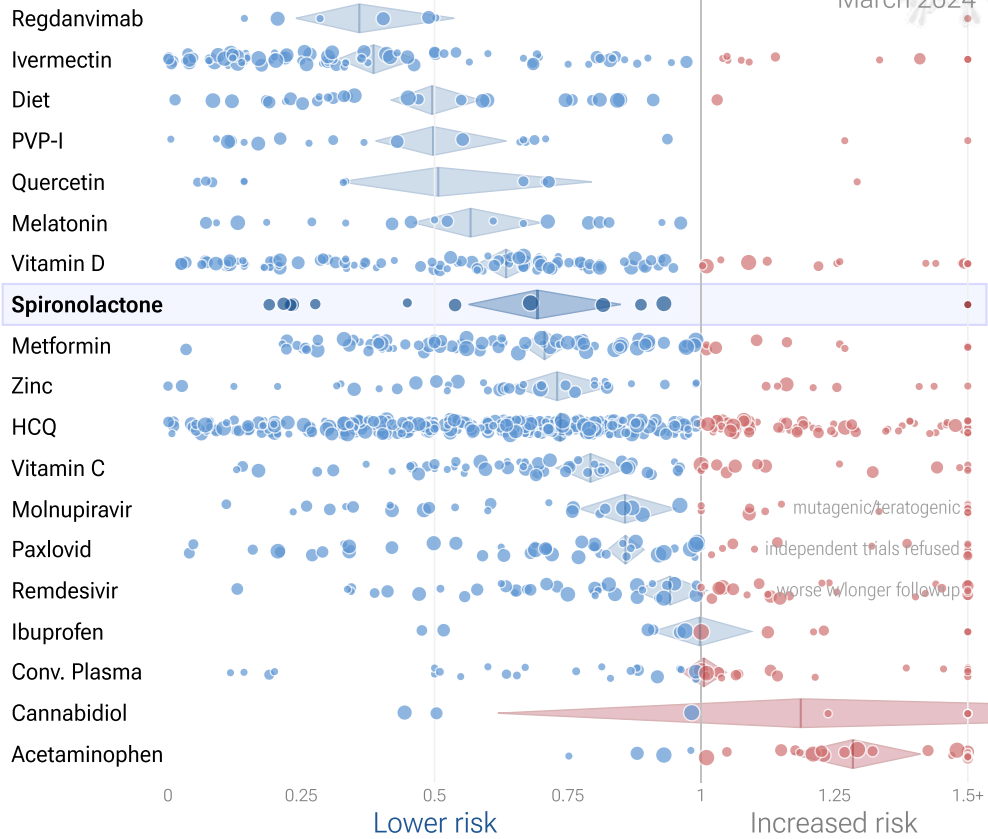


Efficacy in COVID-19 spironolactone studies (pooled effects)



Efficacy in COVID-19 studies (pooled effects)

c19early.org
March 2024



Timeline of COVID-19 spironolactone studies (pooled effects)

c19early.org
March 2024

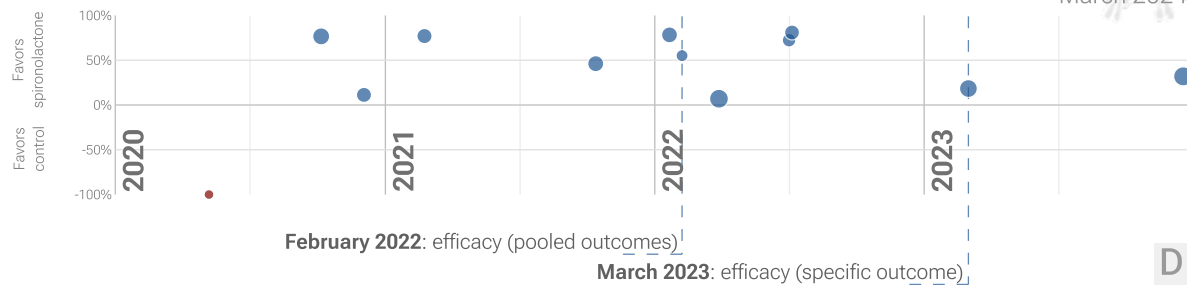


Figure 1. A. Random effects meta-analysis. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the [appendix](#). **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 spironolactone studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of $\geq 10\%$ from ≥ 3 studies for pooled outcomes and one or more specific outcome. Efficacy based on specific outcomes was delayed by 12.7 months, compared to using pooled outcomes.

Introduction

Immediate treatment recommended. SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological 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 spironolactone 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.

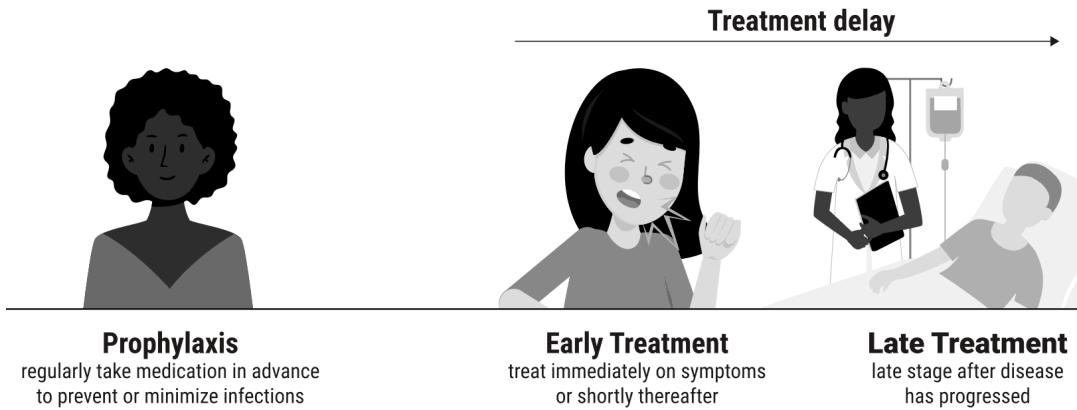


Figure 2. Treatment stages.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 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, progression, recovery, cases, viral clearance, and peer reviewed studies.

	<i>Improvement</i>	<i>Studies</i>	<i>Patients</i>	<i>Authors</i>
All studies	31% [15-44%] ***	12	28,019	107
After exclusions	36% [22-47%] ****	10	27,060	99
Peer-reviewed studies	21% [3-36%] *	9	27,423	76
Randomized Controlled Trials	44% [-14-73%]	3	324	49
Mortality	30% [18-40%] ****	4	25,206	30
Ventilation	42% [-15-71%]	3	26,608	23
ICU admission	47% [-24-78%]	2	1,600	21
Hospitalization	52% [-95-88%]	2	272	29
Recovery	49% [24-66%] ***	5	800	62
Cases	50% [-94-87%]	2	0	12
Viral	46% [-29-77%]	2	300	24

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

	<i>Early treatment</i>	<i>Late treatment</i>	<i>Prophylaxis</i>
All studies	77% [34-92%] **	42% [23-57%] ***	13% [-21-37%]
After exclusions		42% [23-57%] ***	27% [4-44%] *
Peer-reviewed studies		32% [18-43%] ****	13% [-21-37%]
Randomized Controlled Trials		44% [-14-73%]	
Mortality		32% [29-36%] ****	18% [7-29%] **
Ventilation		34% [-48-70%]	55% [-88-89%]
ICU admission		19% [-59-58%]	66% [32-83%] **
Hospitalization		52% [-95-88%]	
Recovery	77% [34-92%] **	44% [17-62%] **	
Cases			50% [-94-87%]
Viral	38% [9-58%] *	87% [-125-99%]	

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

12 spironolactone COVID-19 studies

c19early.org

March 2024



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.

4 spironolactone COVID-19 mortality results

c19early.org

March 2024

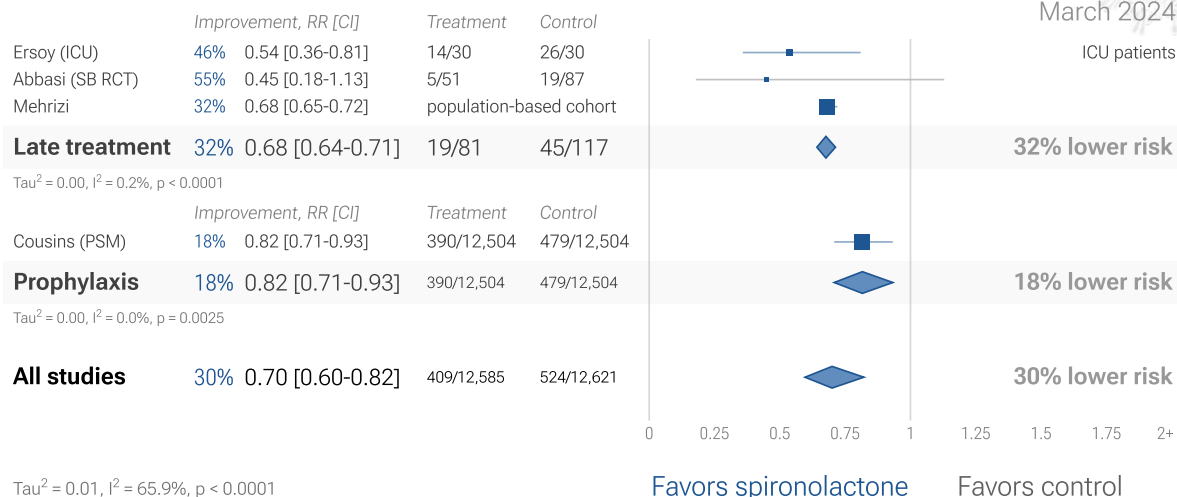


Figure 4. Random effects meta-analysis for mortality results.

3 spironolactone COVID-19 mechanical ventilation results

c19early.org

March 2024

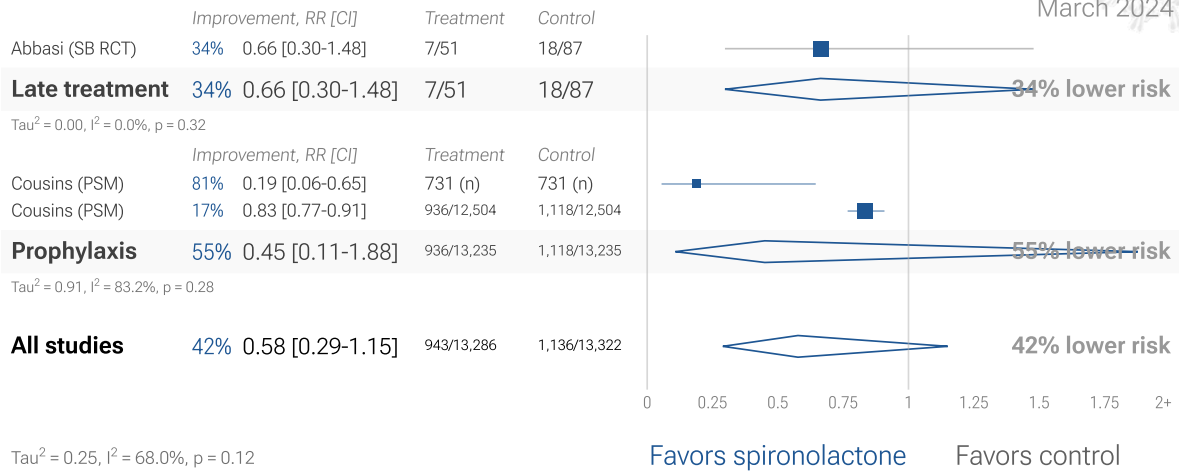


Figure 5. Random effects meta-analysis for ventilation.

2 spironolactone COVID-19 ICU results

c19early.org

March 2024

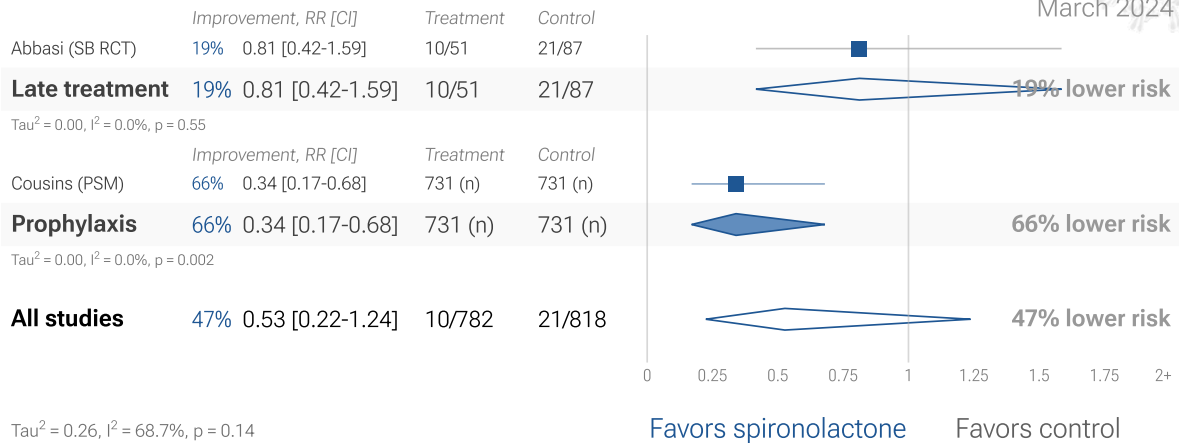


Figure 6. Random effects meta-analysis for ICU admission.

2 spironolactone COVID-19 hospitalization results

c19early.org

March 2024

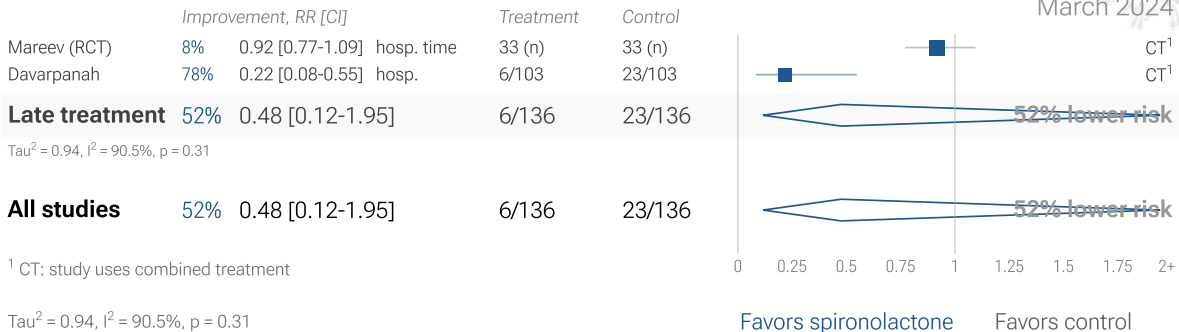


Figure 7. Random effects meta-analysis for hospitalization.

1 spironolactone COVID-19 progression result

c19early.org
March 2024

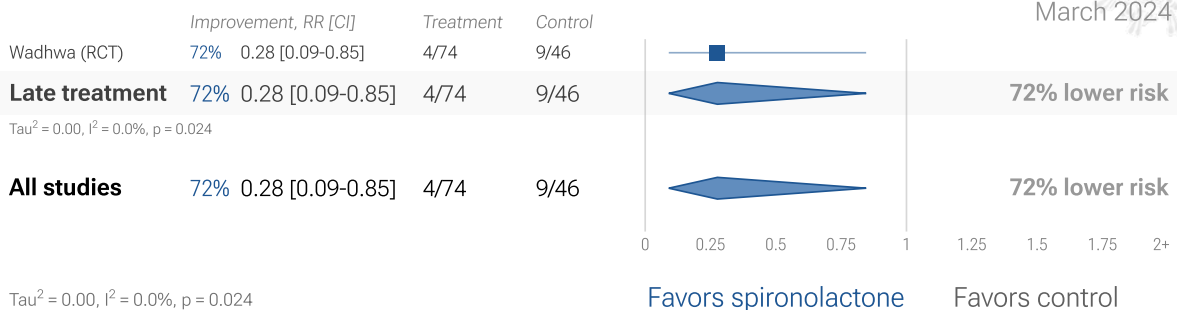


Figure 8. Random effects meta-analysis for progression.

5 spironolactone COVID-19 recovery results

c19early.org
March 2024

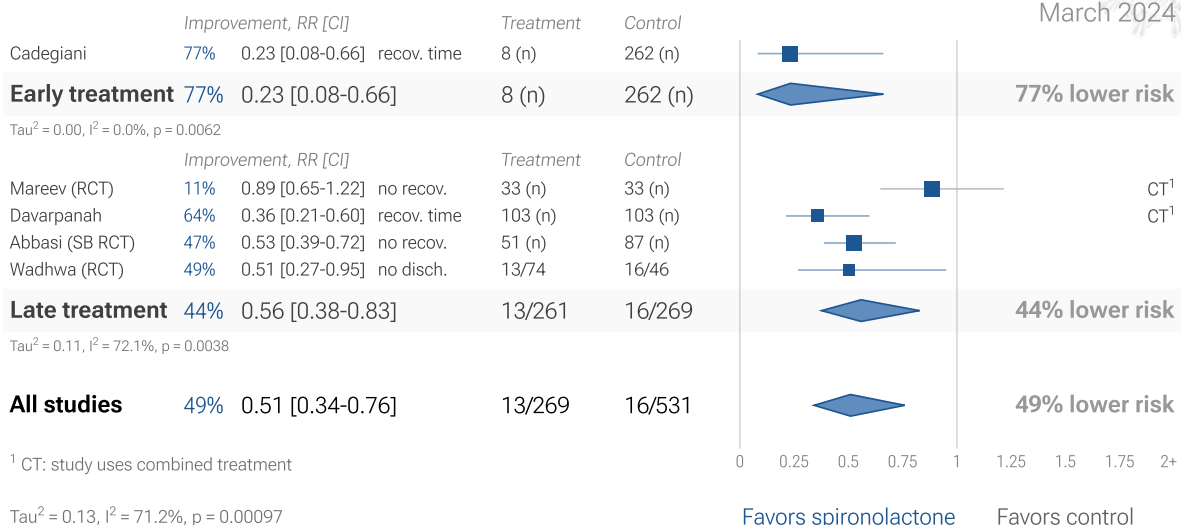


Figure 9. Random effects meta-analysis for recovery.

2 spironolactone COVID-19 case results

c19early.org
March 2024

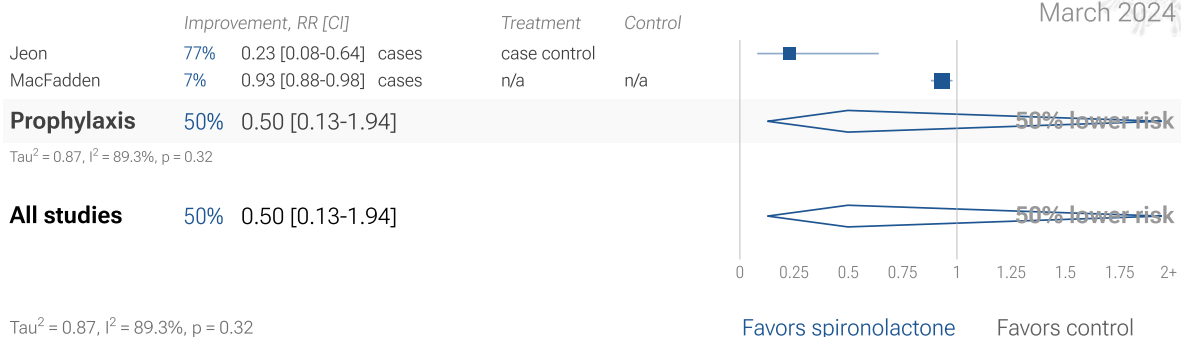


Figure 10. Random effects meta-analysis for cases.

2 spironolactone COVID-19 viral clearance results

c19early.org
March 2024

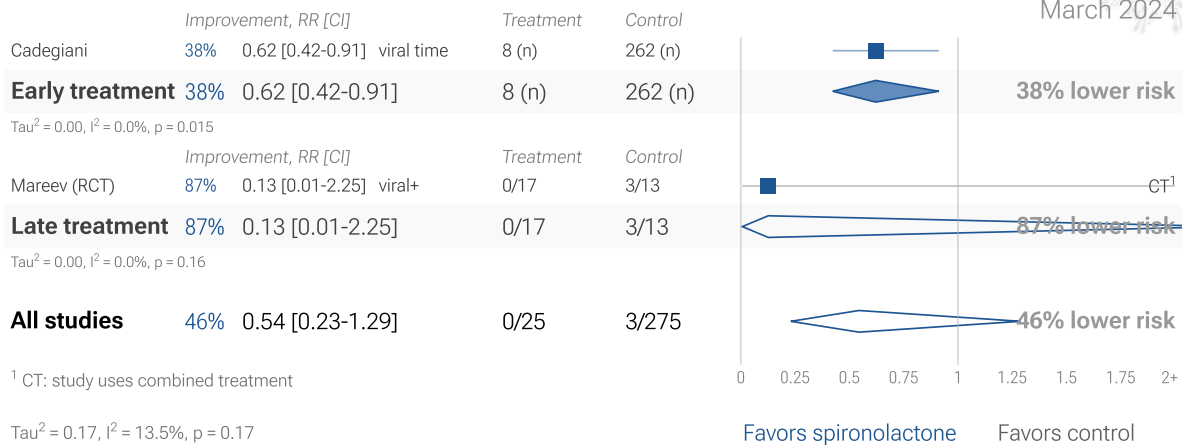


Figure 11. Random effects meta-analysis for viral clearance.

9 spironolactone COVID-19 peer reviewed studies

c19early.org
March 2024

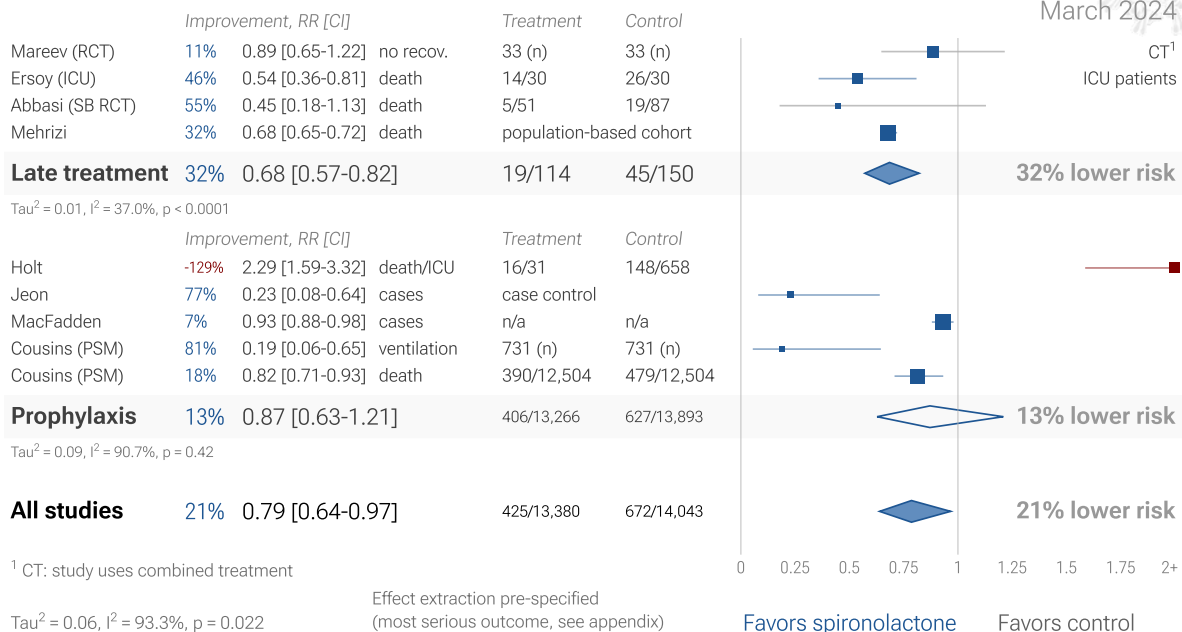


Figure 12. Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 13 shows a comparison of results for RCTs and non-RCT studies. The median effect size for RCTs is 55% improvement, compared to 46% for other studies. Figure 14 and 15 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality 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 ^{Gotzsche}. 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 $\geq 10\%$ 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.

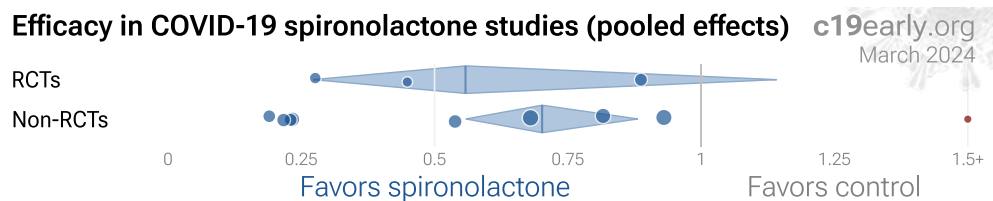


Figure 13. Results for RCTs and non-RCT studies.

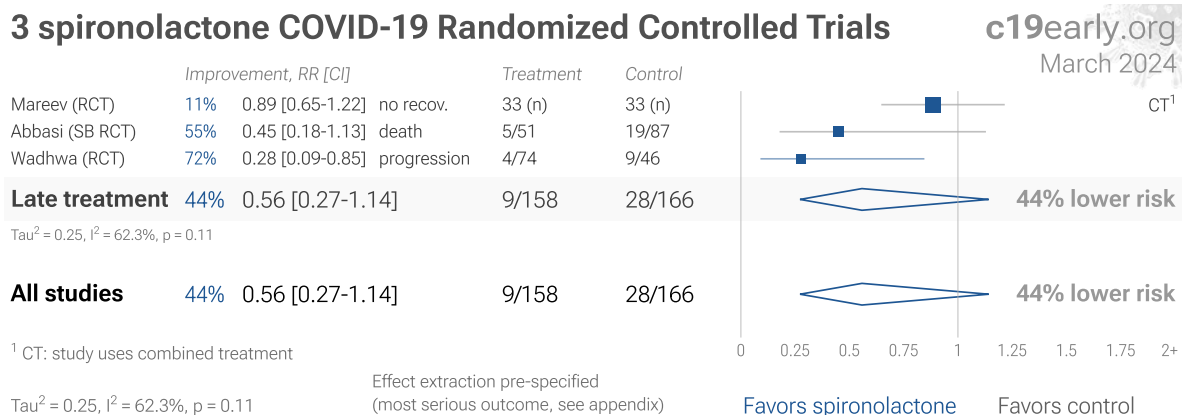


Figure 14. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

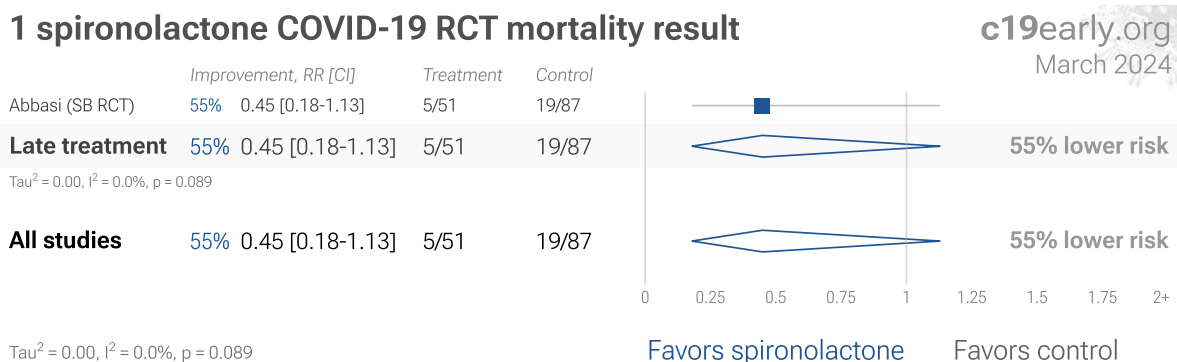


Figure 15. Random effects meta-analysis for RCT mortality results.

Exclusions

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

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

Cadegiani, significant unadjusted differences between groups.

Holt, unadjusted results with no group details.

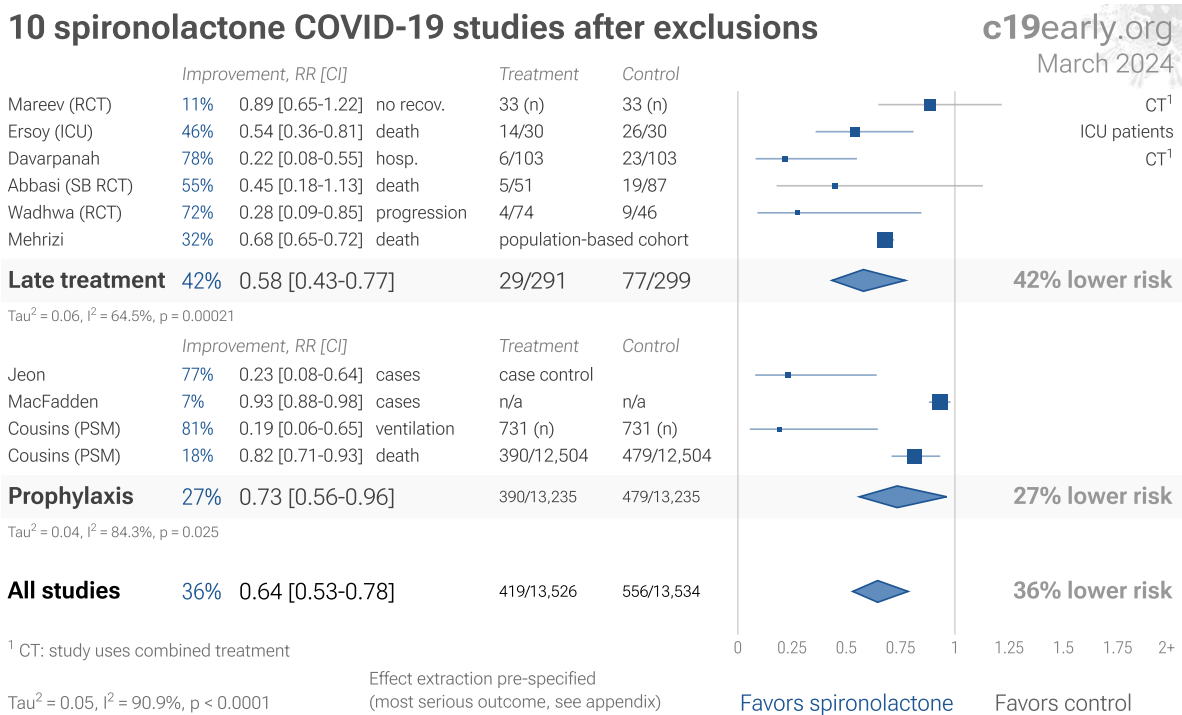


Figure 16. Random effects meta-analysis for all studies after exclusions. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Heterogeneity

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

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

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

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

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

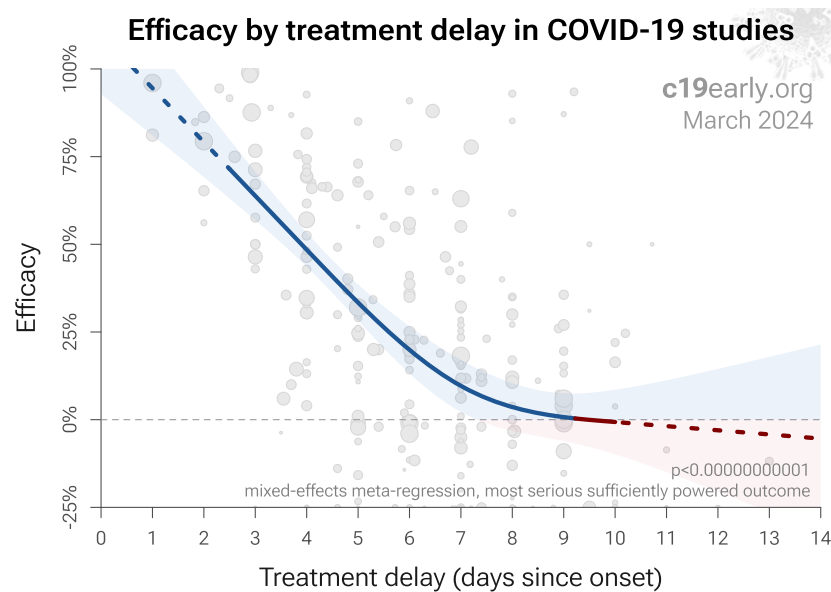


Figure 17. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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

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

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

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

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

Medication quality. The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 18. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in

severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

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

Pooled outcomes identify efficacy faster. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as $\geq 10\%$ 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.

Time when COVID-19 studies showed efficacy

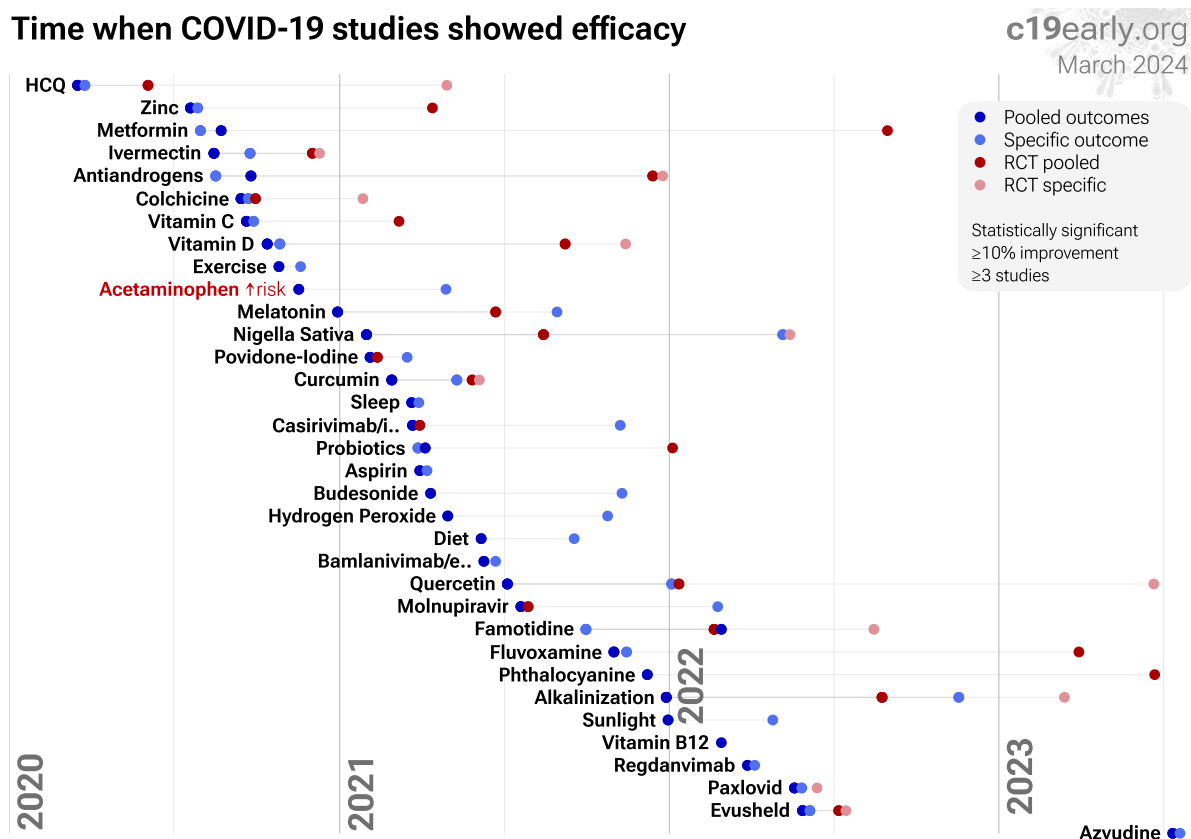


Figure 18. The time when studies showed that treatments were effective, defined as statistically significant improvement of $\geq 10\%$ from ≥ 3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when 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, Meneguzzo*. For spironolactone, there is currently not enough data to evaluate publication bias with high confidence.

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

Figure 19 shows a scatter plot of results for prospective and retrospective studies. 86% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 100% of prospective studies, consistent with a bias toward publishing negative results. The median effect size for retrospective studies is 32% improvement, compared to 72% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

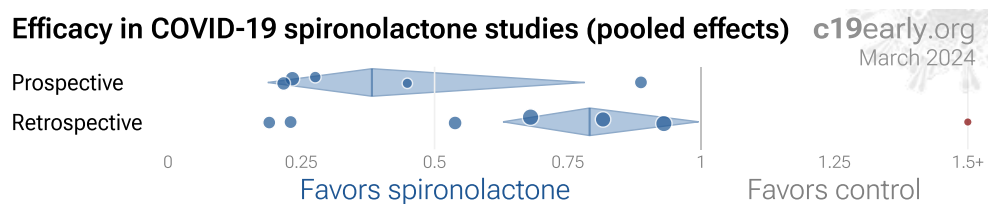


Figure 19. Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 20 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common).

Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

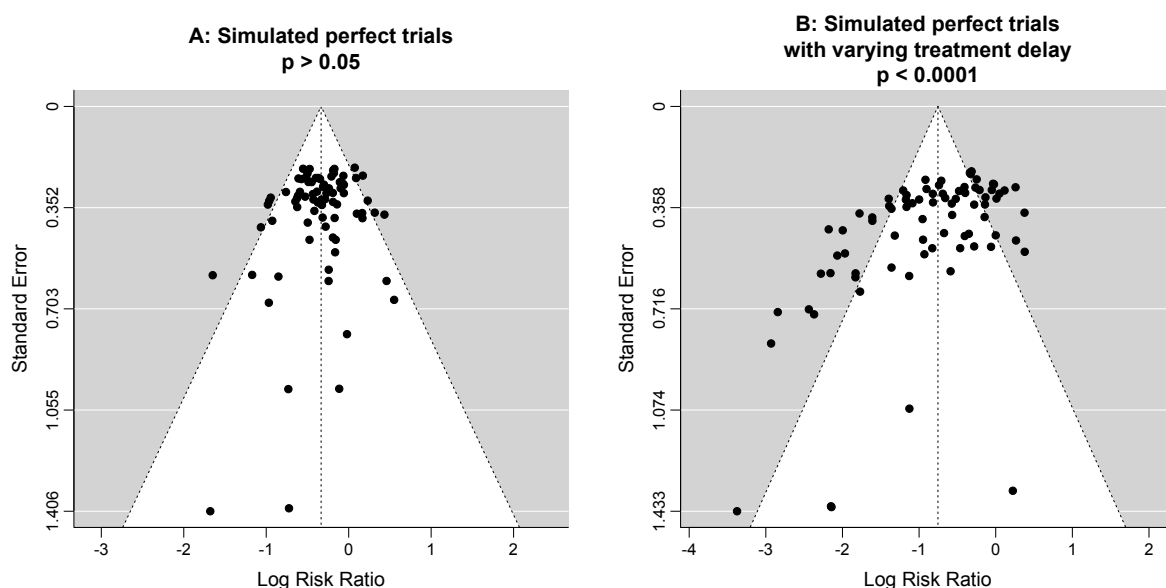


Figure 20. Example funnel plot analysis for simulated perfect trials.

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Spironolactone for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 spironolactone 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 spironolactone 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 *Alsaïdi, 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.

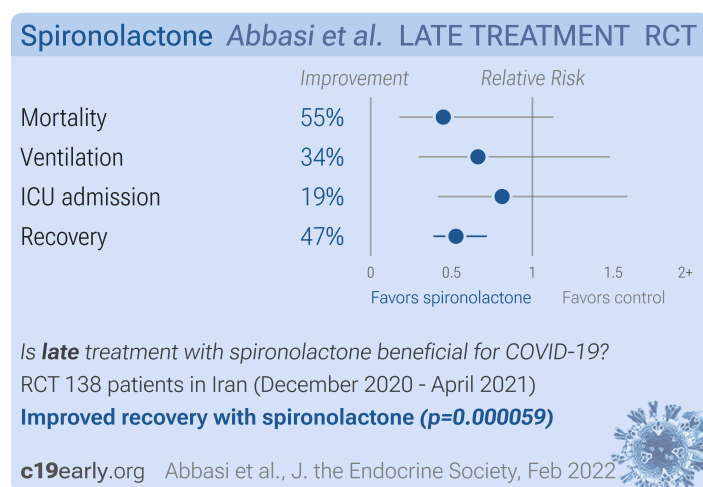
Notes. 2 of 12 studies combine treatments. The results of spironolactone alone may differ. 1 of 3 RCTs use combined treatment.

Conclusion

Studies to date show that spironolactone is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, progression, and recovery. 11 studies from 10 independent teams in 8 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 31% [15-44%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies and slightly worse for peer-reviewed studies. Early treatment is more effective than late treatment. Results are robust — in exclusion sensitivity analysis 4 of 12 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Study Notes

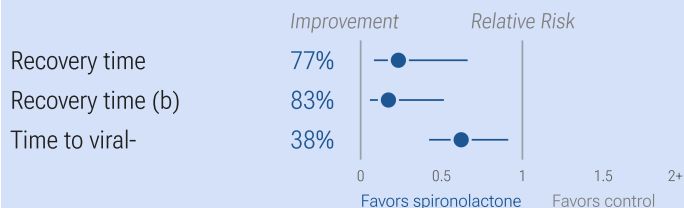
Abbasi



Abbasi: RCT including 51 spironolactone patients and 87 control patients in Iran, showing improved recovery with spironolactone, sitagliptin, and the combination of both.

Cadegiani

Spironolactone Cadegiani et al. EARLY TREATMENT

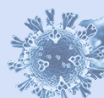


Is early treatment with spironolactone beneficial for COVID-19?

Prospective study of 270 patients in Brazil

Faster recovery ($p=0.0062$) and viral clearance ($p=0.015$)

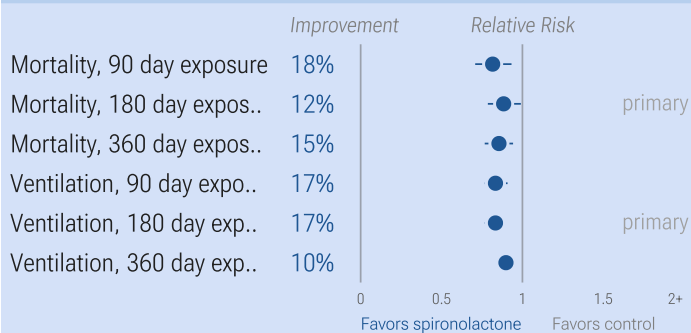
c19early.org Cadegiani et al., medRxiv, October 2020



Cadegiani: Prospective study of 270 female COVID-19 patients in Brazil, 75 with hyperandrogenism, of which 8 were on spironolactone. Results suggest that HA patients may be at increased risk, and that spironolactone use may reduce the risk compared to both other HA patients and non-HA patients. SOC included other treatments and there was no mortality or hospitalization.

Cousins

Spironolactone Cousins et al. Prophylaxis

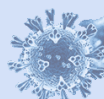


Is prophylaxis with spironolactone beneficial for COVID-19?

PSM retrospective 898,303 patients in the USA

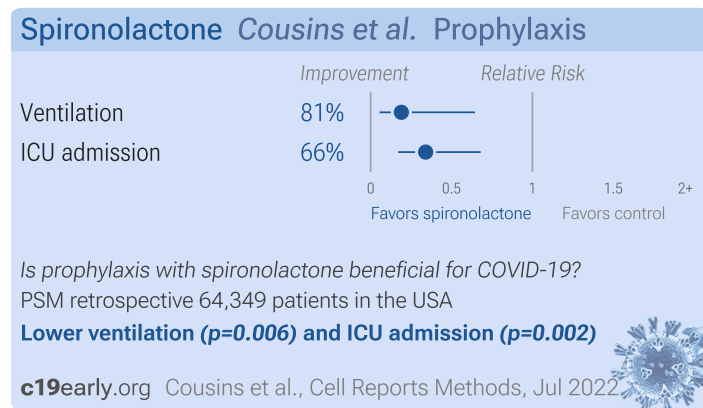
Lower mortality ($p=0.0038$) and ventilation ($p<0.0001$)

c19early.org Cousins et al., medRxiv, March 2023



Cousins: PSM retrospective 898,303 hospitalized COVID-19 patients in the USA, 16,324 on spironolactone, showing lower mortality and ventilation with spironolactone use.

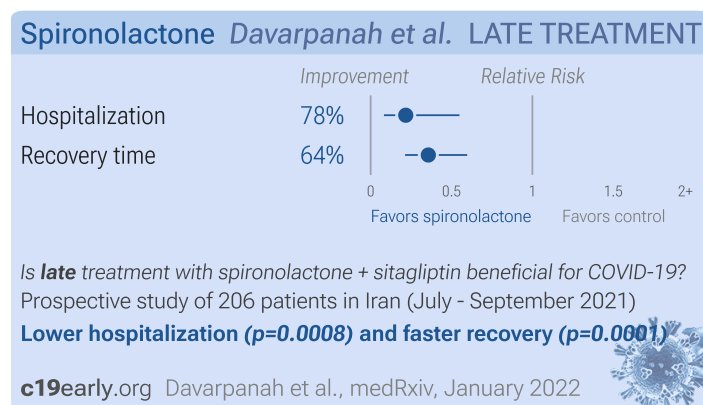
Cousins



Cousins (B): PSM retrospective 64,349 COVID-19 patients in the USA, showing spironolactone associated with lower ICU admission.

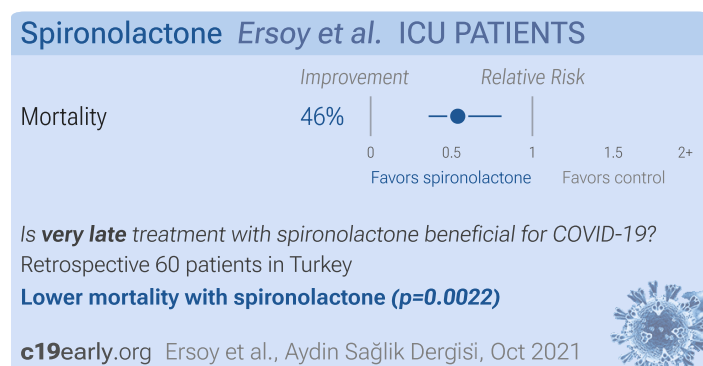
Authors also present In Vitro research showing dose-dependent inhibition in a human lung epithelial cell line.

Davarpanah



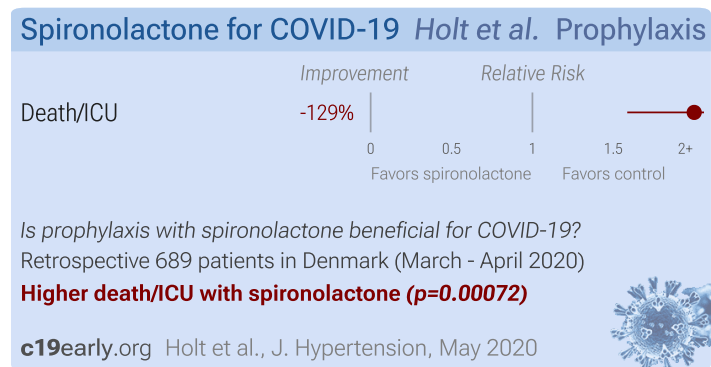
Davarpanah: Prospective study of 206 outpatients in Iran, 103 treated with spironolactone and sitagliptin, showing lower hospitalization and faster recovery with treatment. spironolactone 100mg and sitagliptin 100mg daily.

Ersoy



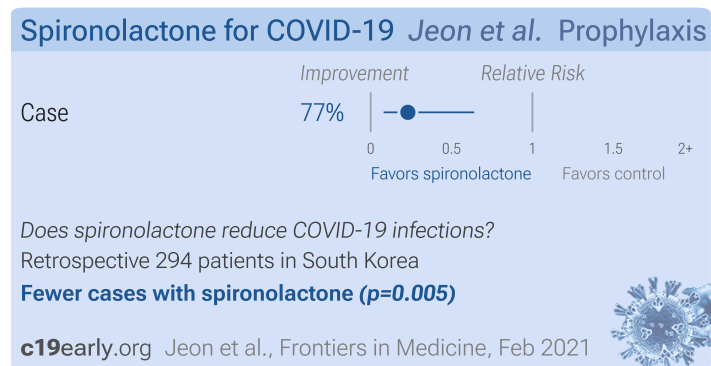
Ersoy: Retrospective 30 COVID-19 ARDS ICU patients and 30 control patients, showing lower mortality with treatment.

Holt



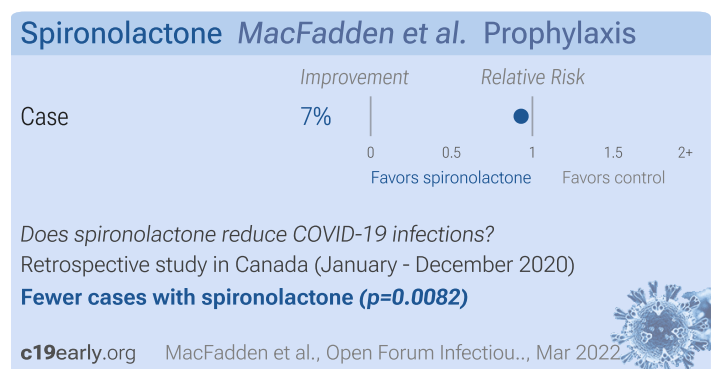
Holt: Retrospective 689 hospitalized COVID-19 patients in Denmark, showing higher risk of ICU/death with spironolactone use in unadjusted results subject to confounding by indication.

Jeon



Jeon: Retrospective 6,462 liver cirrhosis patients in South Korea, with 67 COVID+ cases, showing significantly lower cases with spironolactone treatment. Death and ICU results per group are not provided.

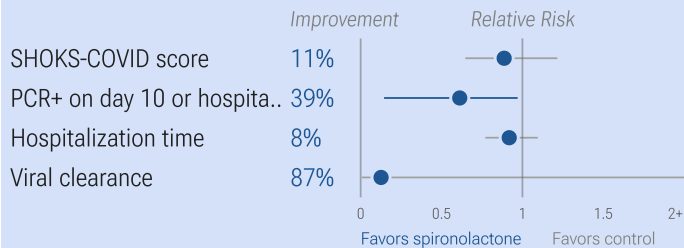
MacFadden



MacFadden: Retrospective 26,121 cases and 2,369,020 controls ≥ 65 yo in Canada, showing lower cases with chronic use of spironolactone.

Mareev

Spironolactone Mareev et al. LATE TREATMENT RCT



Is **late** treatment with spironolactone + bromhexine beneficial for COVID-19?

RCT 66 patients in Russia

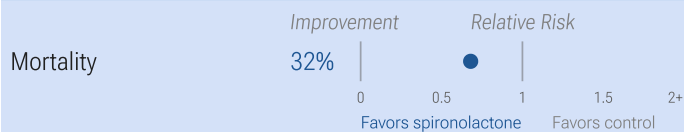
Improved recovery ($p=0.47$) and viral clearance ($p=0.077$), not sig.

c19early.org Mareev et al., Кардиология, December 2020

Mareev: Prospective 103 PCR+ patients in Russia, 33 treated with bromexhine+spironolactone, showing lower PCR+ at day 10 or hospitalization >10 days with treatment. Bromhexine 8mg 4 times daily, spironolactone 25-50 mg/day for 10 days.

Mehrizi

Spironolactone Mehrizi et al. LATE TREATMENT



Is **late** treatment with spironolactone beneficial for COVID-19?

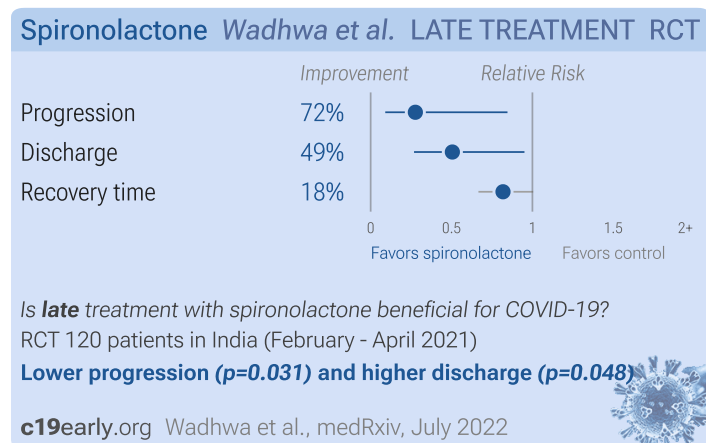
Retrospective 917,198 patients in Iran (February 2020 - March 2022)

Lower mortality with spironolactone ($p<0.000001$)

c19early.org Mehrizi et al., Frontiers in Public He., Dec 2023

Mehrizi: Retrospective study of 917,198 hospitalized COVID-19 cases covered by the Iran Health Insurance Organization over 26 months showing that antithrombotics, corticosteroids, and antivirals reduced mortality while diuretics, antibiotics, and antidiabetics increased it. Confounding makes some results very unreliable. For example, diuretics like furosemide are often used to treat fluid overload, which is more likely in ICU or advanced disease requiring aggressive fluid resuscitation. Hospitalization length has increased risk of significant confounding, for example longer hospitalization increases the chance of receiving a medication, and death may result in shorter hospitalization. Mortality results may be more reliable.

Confounding by indication is likely to be significant for many medications. Authors adjustments have very limited severity information (admission type refers to ward vs. ER department on initial arrival). We can estimate the impact of confounding from typical usage patterns, the prescription frequency, and attenuation or increase of risk for ICU vs. all patients.



Wadhwa: RCT 120 hospitalized patients in India, 74 treated with spironolactone and dexamethasone, and 46 with dexamethasone, showing lower progression with treatment. Spironolactone 50mg once daily day 1, 25mg once daily until day 21.

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 spironolactone 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 spironolactone 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 SpO₂ 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/spmeta.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.

<i>Cadegiani</i> , 10/6/2020, prospective, Brazil, preprint, 4 authors, average treatment delay 3.0 days, excluded in exclusion analyses: significant unadjusted differences between groups.	recovery time, 76.7% lower, relative time 0.23, $p = 0.006$, treatment 8, control 262, excluding anosmia.
	recovery time, 82.8% lower, relative time 0.17, $p = 0.002$, treatment 8, control 262, including anosmia.
	time to viral-, 37.9% lower, relative time 0.62, $p = 0.02$, treatment 8, control 262.

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.

<i>Abbasi</i> , 2/7/2022, Single Blind Randomized Controlled Trial, Iran, peer-reviewed, 11 authors, study period December 2020 - April 2021.	risk of death, 55.1% lower, RR 0.45, $p = 0.10$, treatment 5 of 51 (9.8%), control 19 of 87 (21.8%), NNT 8.3, day 5.
	risk of mechanical ventilation, 33.7% lower, RR 0.66, $p = 0.36$, treatment 7 of 51 (13.7%), control 18 of 87 (20.7%), NNT 14, day 5.
	risk of ICU admission, 18.8% lower, RR 0.81, $p = 0.67$, treatment 10 of 51 (19.6%), control 21 of 87 (24.1%), NNT 22, day 5.

	risk of no recovery, 47.3% lower, RR 0.53, $p < 0.001$, treatment mean 1.64 (± 0.81) $n=51$, control mean 3.11 (± 2.45) $n=87$, relative clinical score, day 5.
<i>Davarpanah</i> , 1/21/2022, prospective, Iran, preprint, 9 authors, study period July 2021 - September 2021, average treatment delay 5.74 days, this trial uses multiple treatments in the treatment arm (combined with sitagliptin) - results of individual treatments may vary.	risk of hospitalization, 78.3% lower, RR 0.22, $p < 0.001$, treatment 6 of 103 (5.8%), control 23 of 103 (22.3%), NNT 6.1, odds ratio converted to relative risk.
	recovery time, 64.4% lower, relative time 0.36, $p < 0.001$, treatment 103, control 103.
<i>Ersoy</i> , 10/13/2021, retrospective, Turkey, peer-reviewed, 7 authors.	risk of death, 46.2% lower, RR 0.54, $p = 0.002$, treatment 14 of 30 (46.7%), control 26 of 30 (86.7%), NNT 2.5.
<i>Mareev</i> , 12/3/2020, Randomized Controlled Trial, Russia, peer-reviewed, 20 authors, this trial uses multiple treatments in the treatment arm (combined with bromhexine) - results of individual treatments may vary, trial NCT04424134 (history).	relative SHOKS-COVID score, 11.3% better, RR 0.89, $p = 0.47$, treatment mean 2.12 (± 1.39) $n=33$, control mean 2.39 (± 1.59) $n=33$.
	risk of PCR+ on day 10 or hospitalization >10 days, 38.8% lower, RR 0.61, $p = 0.02$, treatment 14 of 24 (58.3%), control 20 of 21 (95.2%), NNT 2.7, odds ratio converted to relative risk.
	hospitalization time, 8.2% lower, relative time 0.92, $p = 0.35$, treatment 33, control 33.
	risk of no viral clearance, 87.4% lower, RR 0.13, $p = 0.08$, treatment 0 of 17 (0.0%), control 3 of 13 (23.1%), NNT 4.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 10.
<i>Mehrizi</i> , 12/18/2023, retrospective, Iran, peer-reviewed, 10 authors, study period 1 February, 2020 - 20 March, 2022.	risk of death, 32.0% lower, OR 0.68, $p < 0.001$, RR approximated with OR.
<i>Wadhwa</i> , 7/2/2022, Randomized Controlled Trial, placebo-controlled, India, preprint, 18 authors, study period 1 February, 2021 - 30 April, 2021, trial CTRI/2021/03/031721.	risk of progression, 72.4% lower, RR 0.28, $p = 0.03$, treatment 4 of 74 (5.4%), control 9 of 46 (19.6%), NNT 7.1, progression to WHO >4.
	risk of no hospital discharge, 49.5% lower, RR 0.51, $p = 0.048$, treatment 13 of 74 (17.6%), control 16 of 46 (34.8%), NNT 5.8.
	recovery time, 18.2% lower, relative time 0.82, $p = 0.06$, treatment 74, control 46.

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.

<i>Cousins</i> , 3/2/2023, retrospective, propensity score matching, USA, peer-reviewed, 2 authors.	risk of death, 18.4% lower, RR 0.82, $p = 0.004$, treatment 390 of 12,504 (3.1%), control 479 of 12,504 (3.8%), NNT 140, odds ratio converted to relative risk, 90 day exposure window, propensity score matching.
-----------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

	risk of death, 11.6% lower, RR 0.88, $p = 0.04$, treatment 521 of 16,324 (3.2%), control 592 of 16,324 (3.6%), NNT 230, odds ratio converted to relative risk, 180 day exposure window, propensity score matching, primary outcome.
	risk of death, 14.5% lower, RR 0.85, $p = 0.003$, treatment 671 of 20,690 (3.2%), control 783 of 20,690 (3.8%), NNT 185, odds ratio converted to relative risk, 360 day exposure window, propensity score matching.
	risk of mechanical ventilation, 16.7% lower, RR 0.83, $p < 0.001$, treatment 936 of 12,504 (7.5%), control 1,118 of 12,504 (8.9%), NNT 69, odds ratio converted to relative risk, 90 day exposure window, propensity score matching.
	risk of mechanical ventilation, 16.7% lower, RR 0.83, $p < 0.001$, treatment 1,212 of 16,324 (7.4%), control 1,459 of 16,324 (8.9%), NNT 66, odds ratio converted to relative risk, 180 day exposure window, propensity score matching, primary outcome.
	risk of mechanical ventilation, 10.2% lower, RR 0.90, $p < 0.001$, treatment 1,524 of 20,690 (7.4%), control 1,701 of 20,690 (8.2%), NNT 117, odds ratio converted to relative risk, 360 day exposure window, propensity score matching.
<i>Cousins (B)</i> , 7/6/2022, retrospective, propensity score matching, USA, peer-reviewed, 10 authors.	risk of mechanical ventilation, 81.0% lower, OR 0.19, $p = 0.006$, treatment 731, control 731, propensity score matching, RR approximated with OR.
	risk of ICU admission, 66.0% lower, OR 0.34, $p = 0.002$, treatment 731, control 731, propensity score matching, RR approximated with OR.
<i>Holt</i> , 5/7/2020, retrospective, Denmark, peer-reviewed, median age 70.0, 4 authors, study period 1 March, 2020 - 1 April, 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of death/ICU, 129.5% higher, RR 2.29, $p < 0.001$, treatment 16 of 31 (51.6%), control 148 of 658 (22.5%).
<i>Jeon</i> , 2/23/2021, retrospective, South Korea, peer-reviewed, 3 authors.	risk of case, 77.0% lower, OR 0.23, $p = 0.005$, treatment 6 of 49 (12.2%) cases, 89 of 245 (36.3%) controls, NNT 6.5, case control OR, model 2, within 3 months.
<i>MacFadden</i> , 3/29/2022, retrospective, Canada, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.	risk of case, 7.0% lower, OR 0.93, $p = 0.008$, RR approximated with OR.

Supplementary Data

Supplementary Data

Footnotes

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

References

1. **Abbasi** et al., *A Randomized Trial of Sitagliptin and Spironolactone With Combination Therapy in Hospitalized Adults With COVID-19*, Journal of the Endocrine Society, doi:10.1210/jendso/bvac017.
2. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.
3. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.
4. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.
5. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.
6. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.
7. **Anglemyer** et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews 2014, Issue 4, doi:10.1002/14651858.MR000034.pub2.
8. **Boulware**, D., *Comments regarding paper rejection*, twitter.com/boulware_dr/status/1311331372884205570.
9. **c19early.org**, c19early.org/timeline.html.
10. **c19early.org (B)**, c19early.org/treatments.html.
11. **Cadegiani** et al., *An open-label prospective observational study of antiandrogen and non-antiandrogen early pharmacological approaches in females with mild-to-moderate COVID-19. The Pre-AndroCoV Female Trial*, medRxiv, doi:10.1101/2020.10.05.20206870.
12. **Concato** et al., NEJM, 342:1887-1892, doi:10.1056/NEJM200006223422507.
13. **Cousins** et al., *Association between spironolactone use and COVID-19 outcomes in population-scale claims data: a retrospective cohort study*, medRxiv, doi:10.1101/2023.02.28.23286515.
14. **Cousins (B)** et al., *Integrative analysis of functional genomic screening and clinical data identifies a protective role for spironolactone in severe COVID-19*, Cell Reports Methods, doi:10.1016/j.crmeth.2023.100503.
15. **Davarpanah** et al., *Combination of Spironolactone and Sitagliptin Improves Clinical Outcomes of Outpatients with COVID-19: An Observational Study*, medRxiv, doi:10.1101/2022.01.21.22269322.
16. **Davidson** et al., *No evidence of important difference in summary treatment effects between COVID-19 preprints and peer-reviewed publications: a meta-epidemiological study*, Journal of Clinical Epidemiology, doi:10.1016/j.jclinepi.2023.08.011.
17. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.
18. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.
19. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.
20. **Eberhardt** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.
21. **Egger** et al., *Bias in meta-analysis detected by a simple, graphical test*, BMJ, doi:10.1136/bmj.315.7109.629.

22. **Ersoy** et al., *Assessment Of The Efficacy Of Spironolactone For COVID-19 ARDS Patients*, *Aydin Sağlık Dergisi*, doi:10.17932/IAU.ASD.2015.007/asd_v07i3002.
23. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, *Science*, doi:10.1126/science.abh2644.
24. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, *Viruses*, doi:10.3390/v16020168.
25. **Gøtzsche**, P., *Bias in double-blind trials*, Doctoral Thesis, University of Copenhagen, www.scientificfreedom.dk/2023/05/16/bias-in-double-blind-trials-doctoral-thesis/.
26. **Harbord** et al., *A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints*, *Statistics in Medicine*, doi:10.1002/sim.2380.
27. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, *New England Journal of Medicine*, doi:10.1056/NEJMoa1716197.
28. **Holt** et al., *Influence of inhibitors of the renin–angiotensin system on risk of acute respiratory distress syndrome in Danish hospitalized COVID-19 patients*, *Journal of Hypertension*, doi:10.1097/hjh.0000000000002515.
29. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, *New England Journal of Medicine*, doi:10.1056/NEJMoa1915341.
30. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings, Second Edition*, doi:10.1002/9780470691922.
31. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, *International Journal of Antimicrobial Agents*, doi:10.1016/j.ijantimicag.2022.106542.
32. **Jeon** et al., *Effect of Spironolactone on COVID-19 in Patients With Underlying Liver Cirrhosis: A Nationwide Case-Control Study in South Korea*, *Frontiers in Medicine*, doi:10.3389/fmed.2021.629176.
33. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, *Research Square*, doi:10.21203/rs.3.rs-941811/v1.
34. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, *BMC Pharmacology and Toxicology*, doi:10.1186/s40360-022-00580-8.
35. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, *medRxiv*, doi:10.1101/2021.08.27.21262754.
36. **Kumar** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, *The Lancet Infectious Diseases*, doi:10.1016/S1473-3099(21)00469-2.
37. **Lee** et al., *Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines*, *Arch Intern Med.*, 2011, 171:1, 18-22, doi:10.1001/archinternmed.2010.482.
38. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, *JAMA*, doi:10.1001/jama.2021.3071.
39. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, *Virology*, doi:10.1128/mbio.00392-24.
40. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, *Virus Genes*, doi:10.1007/s11262-021-01869-2.
41. **Macaskill** et al., *A comparison of methods to detect publication bias in meta-analysis*, *Statistics in Medicine*, doi:10.1002/sim.698.
42. **MacFadden** et al., *Screening Large Population Health Databases for Potential COVID-19 Therapeutics: A Pharmacopeia-Wide Association Study (PWAS) of Commonly Prescribed Medications*, *Open Forum Infectious Diseases*, doi:10.1093/ofid/ofac156.
43. **Malone** et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, *Nature Reviews Molecular Cell Biology*, doi:10.1038/s41580-021-00432-z.

44. **Mareev** et al., *Results of Open-Label non-Randomized Comparative Clinical Trial: "Bromhexine and Spironolactone for Coronavirus Infection requiring hospitalization (BISCUIT)*, Кардиология, doi:10.18087/cardio.2020.11.n1440.
45. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.
46. **Meeus**, G., *Online Comment*, twitter.com/gertmeeus_MD/status/1386636373889781761.
47. **Mehrizi** et al., *Drug prescription patterns and their association with mortality and hospitalization duration in COVID-19 patients: insights from big data*, Frontiers in Public Health, doi:10.3389/fpubh.2023.1280434.
48. **Meneguesso**, A., *Médica defende tratamento precoce da Covid-19*, www.youtube.com/watch?v=X5FCrIm_19U.
49. **Moreno** et al., *Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study*, BMC Medical Research Methodology, doi:10.1186/1471-2288-9-2.
50. **Murigneux** et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.
51. **Nichol** et al., *Challenging issues in randomised controlled trials*, Injury, 2010, doi: 10.1016/j.injury.2010.03.033, www.injuryjournal.com/article/S0020-1383(10)00233-0/fulltext.
52. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.
53. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.
54. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.
55. **Peters**, J., *Comparison of Two Methods to Detect Publication Bias in Meta-analysis*, JAMA, doi:10.1001/jama.295.6.676.
56. **Rothstein**, H., *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*, www.wiley.com/en-ae/Publication+Bias+in+Meta+Analysis:+Prevention,+Assessment+and+Adjustments-p-9780470870143.
57. **Rücker** et al., *Arcsine test for publication bias in meta-analyses with binary outcomes*, Statistics in Medicine, doi:10.1002/sim.2971.
58. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.
59. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.
60. **Stanley** et al., *Meta-regression approximations to reduce publication selection bias*, Research Synthesis Methods, doi:10.1002/jrsm.1095.
61. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.
62. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.
63. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.
64. **Wadhwa** et al., *Phase 2 randomised placebo-controlled trial of spironolactone and dexamethasone versus dexamethasone in COVID-19 hospitalised patients in Delhi*, medRxiv, doi:10.1101/2022.07.01.22277163.
65. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.

66. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.
67. **Williams**, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.
68. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, Rapid Communications in Mass Spectrometry, doi:10.1002/rcm.9358.
69. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.
70. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, Research Square, doi:10.21203/rs.3.rs-910467/v1.
71. **Zeraatkar** et al., *Consistency of covid-19 trial preprints with published reports and impact for decision making: retrospective review*, BMJ Medicine, doi:10.1136/bmjmed-2022-0003091.
72. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.