Azvudine for COVID-19: real-time meta analysis of 18 studies

@CovidAnalysis, April 2024, Version 19
https://c19early.org/azvmeta.html

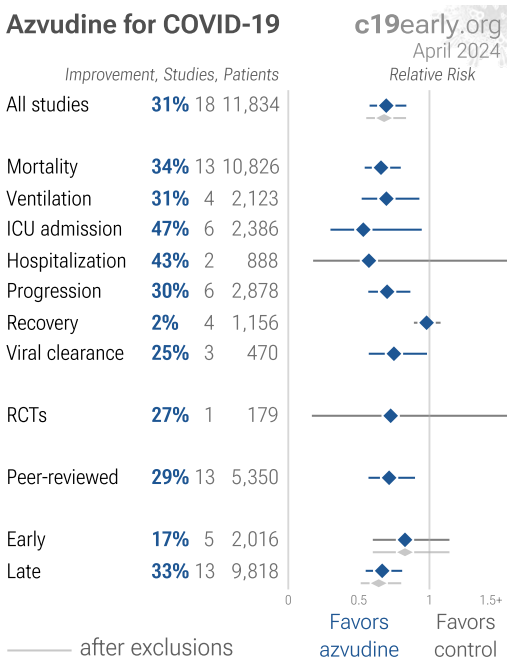
Abstract

Statistically significant lower risk is seen for mortality, ventilation, ICU admission, progression, and viral clearance. 14 studies from 12 independent teams in 2 countries show statistically significant improvements.

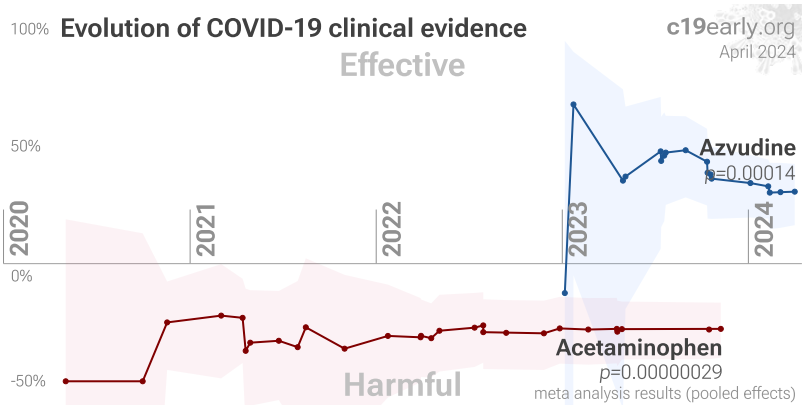
Meta analysis using the most serious outcome reported shows 31% [16-42%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies.

Results are robust — in exclusion sensitivity analysis 8 of 18 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.
Other meta analyses show significant improvements with azvudine for mortality [Wang, Zheng], mechanical ventilation [Zheng], clinical improvement [Zheng], and viral clearance [Zheng].



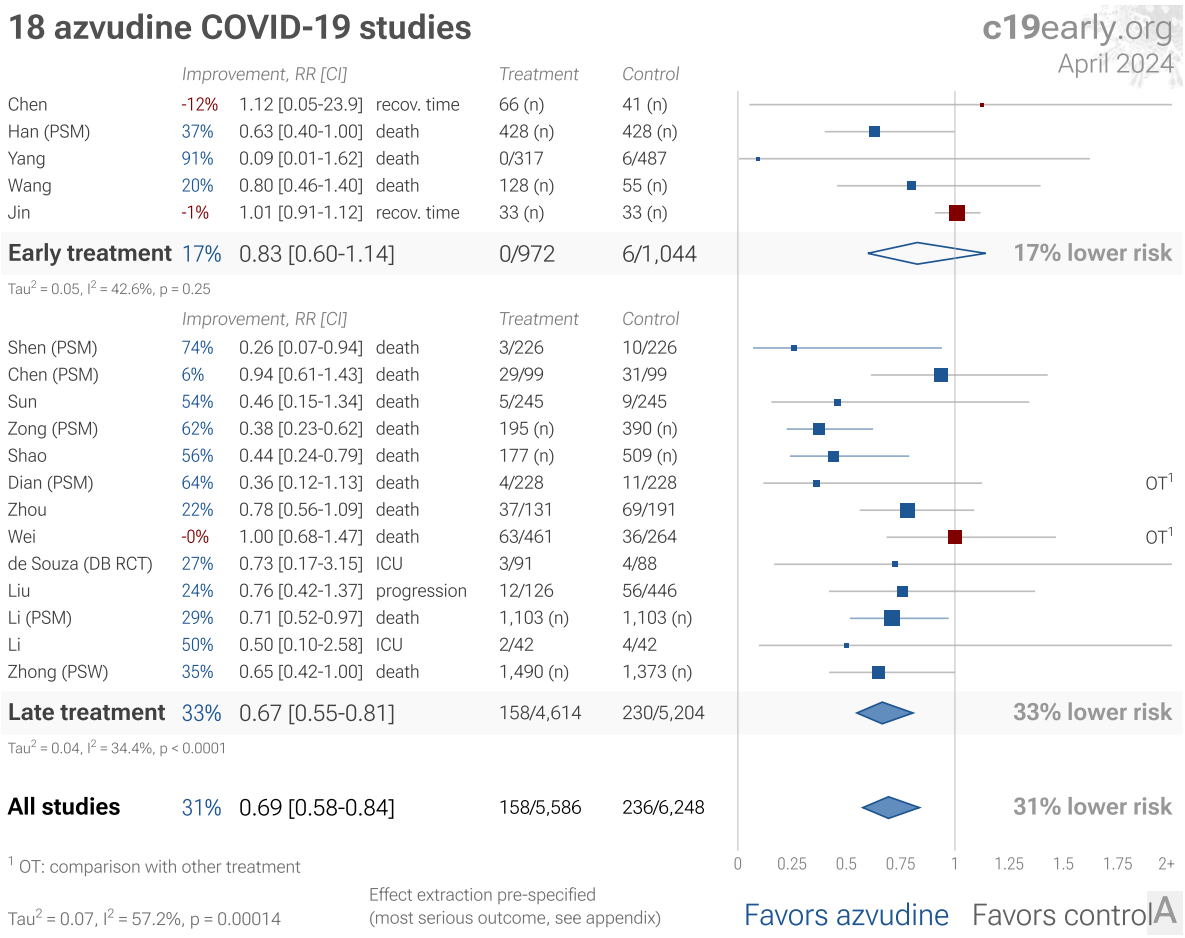
HIGHLIGHTS

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

41st treatment shown effective with ≥3 clinical studies in July 2023, now with p = 0.00014 from 18 studies.

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

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 69 treatments.



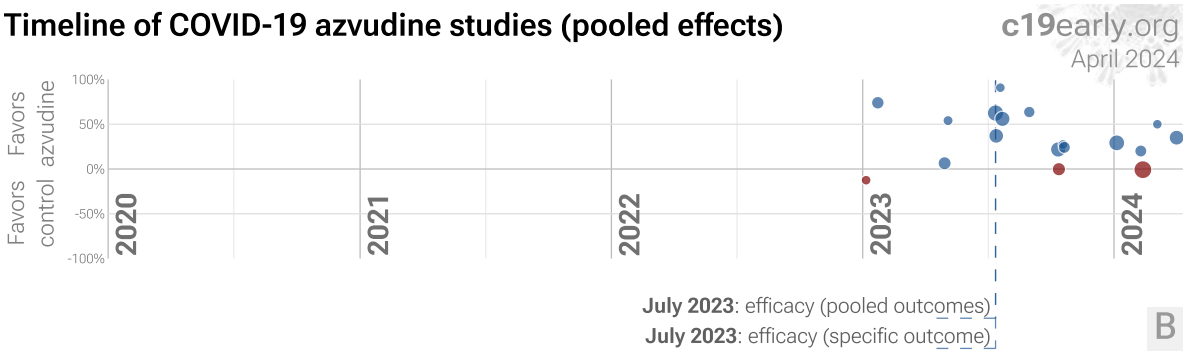


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in azvudine studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes and one or more specific outcome.

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 *Duloquin, Hampshire, 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, Niarakis], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk [c19early.org], 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 azvudine 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.

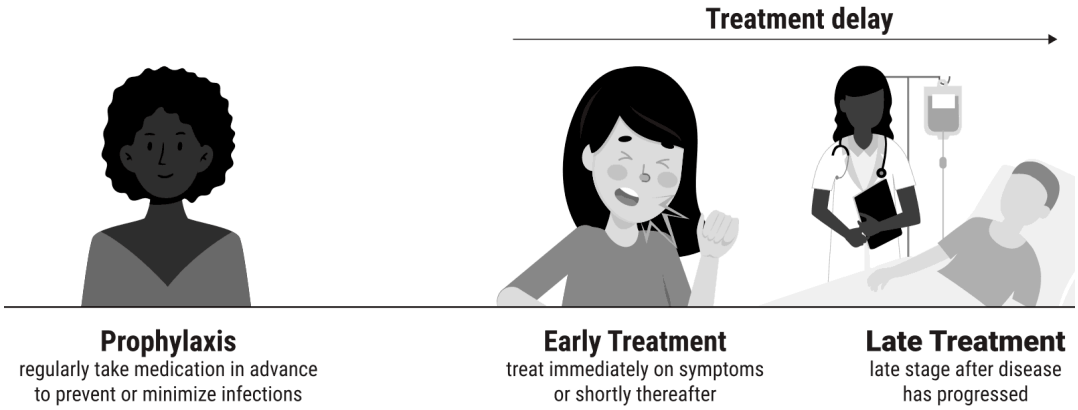


Figure 2. Treatment stages.

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 plots individual results by treatment stage. Figure 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, viral clearance, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	31% [16-42%] ***	18	11,834	199
After exclusions	32% [17-45%] ***	17	11,512	193
Peer-reviewed studies	29% [10-43%] **	13	5,350	144
Randomized Controlled Trials	27% [-215-83%]	1	179	12
Mortality	34% [20-46%] ****	13	10,826	156
Ventilation	31% [7-48%] *	4	2,123	32
ICU admission	47% [5-70%] *	6	2,386	50
Hospitalization	43% [-85-82%]	2	888	17
Recovery	2% [-8-11%]	4	1,156	44
Viral	25% [2-43%] *	3	470	25

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. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	*Late treatment*
All studies	17% [-14-40%]	33% [19-45%] ****
After exclusions	17% [-14-40%]	36% [20-49%] ****
Peer-reviewed studies	10% [-33-38%]	34% [14-49%] **
Randomized Controlled Trials		27% [-215-83%]
Mortality	33% [0-55%] *	35% [19-48%] ***
Ventilation		31% [7-48%] *
ICU admission		47% [5-70%] *
Hospitalization	75% [2-94%] *	11% [-9-27%]
Recovery	2% [-8-11%]	42% [-136-86%]
Viral	32% [1-53%] *	28% [-20-57%]

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

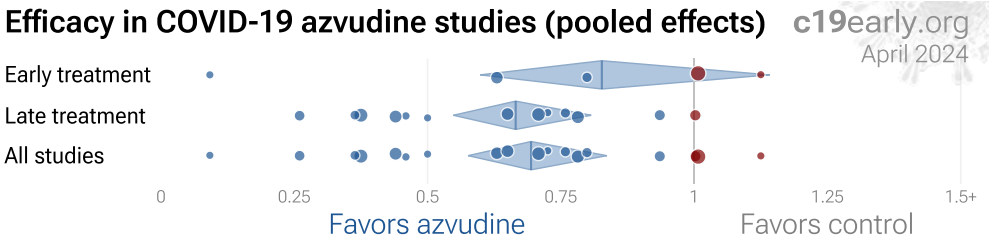


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

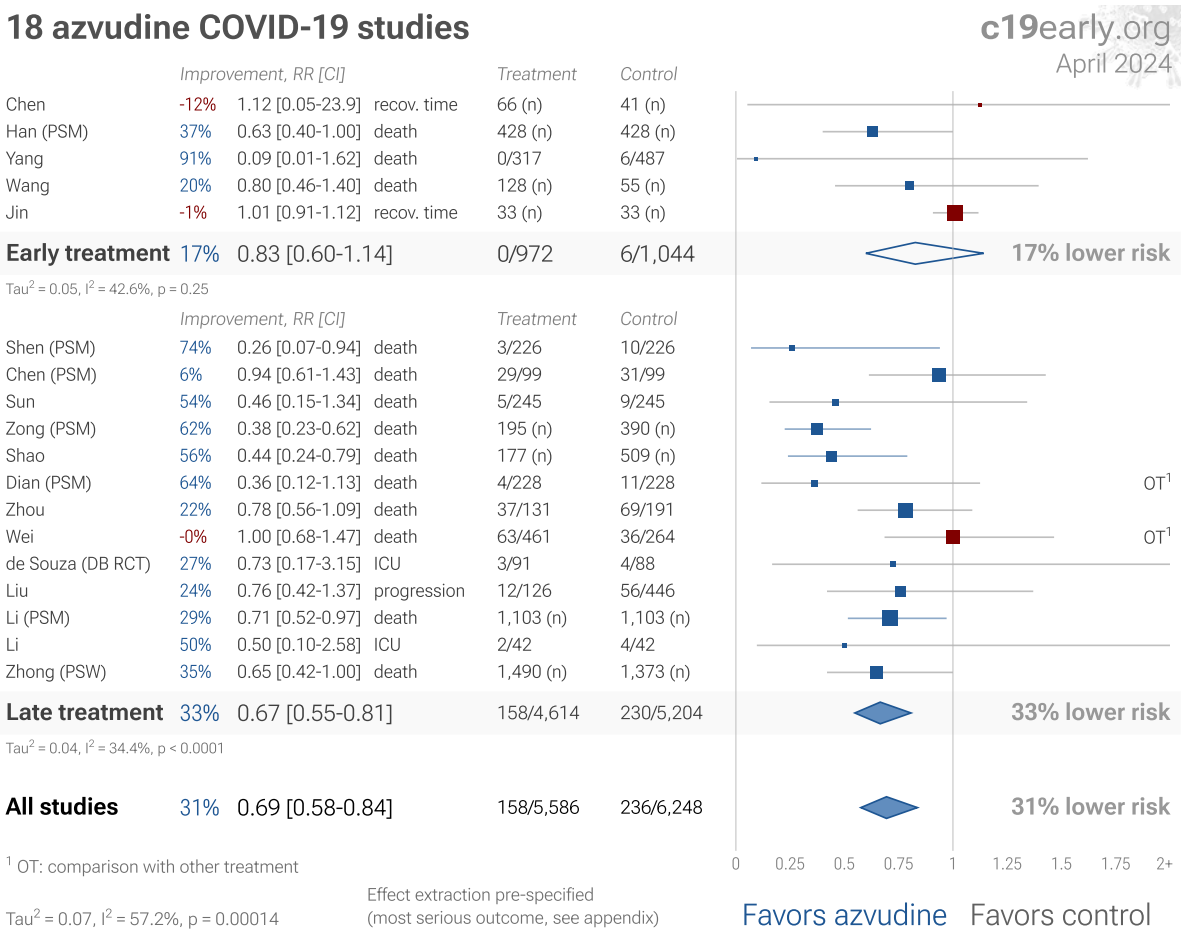


Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

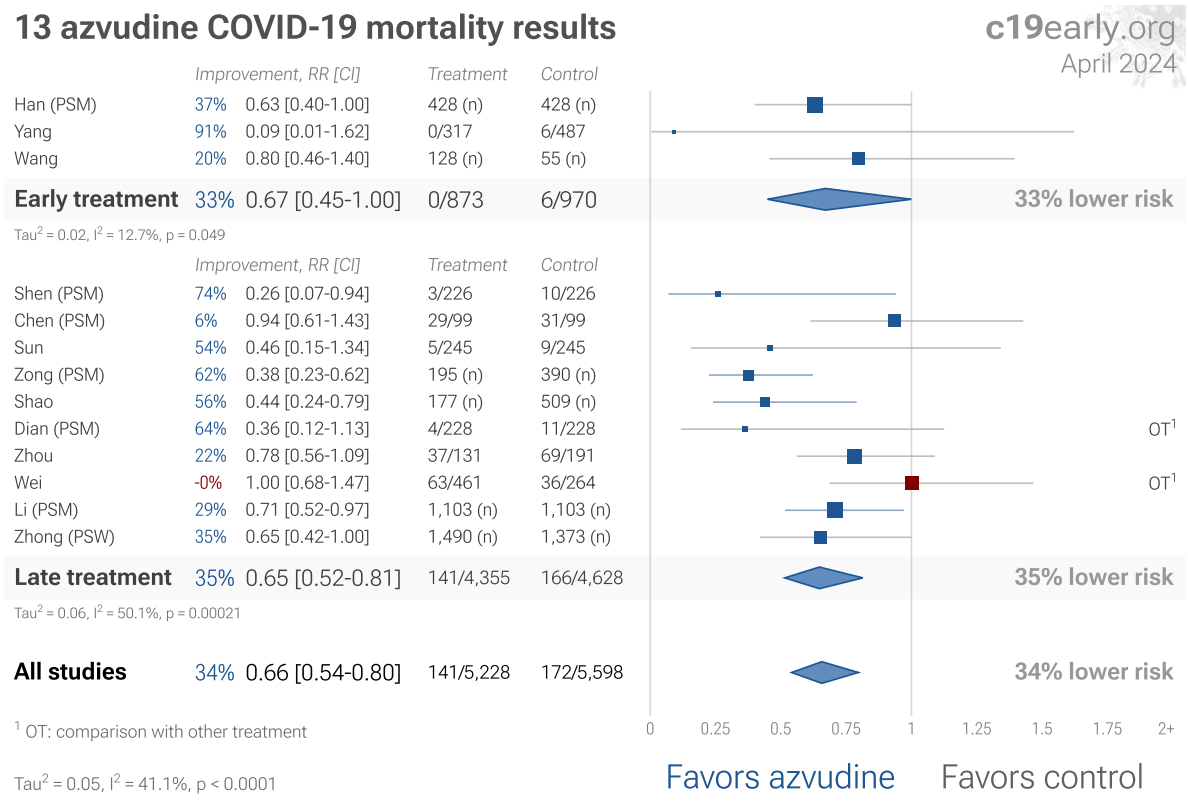


Figure 5. Random effects meta-analysis for mortality results.

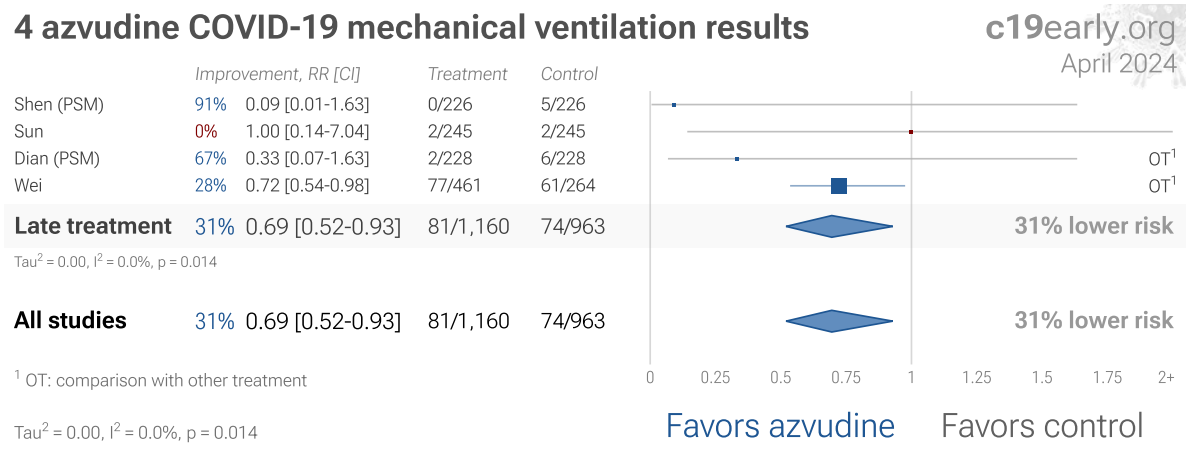


Figure 6. Random effects meta-analysis for ventilation.

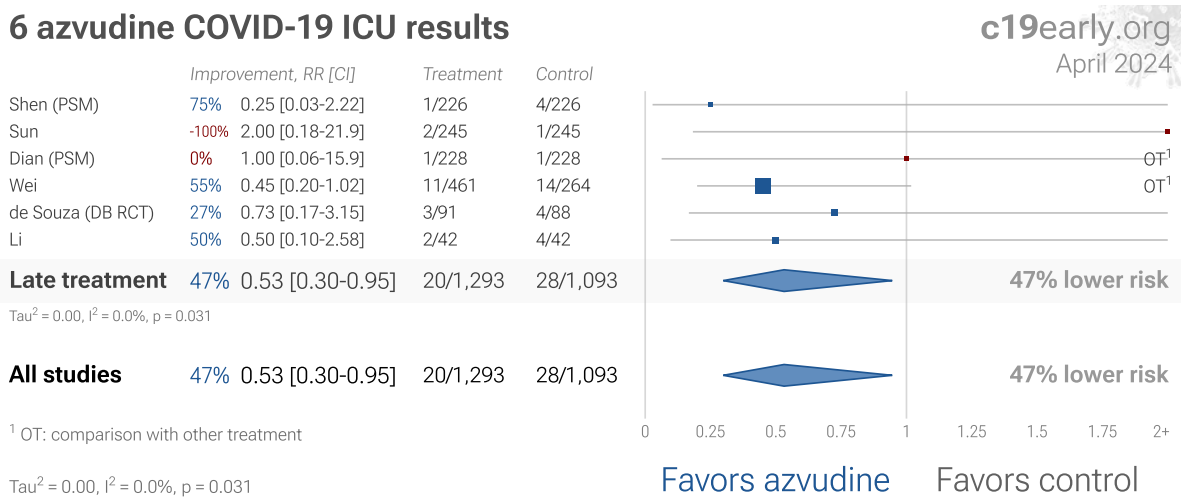


Figure 7. Random effects meta-analysis for ICU admission.

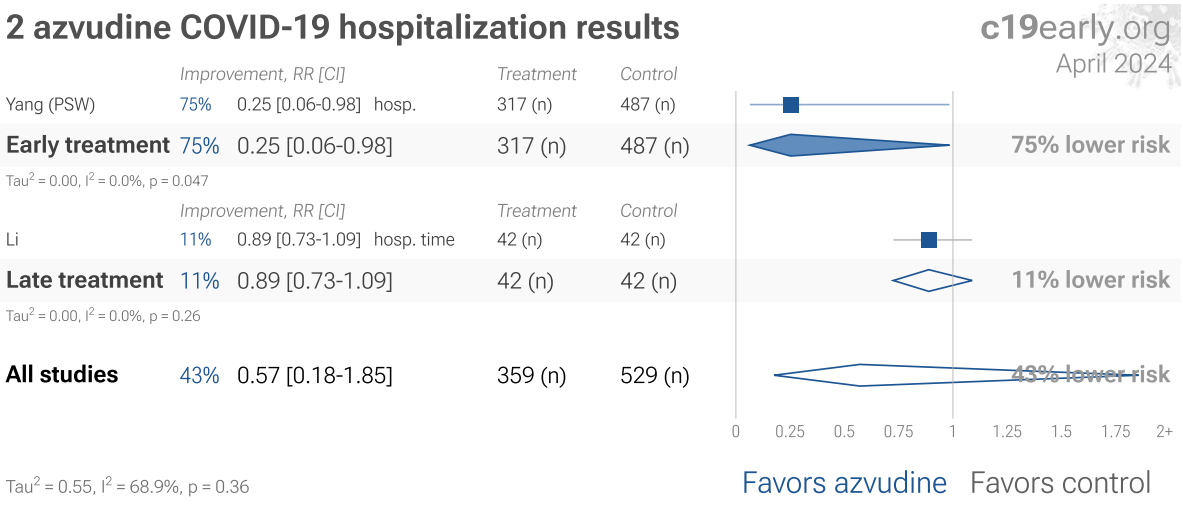


Figure 8. Random effects meta-analysis for hospitalization.

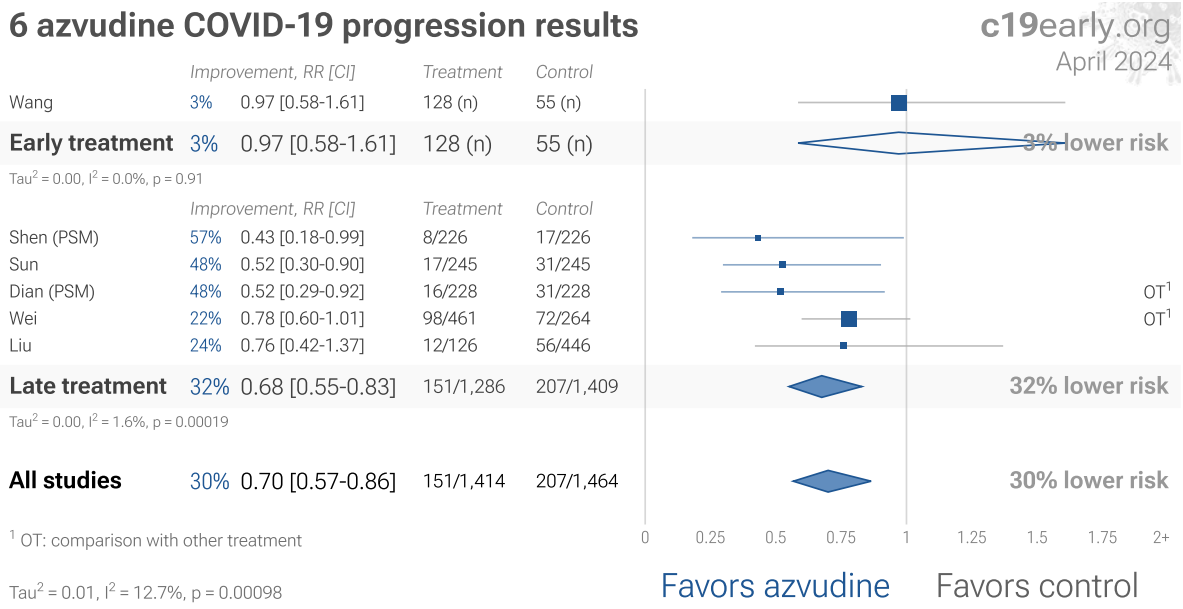


Figure 9. Random effects meta-analysis for progression.

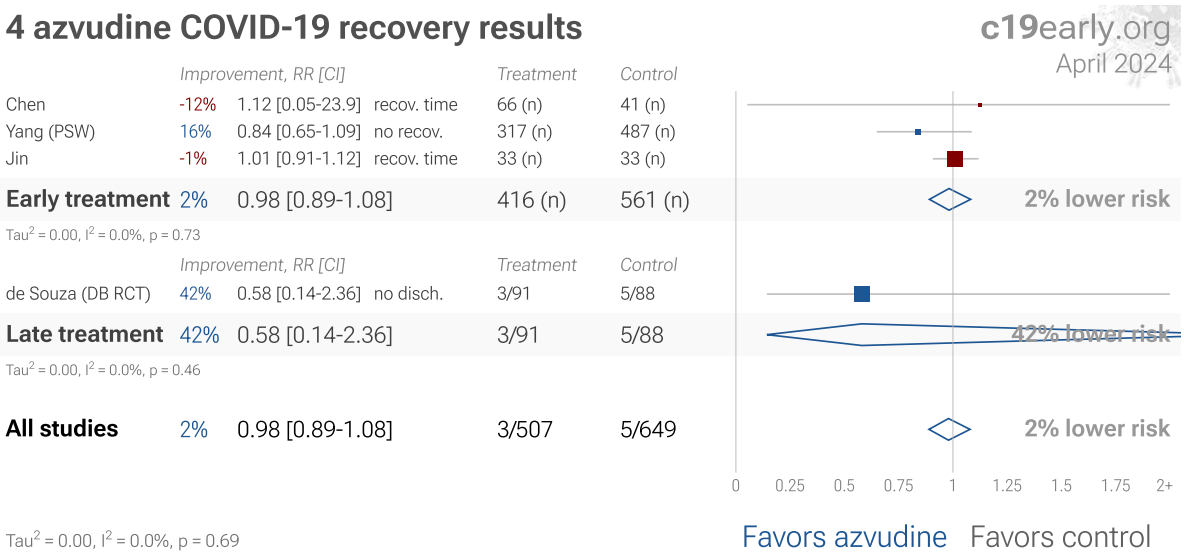


Figure 10. Random effects meta-analysis for recovery.

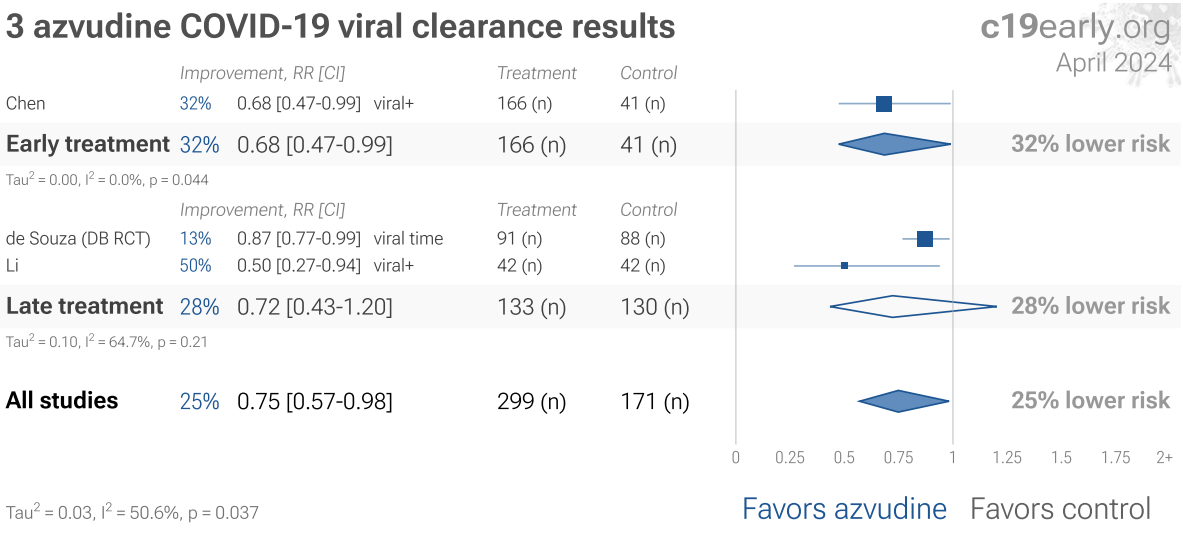


Figure 11. Random effects meta-analysis for viral clearance.

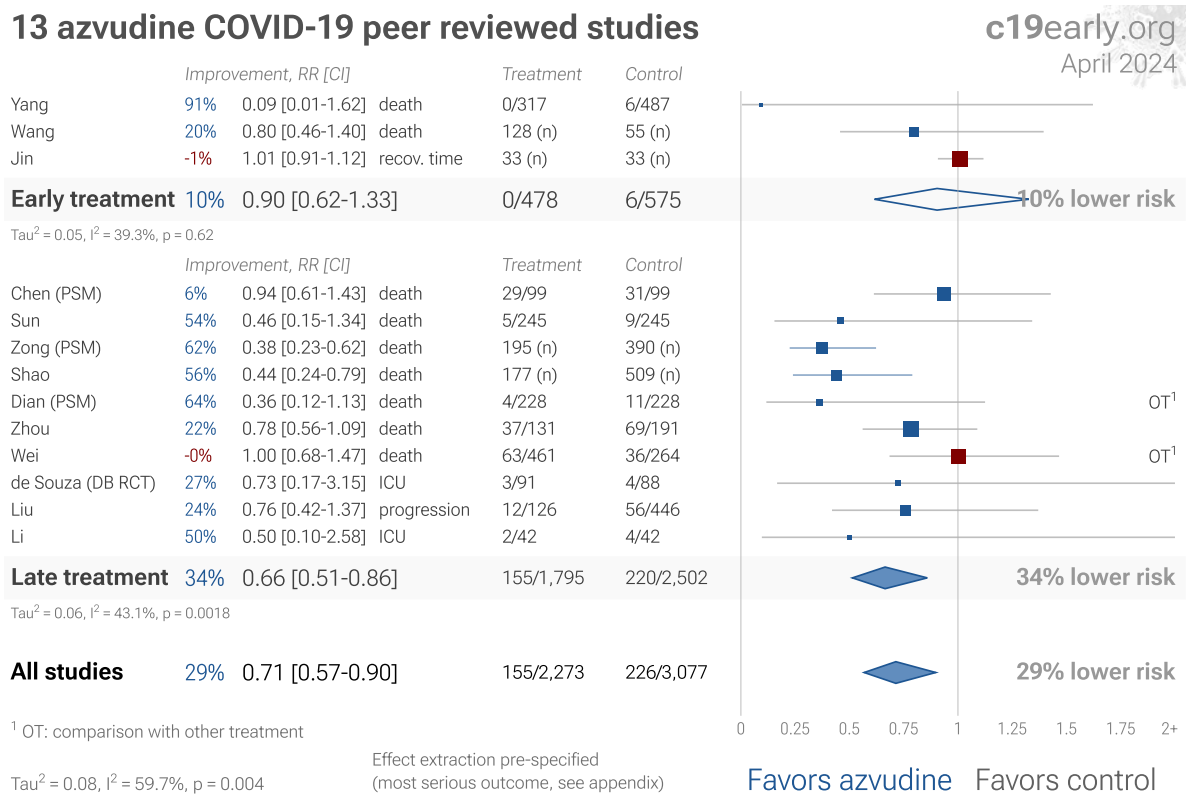


Figure 12. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding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

Randomized Controlled Trials (RCTs)

Figure 13 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1 and Table 2. Currently there is only one RCT.

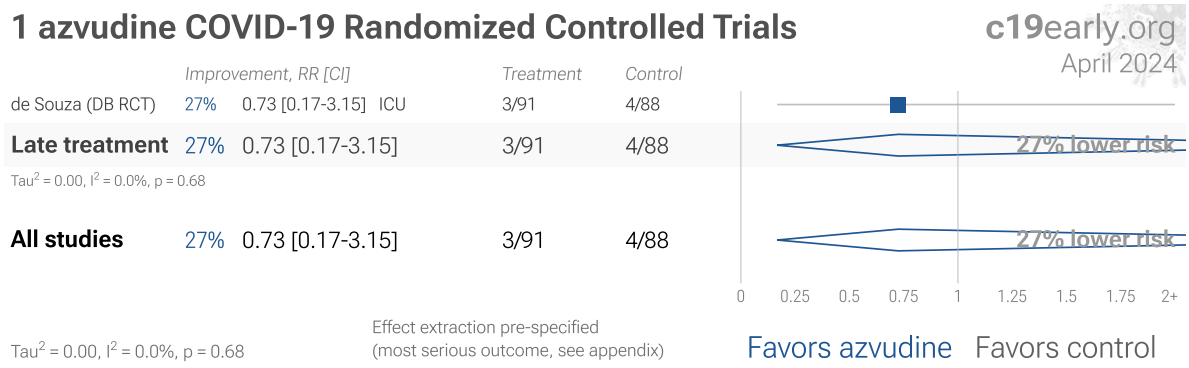


Figure 13. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

RCTs have many potential biases. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases [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, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs. RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 69 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 studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [Deaton, Nichol].

Using all studies identifies efficacy 6+ months faster (7+ months for low-cost treatments). 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 these, 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.

Exclusions

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

The studies excluded are as below. Figure 14 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Zhou, substantial unadjusted confounding by indication likely; unadjusted results with no group details.

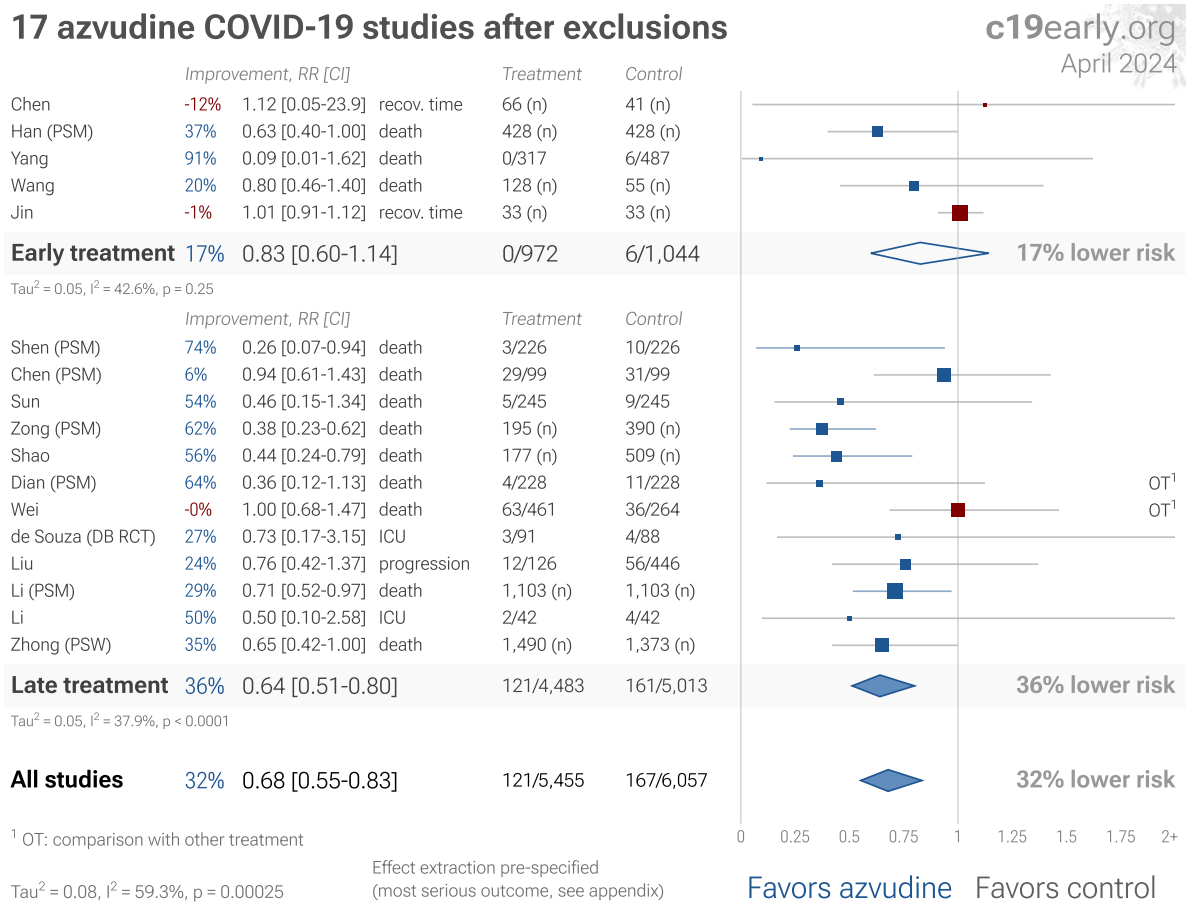


Figure 14. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Heterogeneity

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

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours *McLean, Treanor*. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* 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 15 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 69 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

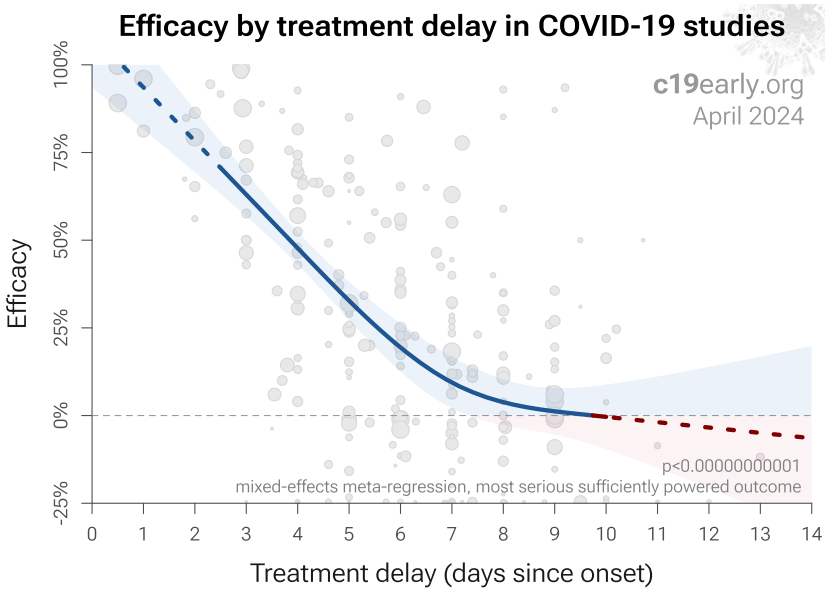


Figure 15. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 69 treatments.

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

Variants. Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [Korves], 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 degree to which TMPRSS2 contributes to viral entry can differ across variants [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 supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic [Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan], therefore efficacy may depend strongly on combined treatments.

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

Effect measured. Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta analysis. The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Combining studies is required. For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results.

Specific outcome and pooled analyses. We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

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

Ethical and practical issues limit high-risk trials. Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster collection of evidence.

Improvement across outcomes. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Validating pooled outcome analysis for COVID-19. Analysis of the the association between different outcomes across studies from all 69 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 16 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 17 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 18 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.0000045$ to $p = 0.0000000067$.

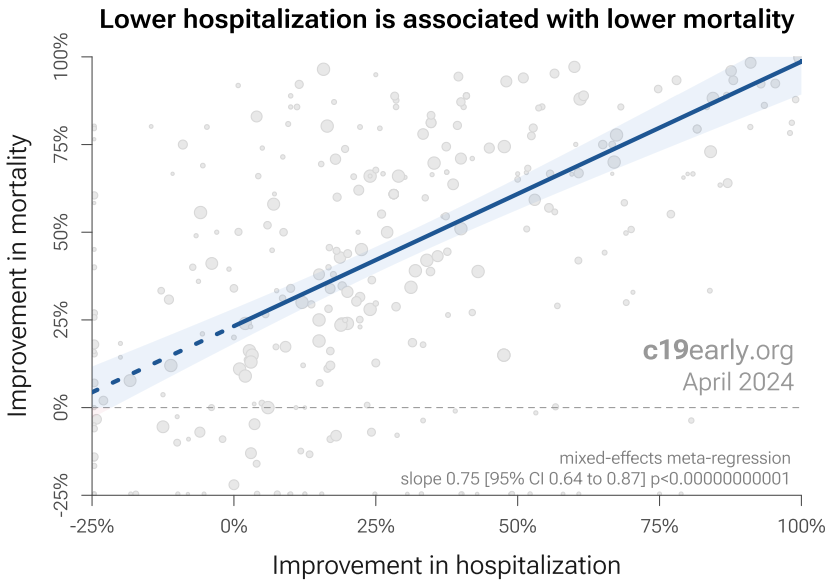


Figure 16. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

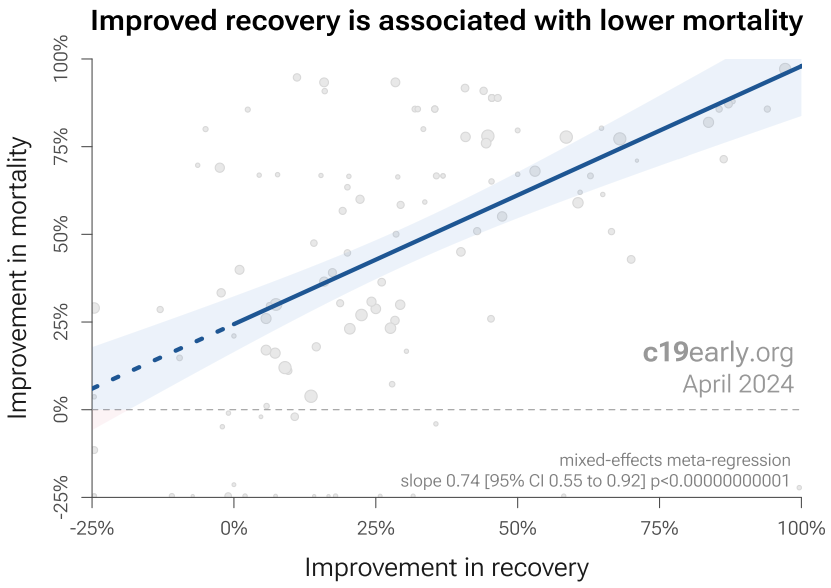


Figure 17. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

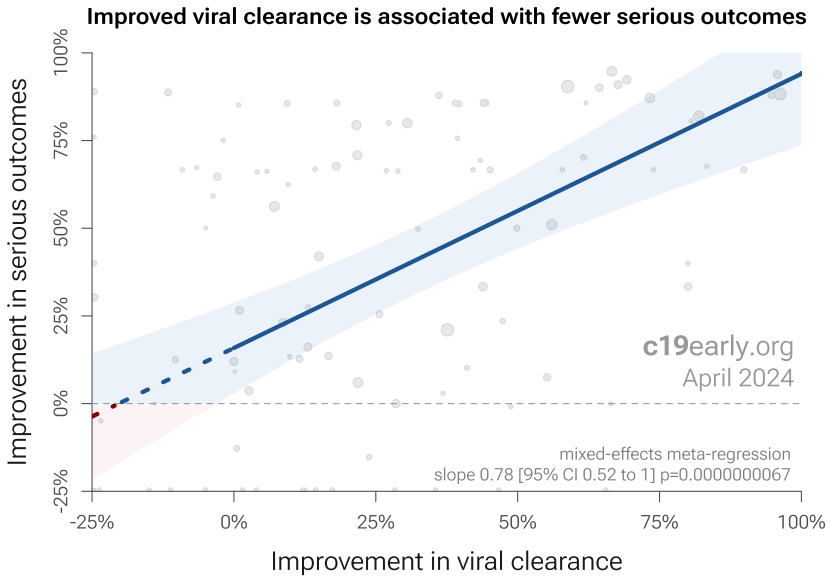


Figure 16. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

Pooled outcomes identify efficacy 4 months faster (6 months for RCTs). 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. 85% of these have been confirmed with one or more specific outcomes, with a mean delay of 3.7 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 5.8 months. Figure 19 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

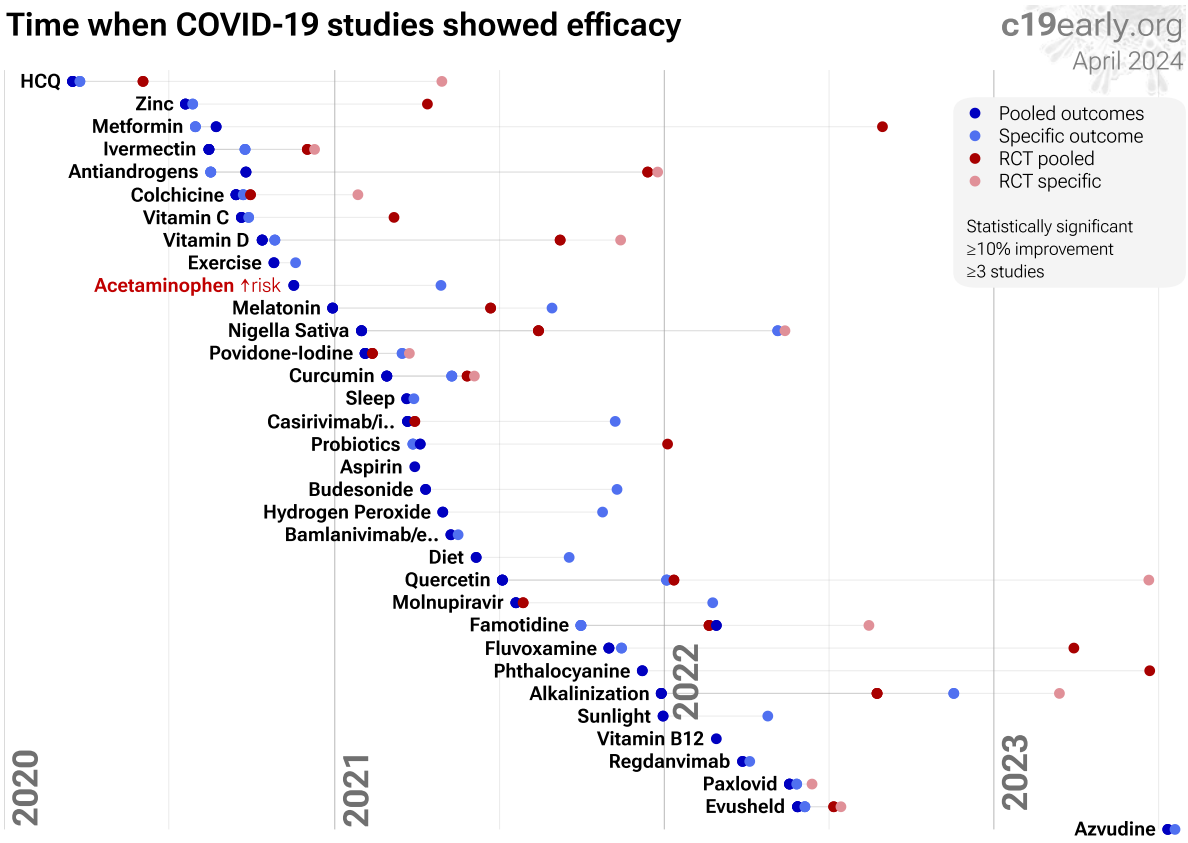


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations. Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary. Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Discussion

Publication bias. Publishing is often biased towards positive results. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and CTRI/2021/08/0354242). For azvudine, there is currently not enough data to evaluate publication bias with high confidence.

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

Figure 20 shows a scatter plot of results for prospective and retrospective studies. 76% 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 35% improvement, compared to 27% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.

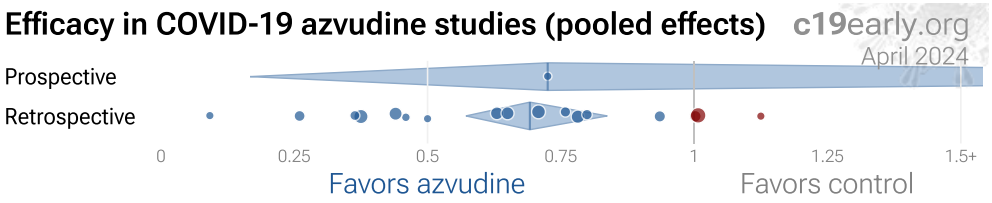


Figure 20. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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

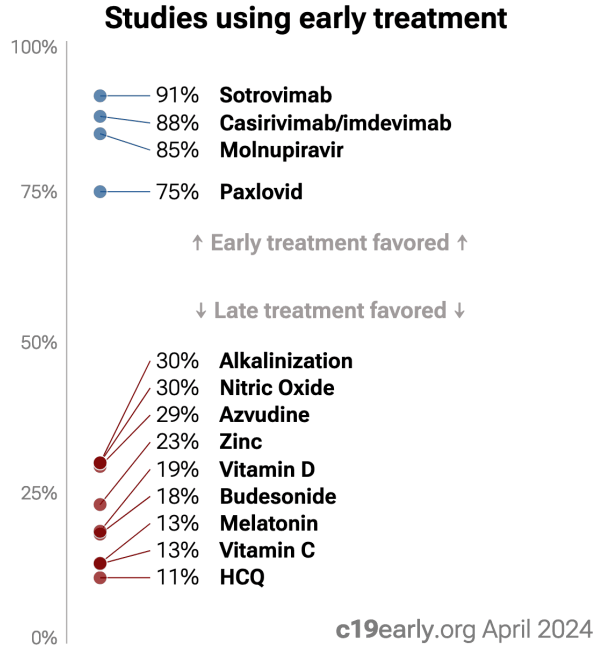


Figure 21. **Patented treatments received mostly early treatment studies, while low cost treatments were typically tested for late treatment.**

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 22 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.

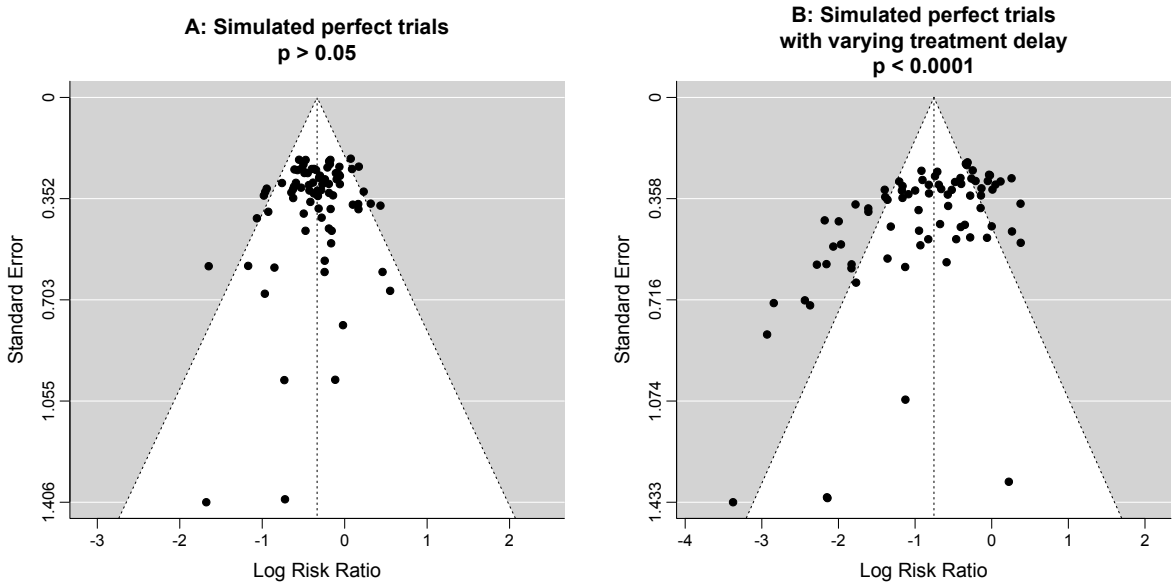


Figure 22. **Example funnel plot analysis for simulated perfect trials.**

Limitations. Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone *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 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 the 18 studies compare against other treatments, which may reduce the effect seen. Other meta analyses show significant improvements with azvudine for mortality *Wang, Zheng*, mechanical ventilation *Zheng*, clinical improvement *Zheng*, and viral clearance *Zheng*.

Perspective

Results compared with other treatments. SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors *Lui, Lv, Malone, Murigneux, Niarakis*, providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk *c19early.org*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 23 shows an overview of the results for azvudine in the context of multiple COVID-19 treatments, and Figure 24 shows a plot of efficacy vs. cost for COVID-19 treatments.

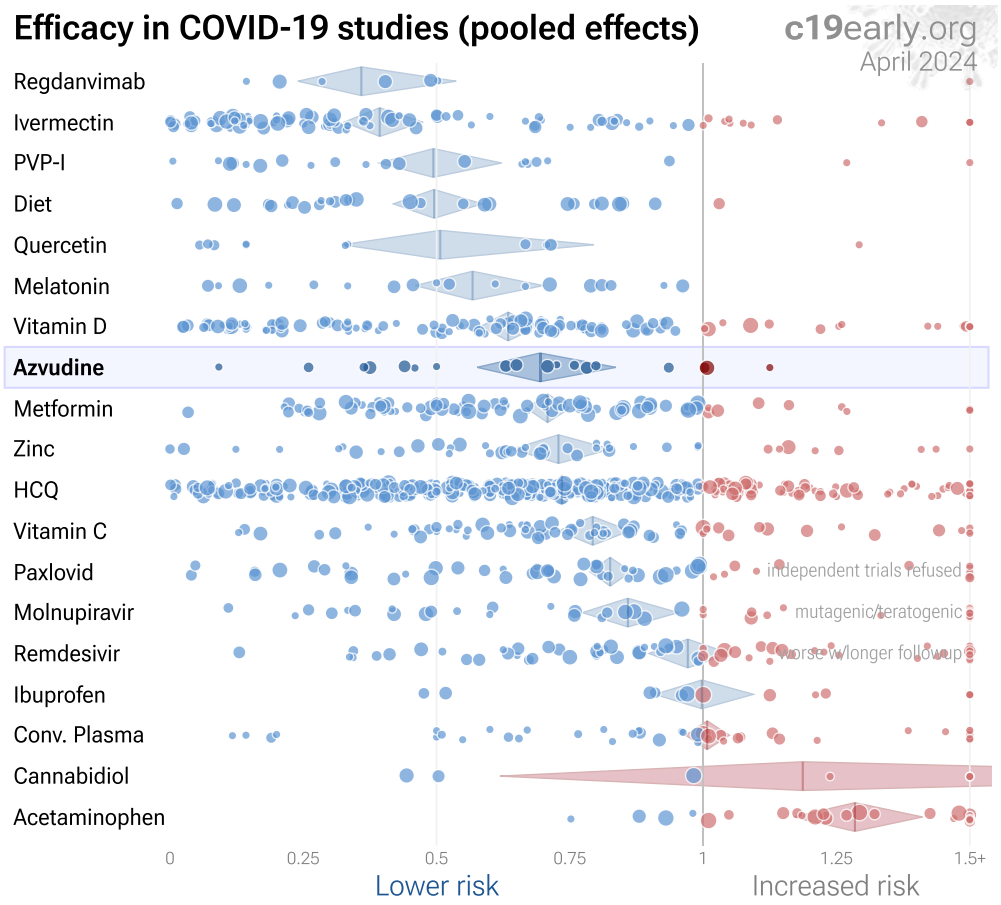


Figure 23. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy *c19early.org (B)*.

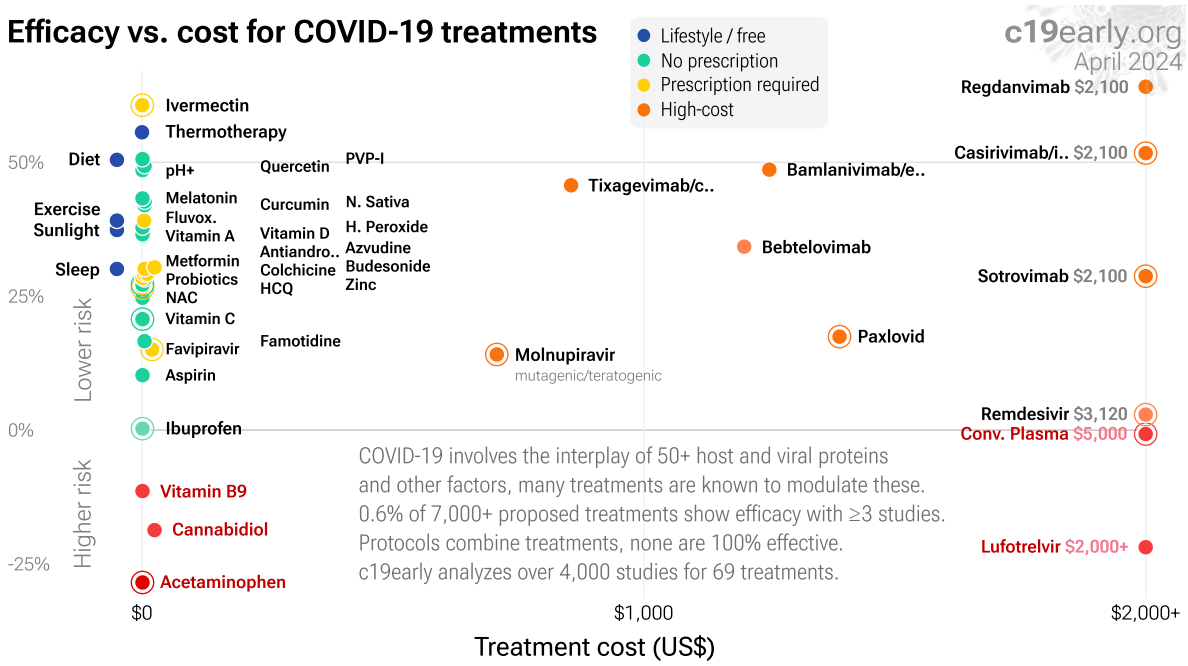


Figure 24. Efficacy vs. cost for COVID-19 treatments.

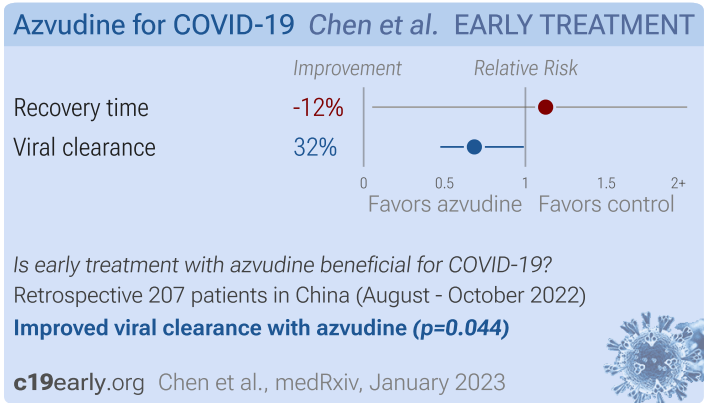
Conclusion

Azvudine is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, ventilation, ICU admission, progression, and viral clearance. 14 studies from 12 independent teams in 2 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 31% [16-42%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Results are robust — in exclusion sensitivity analysis 8 of 18 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Other meta analyses show significant improvements with azvudine for mortality *Wang, Zheng*, mechanical ventilation *Zheng*, clinical improvement *Zheng*, and viral clearance *Zheng*.

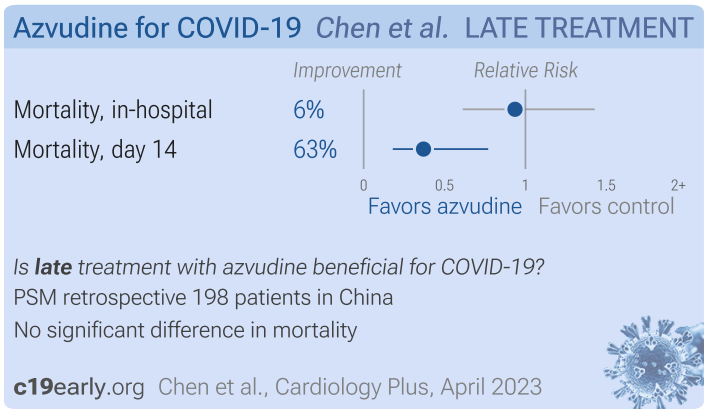
Study Notes

Chen



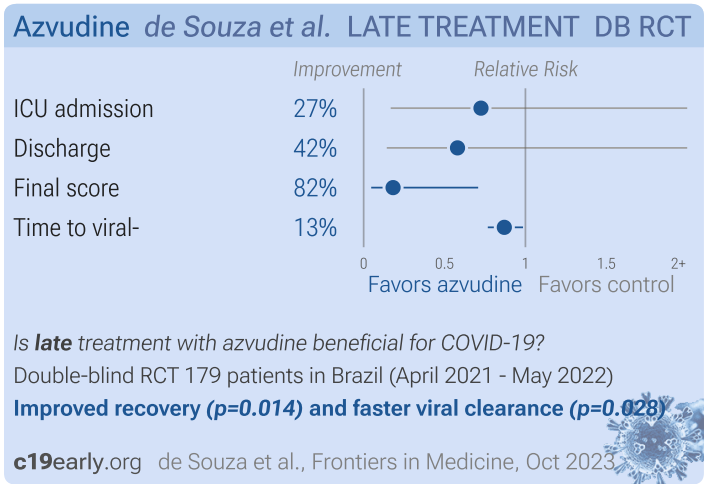
Chen: Retrospective 207 COVID-19 patients in China, showing azvudine associated with faster viral clearance, with azvudine-treated patients obtaining a negative PCR test result 1.7 days faster on average compared to supportive care alone after adjusting for age and sex.

Chen



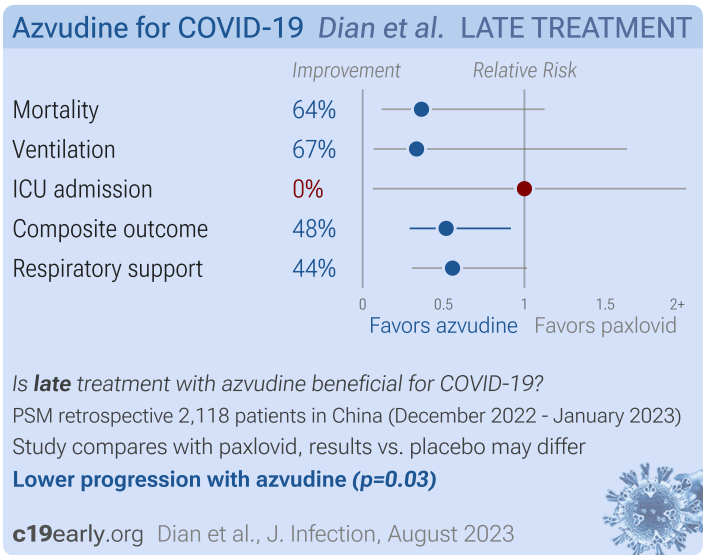
Chen (B): PSM retrospective 332 hospitalized moderate to critically ill COVID-19 patients with myocardial injury in China, showing improved 14 day mortality but no difference in overall in-hospital mortality with azvudine treatment.

de Souza



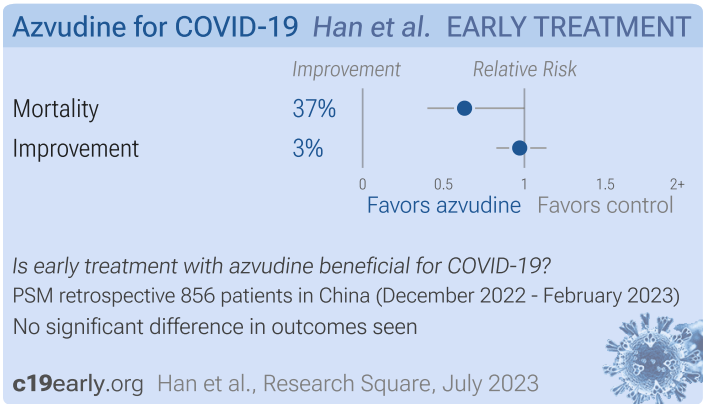
de Souza: RCT 179 hospitalized patients in Brazil, showing improved recovery with azvudine treatment.

Dian



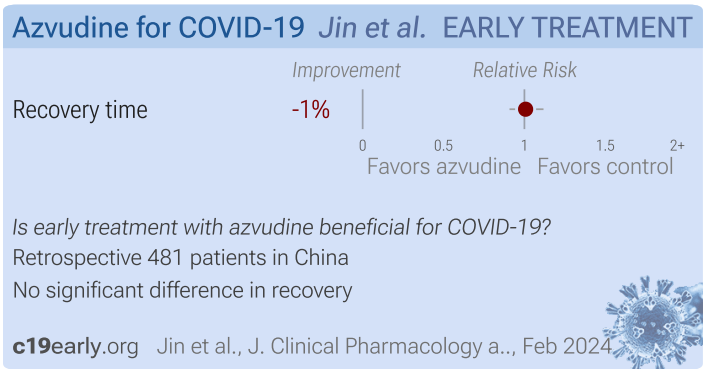
Dian: Retrospective 2,118 hospitalized COVID-19 patients in China, showing improved results with azvudine vs. paxlovid.

Han



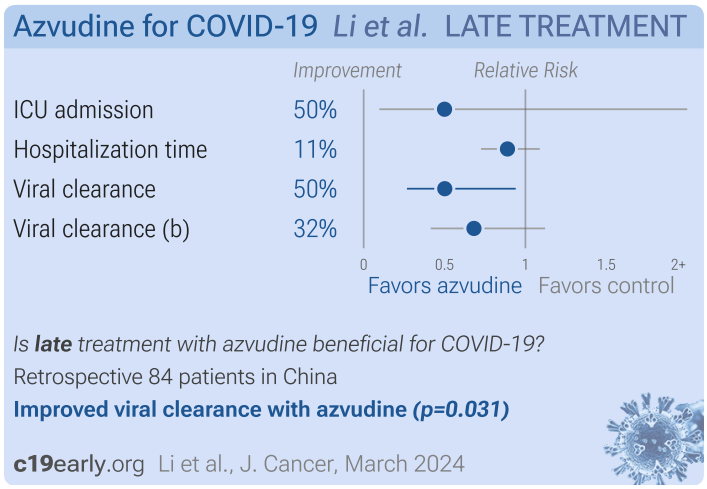
Han: PSM retrospective 6,218 hospitalized COVID-19 patients in China showing lower 28-day all-cause mortality with azvudine treatment compared to controls (HR 0.63, 95% CI 0.40-1.00). Subgroup analysis found significantly faster clinical improvement when azvudine was initiated within 5 days of symptom onset compared to controls.

Jin



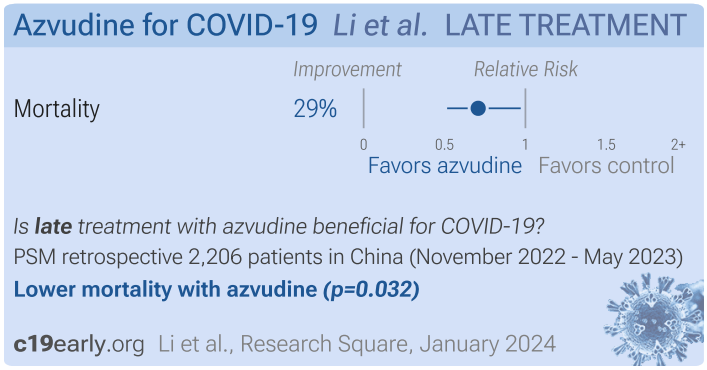
Jin: Retrospective 481 low-risk COVID-19 patients in China showing no significant difference in recovery or symptomatic severity with azvudine, but slightly lower total viral load.

Li



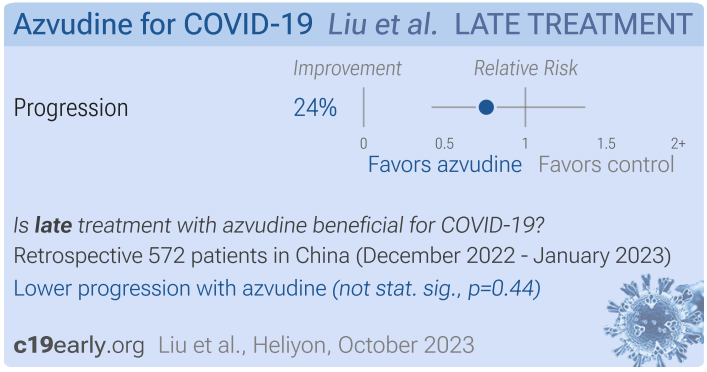
Li: PSM retrospective 84 hospitalized COVID-19 patients with pre-existing cancer in China, showing faster viral clearance with azvudine. There was no significant difference in length of hospital stay or ICU admission.

Li



Li (B): Retrospective 4,201 hospitalized COVID-19 patients in China, showing lower mortality with azvudine.

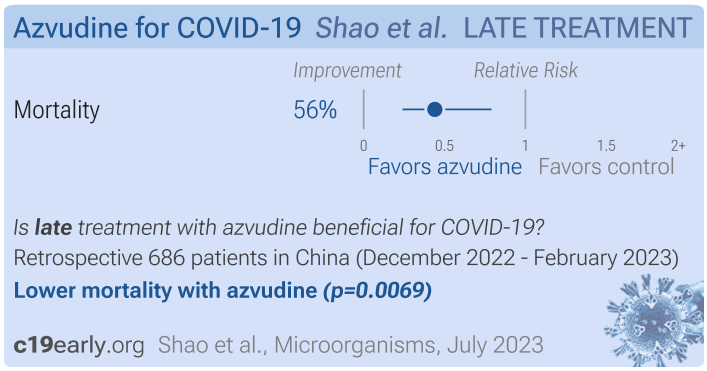
Liu



Liu: Retrospective 572 fully vaccinated hospitalized patients in China, showing lower risk with azvudine treatment, without statistical significance. The composite outcome included intubation, non-invasive respiratory support, ICU admission, and all-cause death. Azvudine was not included in the multivariable analysis (only combined antiviral

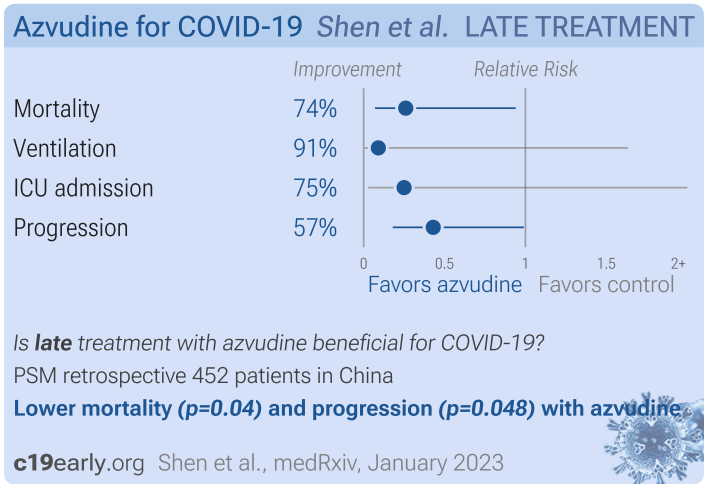
therapy was used without explanation).

Shao



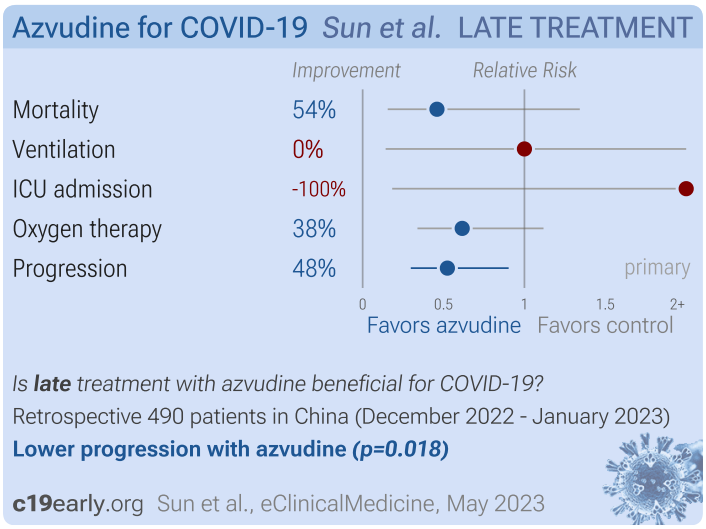
Shao: Retrospective 1,082 severely and critically ill COVID-19 patients in China showing lower 60 day mortality with azvudine. Mortality was also lower with paxlovid, but without statistical significance, and health related quality of life was significantly lower for paxlovid patients at 60 days.

Shen



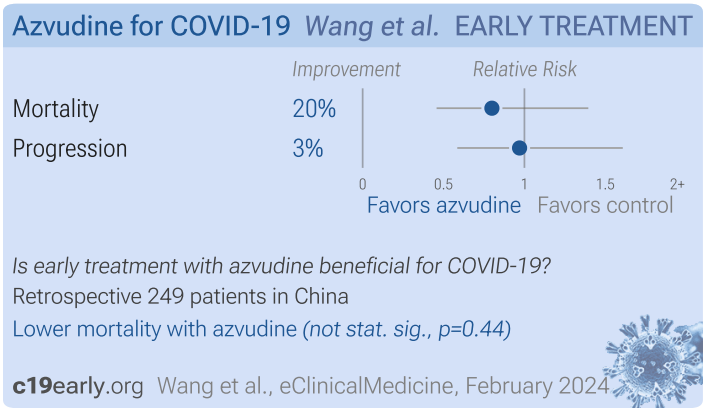
Shen: PSM retrospective 900 hospitalized COVID-19 patients in China showing lower risk of disease progression and death with azvudine treatment.

Sun



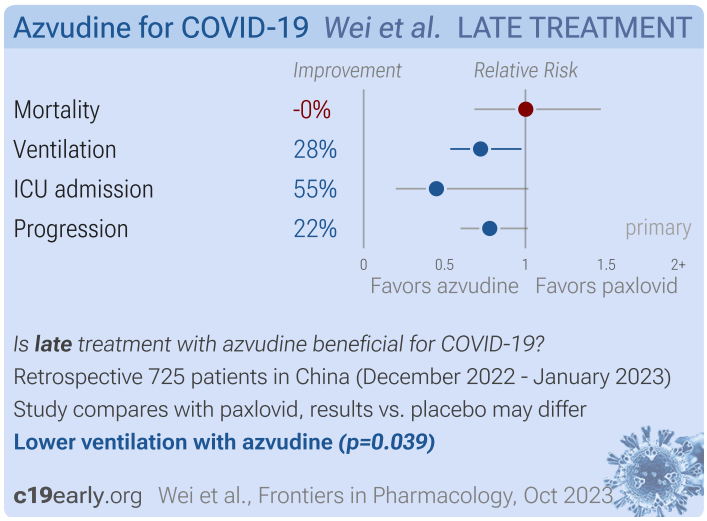
Sun: PSM retrospective 490 hospitalized COVID-19 patients with pre-existing conditions in China showing that azvudine was associated with a significantly lower risk of the composite outcome of disease progression, driven largely by lower rates of non-invasive respiratory support. However, there was no significant difference in all-cause mortality or other individual outcomes like ICU admission or invasive mechanical ventilation between the azvudine and control groups.

Wang



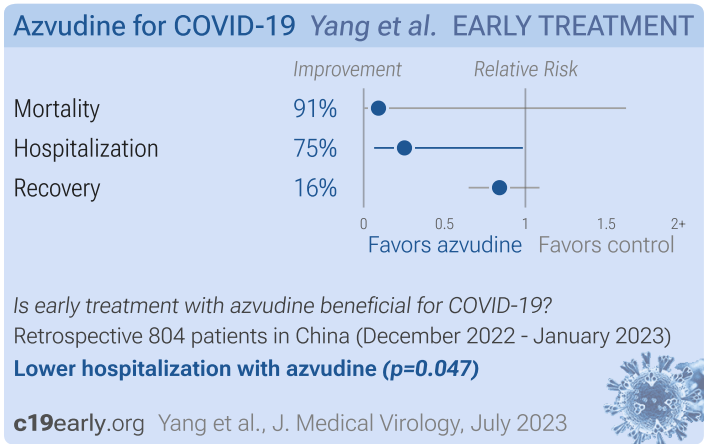
Wang (B): Retrospective 249 elderly patients with severe COVID-19, 128 treated with azvudine, 66 treated with paxlovid, and 55 receiving neither treatment, showing no significant differences for Ct value changes, progression, or survival for either treatment. Early viral decline was faster with paxlovid, without statistical significance.

Wei



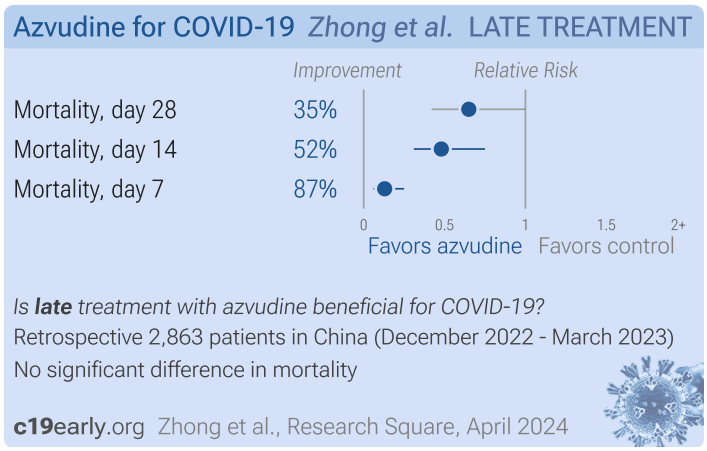
Wei: PSM retrospective 725 hospitalized COVID-19 patients in China compared the effectiveness and safety of the oral antivirals azvudine and paxlovid. There was no significant difference in the risk of disease progression between groups, but azvudine was associated with lower ICU admission and invasive ventilation use.

Yang



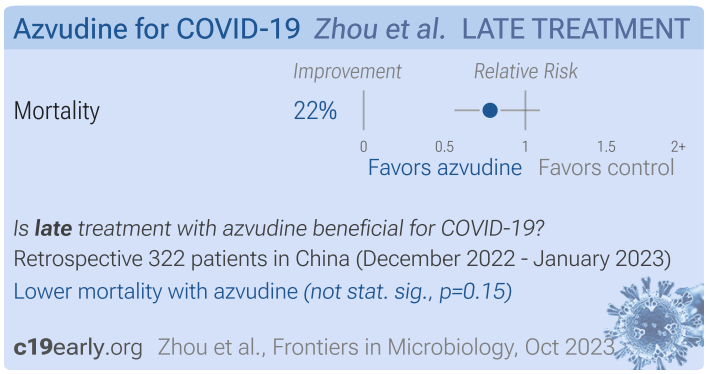
Yang (B): PSM retrospective 804 high-risk, nonhospitalized adults with mild to moderate COVID-19 in China. The study compared outcomes between 317 patients who received azvudine with 487 patients who received standard supportive treatment only. The azvudine group had a lower rate of disease progression (composite of death or COVID-19 hospitalization) at 28 days, as well as a lower rate of COVID-19 hospitalization specifically after adjusting for factors. In addition, azvudine shortened the duration of fever if given within 3 days of symptom onset. However, azvudine treatment was associated with a higher incidence of adverse effects, including mainly mild gastrointestinal and nervous system effects.

Zhong



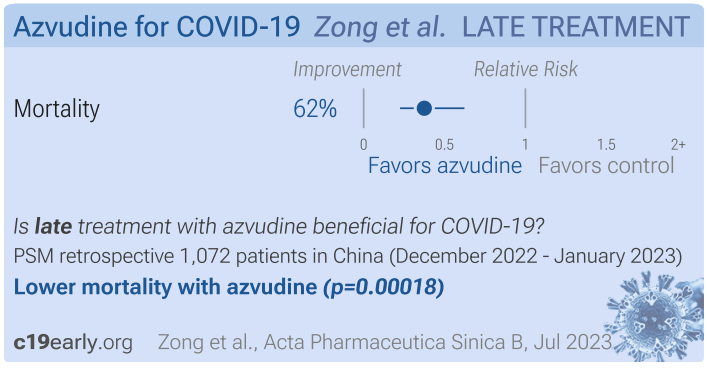
Zhong: Retrospective 2,862 hospitalized COVID-19 patients in China showing lower mortality with azvudine treatment.

Zhou



Zhou: Retrospective 322 hospitalized patients ≥65 in China, showing lower mortality with azvudine treatment, without statistical significance.

Zong



Zong: PSM retrospective 1072 hospitalized patients with COVID-19 pneumonia in China, showing lower mortality with azvudine treatment.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are azvudine 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 azvudine 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 (5.20.0).

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/azvmeta.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.

Chen, 1/6/2023, retrospective, China, preprint, 7 authors, study period August 2022 - October 2022.	recovery time, 12.5% higher, relative time 1.12, $p = 0.94$, treatment 66, control 41.
	risk of no viral clearance, 31.6% lower, HR 0.68, $p = 0.04$, treatment 166, control 41, adjusted per study, inverted to make HR<1 favor treatment, multivariable, Cox proportional hazards.
Han, 7/14/2023, retrospective, China, preprint, 22 authors, study period 10 December, 2022 - 20 February, 2023.	risk of death, 37.0% lower, HR 0.63, $p = 0.048$, treatment 428, control 428, propensity score matching.
	risk of no improvement, 2.9% lower, HR 0.97, $p = 0.73$, treatment 428, control 428, inverted to make HR<1 favor treatment, propensity score matching.
Jin, 2/12/2024, retrospective, China, peer-reviewed, 14 authors.	recovery time, 0.7% higher, relative time 1.01, $p = 0.90$, treatment mean 12.21 (±2.84) n=33, control mean 12.12 (±2.82) n=33.
Wang (B), 2/9/2024, retrospective, China, peer-reviewed, 47 authors.	risk of death, 20.1% lower, HR 0.80, $p = 0.44$, treatment 128, control 55, adjusted per study, multivariable, Cox proportional hazards.
	risk of progression, 3.0% lower, HR 0.97, $p = 0.91$, treatment 128, control 55, adjusted per study, ICU, mechanical ventilation, or death, multivariable, Cox proportional hazards.
Yang (B), 7/20/2023, retrospective, China, peer-reviewed, 11 authors, study period 19 December, 2022 - 5 January, 2023.	risk of death, 90.8% lower, RR 0.09, $p = 0.09$, treatment 0 of 317 (0.0%), control 6 of 487 (1.2%), NNT 81, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 74.8% lower, RR 0.25, $p = 0.047$, treatment 317, control 487, propensity score weighting.
	risk of no recovery, 16.0% lower, RR 0.84, $p = 0.19$, treatment 317, control 487, propensity score weighting.

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.

Chen (B), 4/30/2023, retrospective, China, peer-reviewed, 9 authors.	risk of death, 6.5% lower, RR 0.94, $p = 0.88$, treatment 29 of 99 (29.3%), control 31 of 99 (31.3%), NNT 49, in-hospital mortality, propensity score matching.
	risk of death, 63.0% lower, HR 0.37, $p = 0.007$, treatment 99,

	control 99, propensity score matching, day 14.
de Souza, 10/19/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Brazil, peer-reviewed, median age 48.0, 12 authors, study period April 2021 - May 2022, trial NCT04668235 (history).	risk of ICU admission, 27.5% lower, RR 0.73, *p* = 0.72, treatment 3 of 91 (3.3%), control 4 of 88 (4.5%), NNT 80.
	risk of no hospital discharge, 42.0% lower, RR 0.58, *p* = 0.49, treatment 3 of 91 (3.3%), control 5 of 88 (5.7%), NNT 42.
	relative final score, 81.8% better, RR 0.18, *p* = 0.01, treatment mean 0.02 (±0.15) n=91, control mean 0.11 (±0.31) n=88.
	time to viral-, 13.0% lower, relative time 0.87, *p* = 0.03, treatment 91, control 88.
Dian, 8/31/2023, retrospective, China, peer-reviewed, 5 authors, study period 5 December, 2022 - 31 January, 2023, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 63.6% lower, RR 0.36, *p* = 0.11, treatment 4 of 228 (1.8%), control 11 of 228 (4.8%), NNT 33, propensity score matching.
	risk of mechanical ventilation, 66.7% lower, RR 0.33, *p* = 0.28, treatment 2 of 228 (0.9%), control 6 of 228 (2.6%), NNT 57, propensity score matching.
	risk of ICU admission, no change, RR 1.00, *p* = 1.00, treatment 1 of 228 (0.4%), control 1 of 228 (0.4%), propensity score matching.
	composite outcome, 48.4% lower, RR 0.52, *p* = 0.03, treatment 16 of 228 (7.0%), control 31 of 228 (13.6%), NNT 15, non-invasive respiratory support, endotracheal intubation, ICU admission, all-cause death, propensity score matching.
	respiratory support, 44.4% lower, RR 0.56, *p* = 0.07, treatment 15 of 228 (6.6%), control 27 of 228 (11.8%), NNT 19, propensity score matching.
Li, 3/4/2024, retrospective, China, peer-reviewed, 6 authors.	risk of ICU admission, 50.0% lower, RR 0.50, *p* = 0.68, treatment 2 of 42 (4.8%), control 4 of 42 (9.5%), NNT 21.
	hospitalization time, 11.1% lower, relative time 0.89, *p* = 0.26, treatment 42, control 42.
	risk of no viral clearance, 49.8% lower, HR 0.50, *p* = 0.03, treatment 42, control 42, adjusted per study, inverted to make HR<1 favor treatment, multivariable, Cox proportional hazards.
	risk of no viral clearance, 31.8% lower, RR 0.68, *p* = 0.19, treatment 15 of 42 (35.7%), control 22 of 42 (52.4%), NNT 6.0.
Li (B), 1/5/2024, retrospective, China, preprint, 7 authors, study period 1 November, 2022 - 31 May, 2023, trial NCT06006611 (history).	risk of death, 29.2% lower, HR 0.71, *p* = 0.03, treatment 1,103, control 1,103, propensity score matching, Cox proportional hazards.
Liu, 10/21/2023, retrospective, China, peer-reviewed, 4 authors, study period 5 December, 2022 - 31 January, 2023.	risk of progression, 24.1% lower, RR 0.76, *p* = 0.44, treatment 12 of 126 (9.5%), control 56 of 446 (12.6%), NNT 33, intubation, non-invasive respiratory support, ICU admission, and all-cause death.

Shao, 7/23/2023, retrospective, China, peer-reviewed, 9 authors, study period 8 December, 2022 - 9 February, 2023.	**risk of death, 56.0% lower, HR 0.44, $p = 0.007$**, treatment 177, control 509, adjusted per study, day 60.
Shen, 1/23/2023, retrospective, China, preprint, 12 authors.	**risk of death, 74.0% lower, HR 0.26, $p = 0.04$**, treatment 3 of 226 (1.3%), control 10 of 226 (4.4%), NNT 32, propensity score matching, Cox proportional hazards.
	risk of mechanical ventilation, 90.9% lower, RR 0.09, $p = 0.06$, treatment 0 of 226 (0.0%), control 5 of 226 (2.2%), NNT 45, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching.
	risk of ICU admission, 75.0% lower, RR 0.25, $p = 0.37$, treatment 1 of 226 (0.4%), control 4 of 226 (1.8%), NNT 75, propensity score matching.
	risk of progression, 57.0% lower, HR 0.43, $p = 0.048$, treatment 8 of 226 (3.5%), control 17 of 226 (7.5%), NNT 25, all-cause death, intensive care unit admission, initiation of invasive mechanical ventilation, and need for high-flow oxygen therapy, propensity score matching, Cox proportional hazards.
Sun, 5/5/2023, retrospective, China, peer-reviewed, 7 authors, study period 5 December, 2022 - 31 January, 2023.	**risk of death, 54.1% lower, HR 0.46, $p = 0.16$**, treatment 5 of 245 (2.0%), control 9 of 245 (3.7%), NNT 61, odds ratio converted to relative risk, Cox proportional hazards.
	risk of mechanical ventilation, no change, RR 1.00, $p = 1.00$, treatment 2 of 245 (0.8%), control 2 of 245 (0.8%).
	risk of ICU admission, 100% higher, RR 2.00, $p = 1.00$, treatment 2 of 245 (0.8%), control 1 of 245 (0.4%).
	risk of oxygen therapy, 38.5% lower, RR 0.62, $p = 0.15$, treatment 16 of 245 (6.5%), control 26 of 245 (10.6%), NNT 25.
	risk of progression, 47.6% lower, HR 0.52, $p = 0.02$, treatment 17 of 245 (6.9%), control 31 of 245 (12.7%), NNT 18, odds ratio converted to relative risk, non-invasive respiratory support, endotracheal intubation, ICU admission, and all-cause death, Cox proportional hazards, primary outcome.
Wei, 10/13/2023, retrospective, China, peer-reviewed, 8 authors, study period 1 December, 2022 - 31 January, 2023, this trial compares with another treatment - results may be better when compared to placebo.	**risk of death, 0.2% higher, RR 1.00, $p = 1.00$**, treatment 63 of 461 (13.7%), control 36 of 264 (13.6%).
	risk of mechanical ventilation, 27.7% lower, RR 0.72, $p = 0.04$, treatment 77 of 461 (16.7%), control 61 of 264 (23.1%), NNT 16.
	risk of ICU admission, 55.0% lower, RR 0.45, $p = 0.05$, treatment 11 of 461 (2.4%), control 14 of 264 (5.3%), NNT 34.
	risk of progression, 22.1% lower, RR 0.78, $p = 0.07$, treatment 98 of 461 (21.3%), control 72 of 264 (27.3%), NNT 17, ICU admission, invasive mechanical ventilation, and in-hospital

	death, primary outcome.
Zhong, 4/1/2024, retrospective, China, preprint, 7 authors, study period 1 December, 2022 - 31 March, 2023.	risk of death, 35.0% lower, HR 0.65, $p = 0.048$, treatment 1,490, control 1,373, propensity score weighting, day 28.
	risk of death, 52.0% lower, HR 0.48, $p = 0.001$, treatment 1,490, control 1,373, propensity score weighting, day 14.
	risk of death, 87.0% lower, HR 0.13, $p = 0.001$, treatment 1,490, control 1,373, propensity score weighting, day 7.
Zhou, 10/12/2023, retrospective, China, peer-reviewed, median age 81.0, 6 authors, study period 1 December, 2022 - 31 January, 2023, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; unadjusted results with no group details.	risk of death, 21.8% lower, RR 0.78, $p = 0.15$, treatment 37 of 131 (28.2%), control 69 of 191 (36.1%), NNT 13.
Zong, 7/13/2023, retrospective, China, peer-reviewed, 6 authors, study period 8 December, 2022 - 20 January, 2023.	risk of death, 62.5% lower, OR 0.38, $p < 0.001$, treatment 195, control 390, propensity score matching, 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.

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