Sotrovimab for COVID-19: real-time meta analysis of 22 studies

@CovidAnalysis, May 2024, Version 38
https://c19early.org/vmeta.html

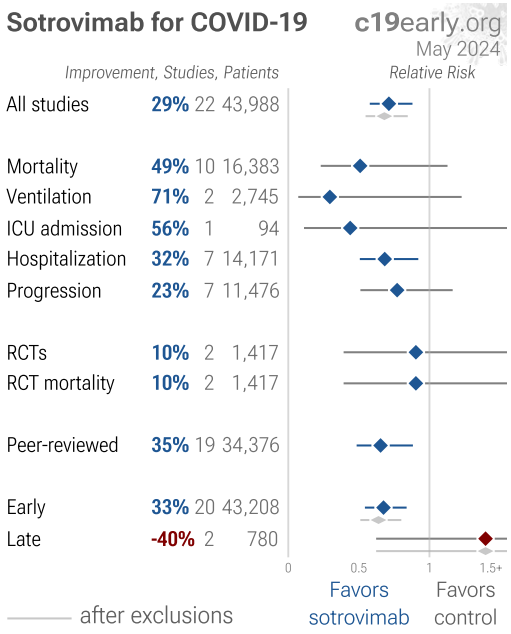
Abstract

Statistically significant lower risk is seen for hospitalization. 12 studies from 12 independent teams in 6 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 29% [12-42%] lower risk. Results are similar for higher quality and peer-reviewed studies and worse for Randomized Controlled Trials. Early treatment shows efficacy while late treatment does not, consistent with expectations for an antiviral treatment.

Results are robust — in exclusion sensitivity analysis 12 of 22 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

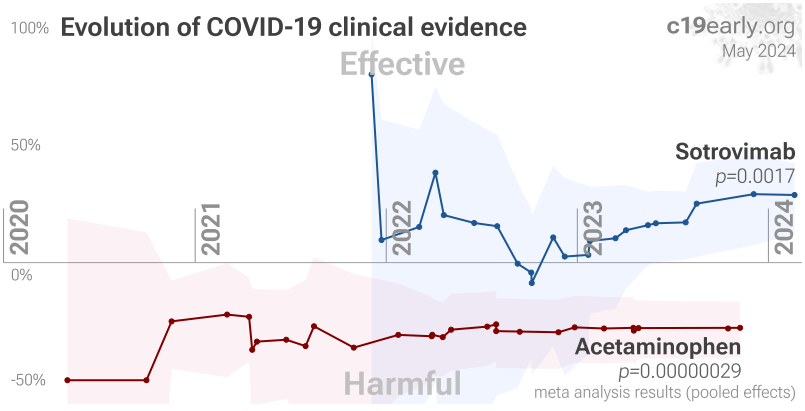
Efficacy is variant dependent. *In Vitro* studies suggest lower efficacy for omicron BA.1 *Liu, Sheward, VanBlargan*, BA.4, BA.5 *Haars*, XBB.1.9.3, XBB.1.5.24, XBB.2.9, CH.1.1 *Pochtovyi*, and no efficacy for BA.2 *Zhou*, XBB.1.9.1, XBB.1.16, BQ.1.1.45, and CL.1 *Pochtovyi*. US EUA has been revoked. mAb use may create new variants that spread globally *Focosi, Leducq*, and may be associated with prolonged viral loads, clinical deterioration, and immune escape *Choudhary, Günther, Leducq*.



Prescription treatments have been preferentially used by patients at lower risk *Wilcock*. Retrospective studies may overestimate efficacy, for example patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

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 are more effective.

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



HIGHLIGHTS

Sotrovimab reduces risk for COVID-19 with very high confidence for pooled analysis, high confidence for hospitalization, low confidence for mortality and ventilation, and very low confidence for ICU admission and progression. Efficacy is variant dependent.

38th treatment shown effective with ≥3 clinical studies in May 2023, now with p = 0.0017 from 22 studies, and recognized in 37 countries.

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.

22 sotrovimab COVID-19 studies

c19early.org
May 2024

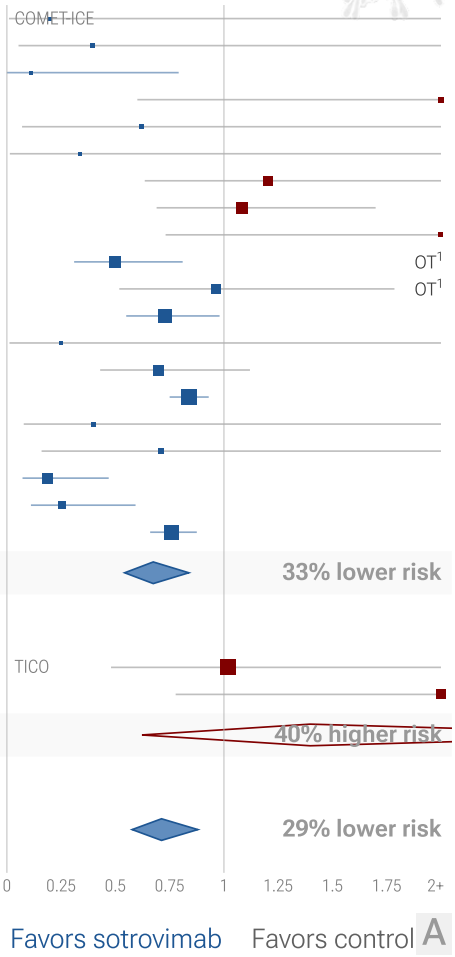
	Improvement	RR [CI]		Treatment	Control
Gupta (DB RCT)	80%	0.20 [0.01-4.16]	death	0/528	2/529
Ong	61%	0.39 [0.05-2.90]	death	1/19	10/75
Aggarwal (PSM)	89%	0.11 [0.00-0.79]	death	0/522	15/1,563
Zaqout	-165%	2.65 [0.60-11.3]	progression	4/345	3/583
Aggarwal	38%	0.62 [0.07-2.77]	death	1/1,542	7/3,663
Piccicacco	66%	0.34 [0.01-8.13]	death	0/88	1/90
Kneidinger	-20%	1.20 [0.64-2.27]	severe case	21/125	13/93
Suzuki	-8%	1.08 [0.69-1.70]	progression	672 (n)	1,257 (n)
Brown	-258%	3.58 [0.73-17.5]	hosp.	6/186	2/222
Zheng	50%	0.50 [0.31-0.81]	death/hosp.	34/3,331	61/2,689
Zheng (PSW)	4%	0.96 [0.52-1.79]	death/hosp.	2,847 (n)	4,836 (n)
Evans	27%	0.73 [0.55-0.98]	death/hosp.	1,079 (n)	4,973 (n)
Goodwin	75%	0.25 [0.01-5.17]	death	0/169	2/336
Kip	30%	0.70 [0.43-1.12]	death/hosp.	22/500	63/999
Tazare	16%	0.84 [0.75-0.93]	death/hosp.		
Miyashita	60%	0.40 [0.08-2.06]	ventilation	2/844	5/844
Drysdale (PSW)	29%	0.71 [0.16-3.20]	death	599 (n)	5,191 (n)
De Vito	81%	0.19 [0.07-0.47]	death	18/341	63/348
Behzad	74%	0.26 [0.11-0.59]	death/ICU	569 (n)	611 (n)
Bell (PSW)	24%	0.76 [0.66-0.88]	death/hosp.	population-based cohort	
Early treatment	33%	0.67 [0.54-0.84]		109/14,306	247/28,902

Tau^2 = 0.09, I^2 = 67.9%, p = 0.00041

	Improvement	RR [CI]		Treatment	Control
Self (DB RCT)	-2%	1.02 [0.48-2.17]	death	14/182	13/178
Woo (PSM)	-140%	2.40 [0.78-7.41]	death	4/60	10/360
Late treatment	-40%	1.40 [0.62-3.14]		18/242	23/538

Tau^2 = 0.13, I^2 = 36.1%, p = 0.43

All studies	29%	0.71 [0.58-0.88]		127/14,548	270/29,440



[1] OT: comparison with other treatment

Tau^2 = 0.09, I^2 = 67.0%, p = 0.0017

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

A

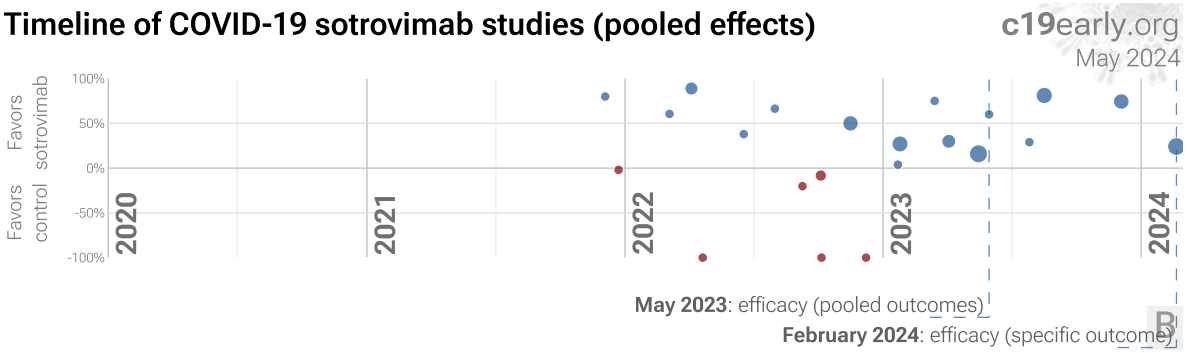


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in sotrovimab 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. Efficacy based on specific outcomes was delayed by 8.7 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 *Duloquin, Hampshire, Scardua-Silva, Sodagar, 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 sotrovimab 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.

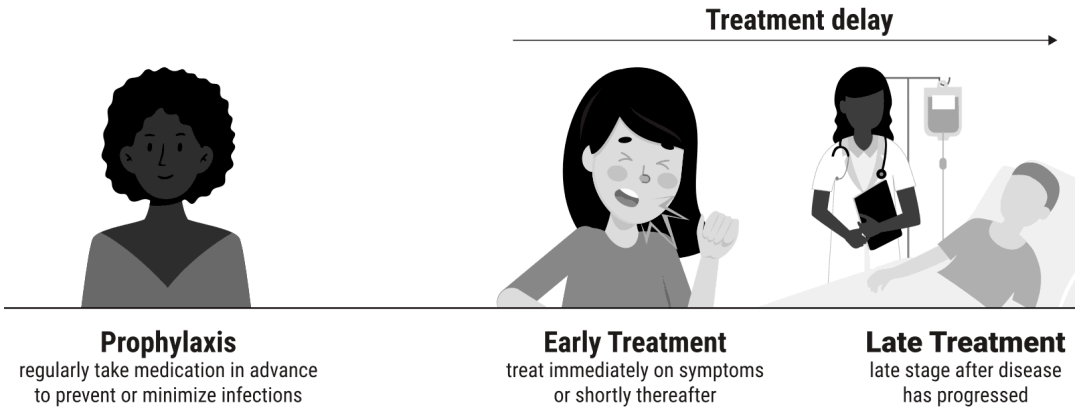


Figure 2. Treatment stages.

Variant Dependence

Efficacy is variant dependent, for example *in vitro* research suggests that sotrovimab is not effective for omicron BA.2 *Zhou*.

	Bamlanivimab/ etesevimab	*Casirivimab/ imdevimab*	*Sotrovimab*	*Bebtelovimab*	*Tixagevimab/ cilgavimab*
Alpha B.1.1.7					
Beta/Gamma BA1.351/P.1					
Delta B.1.617.2					
Omicron BA.1/BA.1.1					
Omicron BA.2					
Omicron BA.5					
Omicron BA.4.6					
Omicron BQ.1.1					

Table 1. Predicted efficacy by variant from *Davis* (not updated for more recent variants). : likely effective : likely ineffective : unknown. Submit updates.

Results

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

	Improvement	*Studies*	*Patients*	*Authors*
All studies	29% [12-42%] **	22	43,988	441
After exclusions	32% [15-45%] ***	20	35,897	415
Peer-reviewed studies	35% [12-52%] **	19	34,376	348
Randomized Controlled Trials	**10%** [-109-61%]	2	1,417	135
Mortality	49% [-13-77%]	10	16,383	218
Ventilation	71% [-23-93%]	2	2,745	75
Hospitalization	32% [8-49%] *	7	14,171	77
RCT mortality	**10%** [-109-61%]	2	1,417	135

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

	Early treatment	*Late treatment*
All studies	33% [16-46%] ***	-40% [-214-38%]
After exclusions	36% [20-49%] ***	-40% [-214-38%]
Peer-reviewed studies	41% [19-57%] **	-40% [-214-38%]
Randomized Controlled Trials	80% [-316-99%]	-2% [-117-52%]
Mortality	77% [64-85%] ****	-40% [-214-38%]
Ventilation	71% [-23-93%]	
Hospitalization	32% [8-49%] *	
RCT mortality	80% [-316-99%]	-2% [-117-52%]

Table 3. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

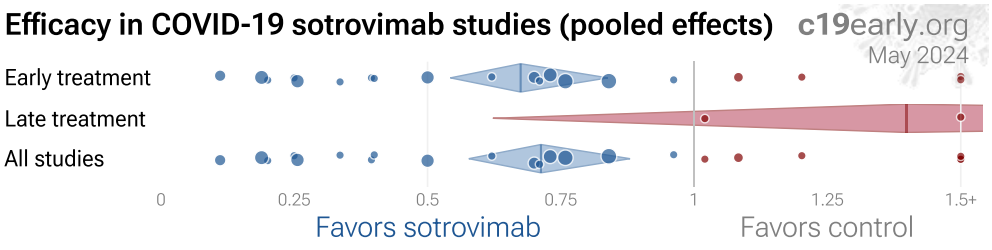


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

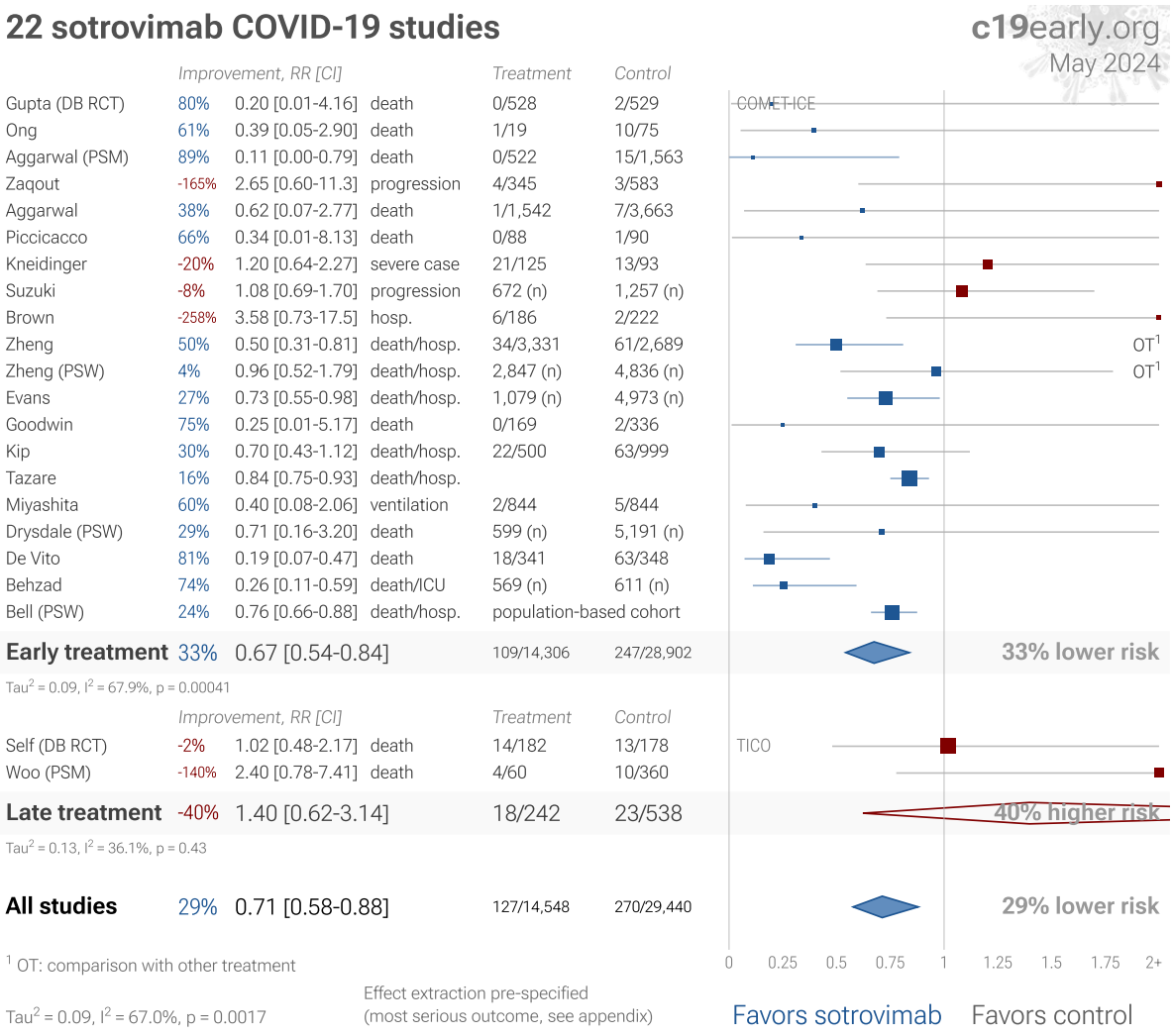


Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

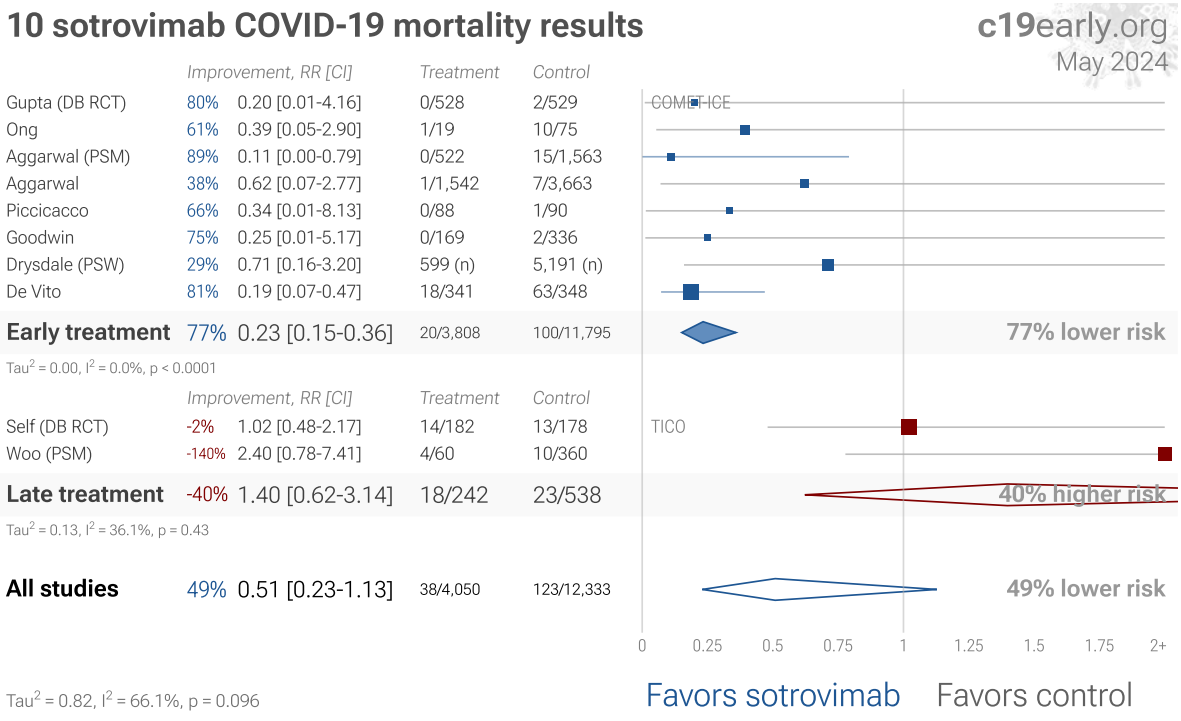


Figure 5. Random effects meta-analysis for mortality results.

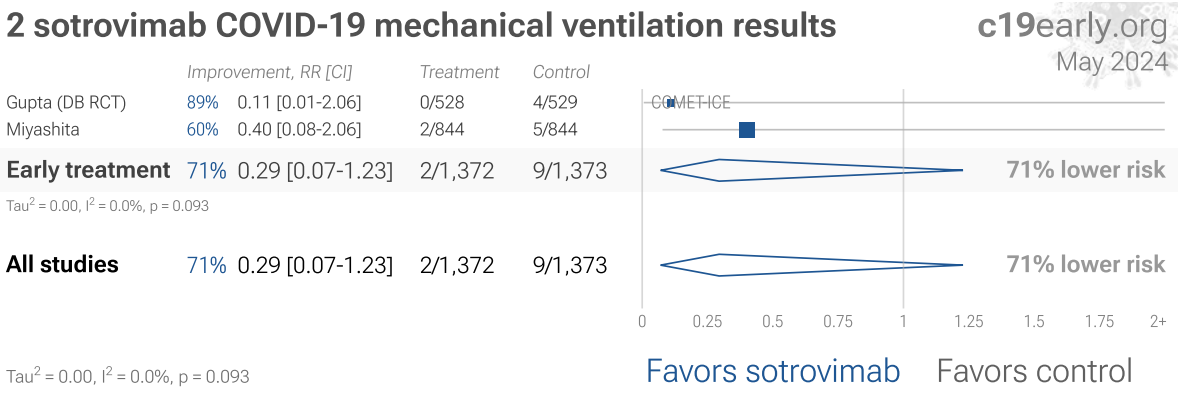


Figure 6. Random effects meta-analysis for ventilation.

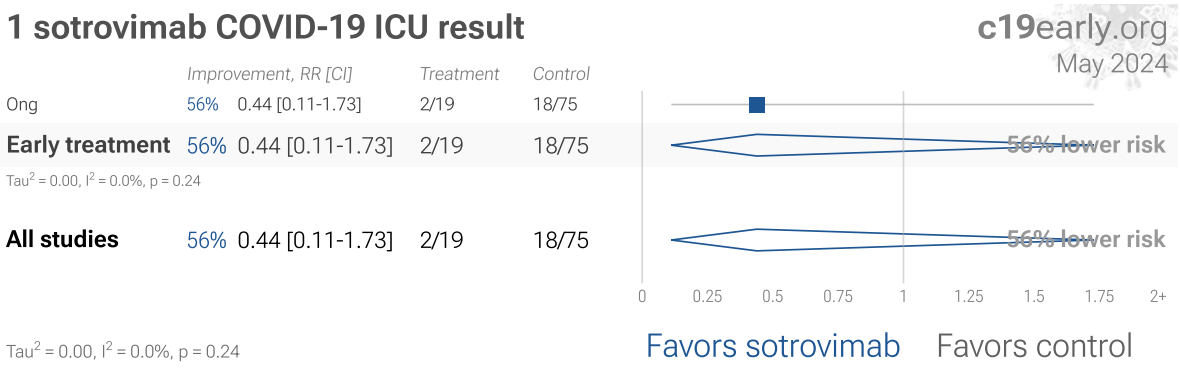


Figure 7. Random effects meta-analysis for ICU admission.

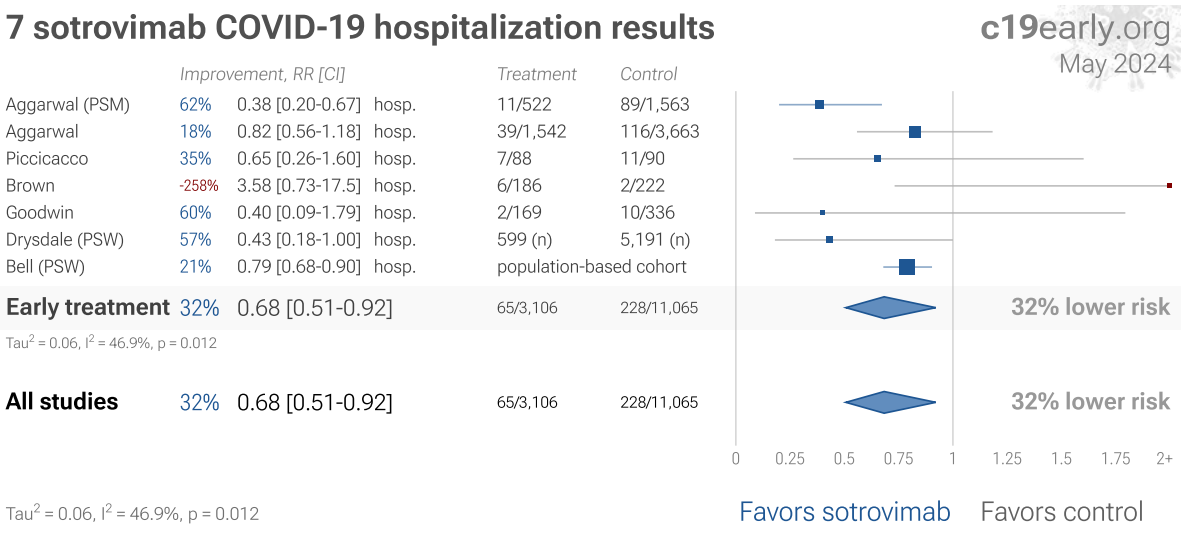


Figure 8. Random effects meta-analysis for hospitalization.

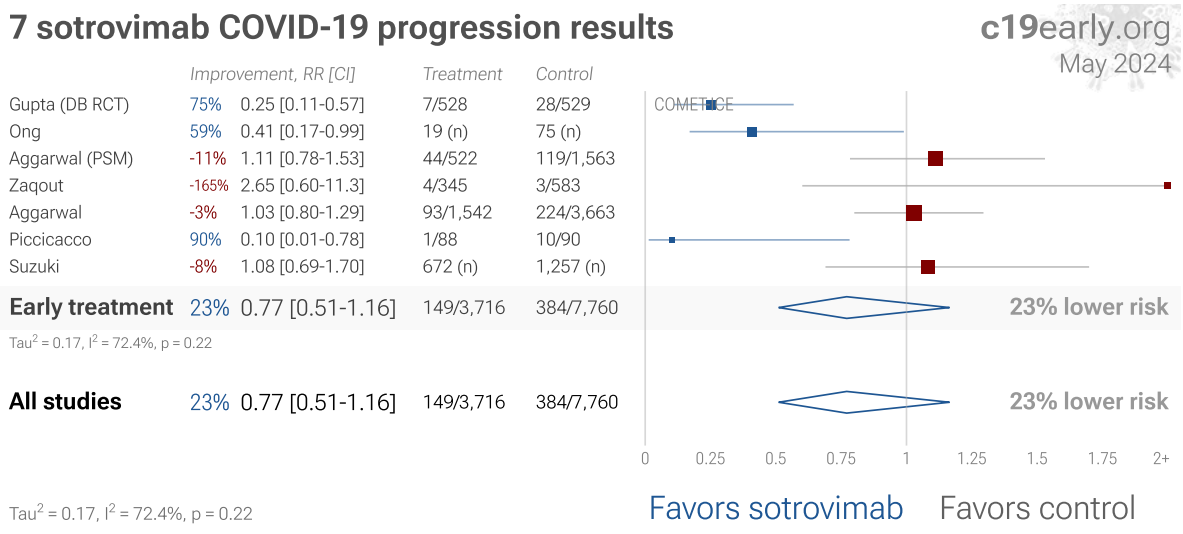


Figure 9. Random effects meta-analysis for progression.

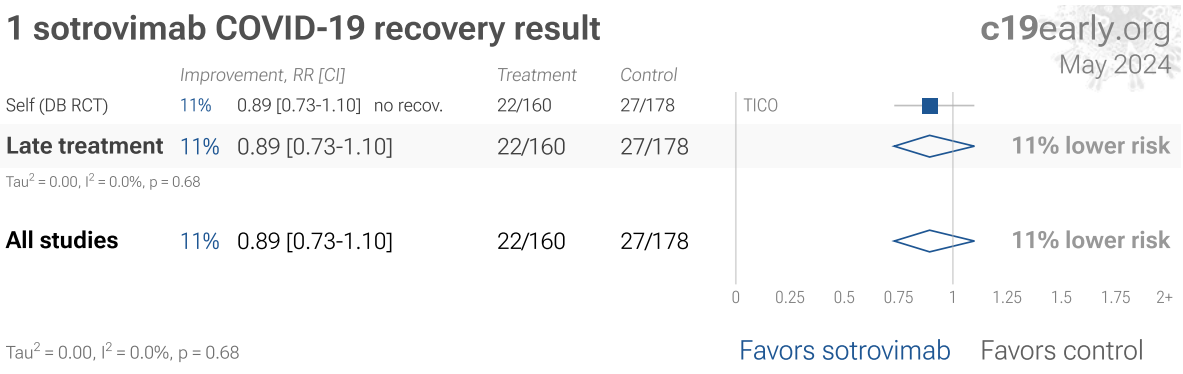


Figure 10. Random effects meta-analysis for recovery.

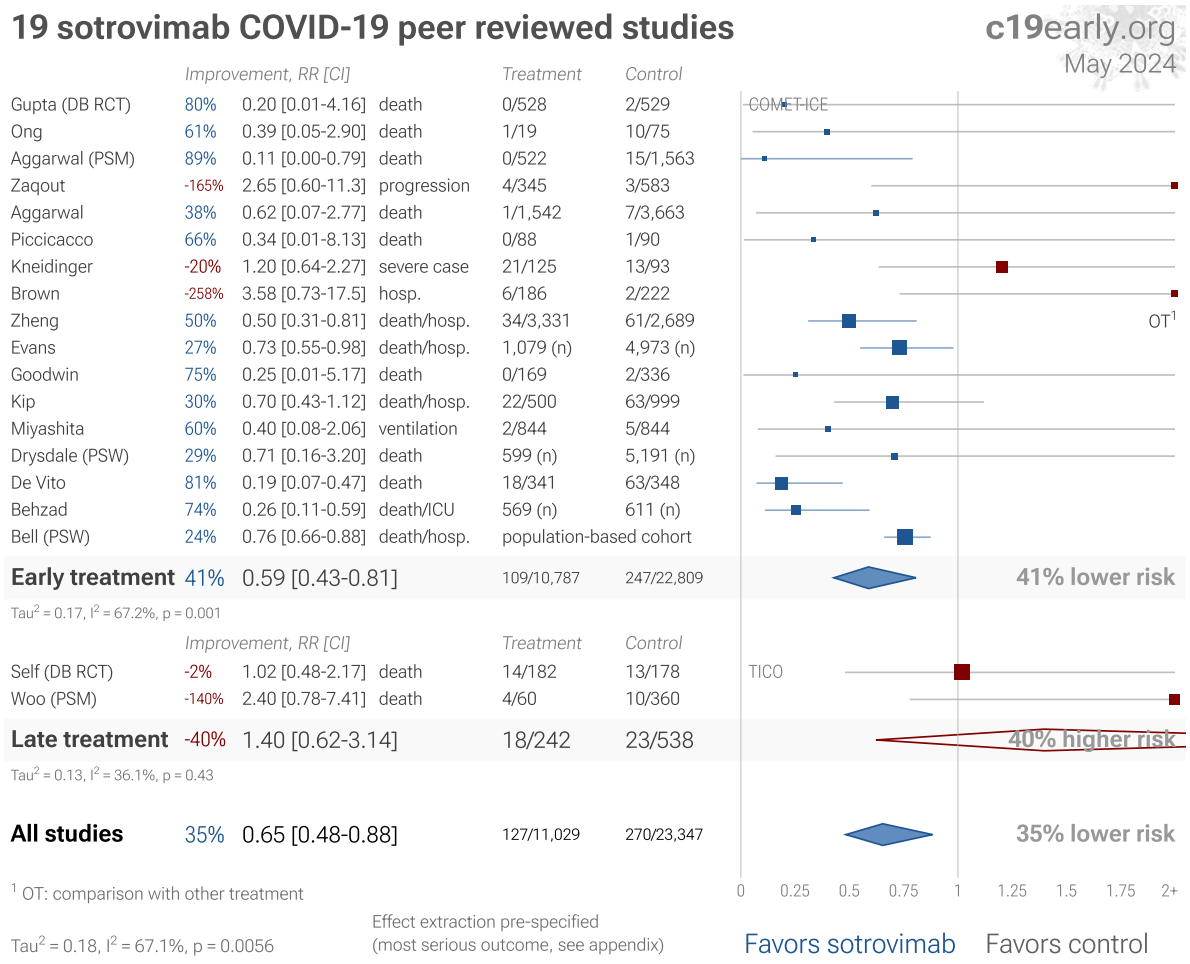


Figure 11. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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 12 shows a comparison of results for RCTs and non-RCT studies. Figure 13 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 2 and Table 3.

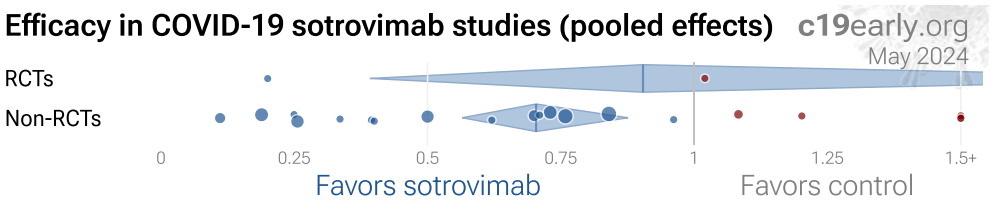


Figure 12. **Results for RCTs and non-RCT studies.**

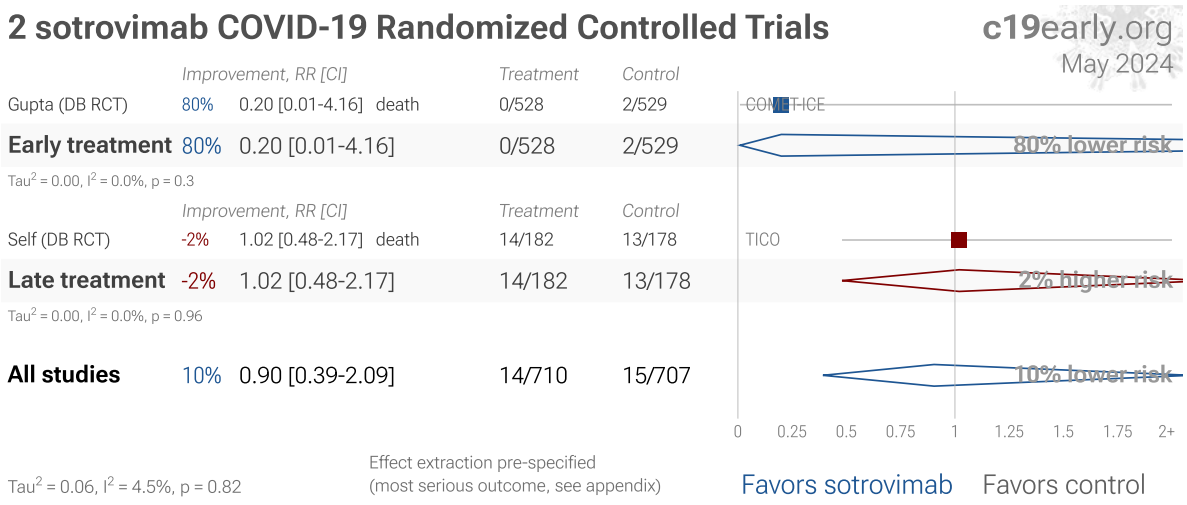


Figure 13. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious 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 7+ months faster (8+ 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 7.0 months. When considering only low cost treatments, 23 have been confirmed with a delay of 8.4 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.

Brown, unadjusted results with no group details; significant unadjusted confounding possible.

Zheng, study compares against another treatment showing significant efficacy.

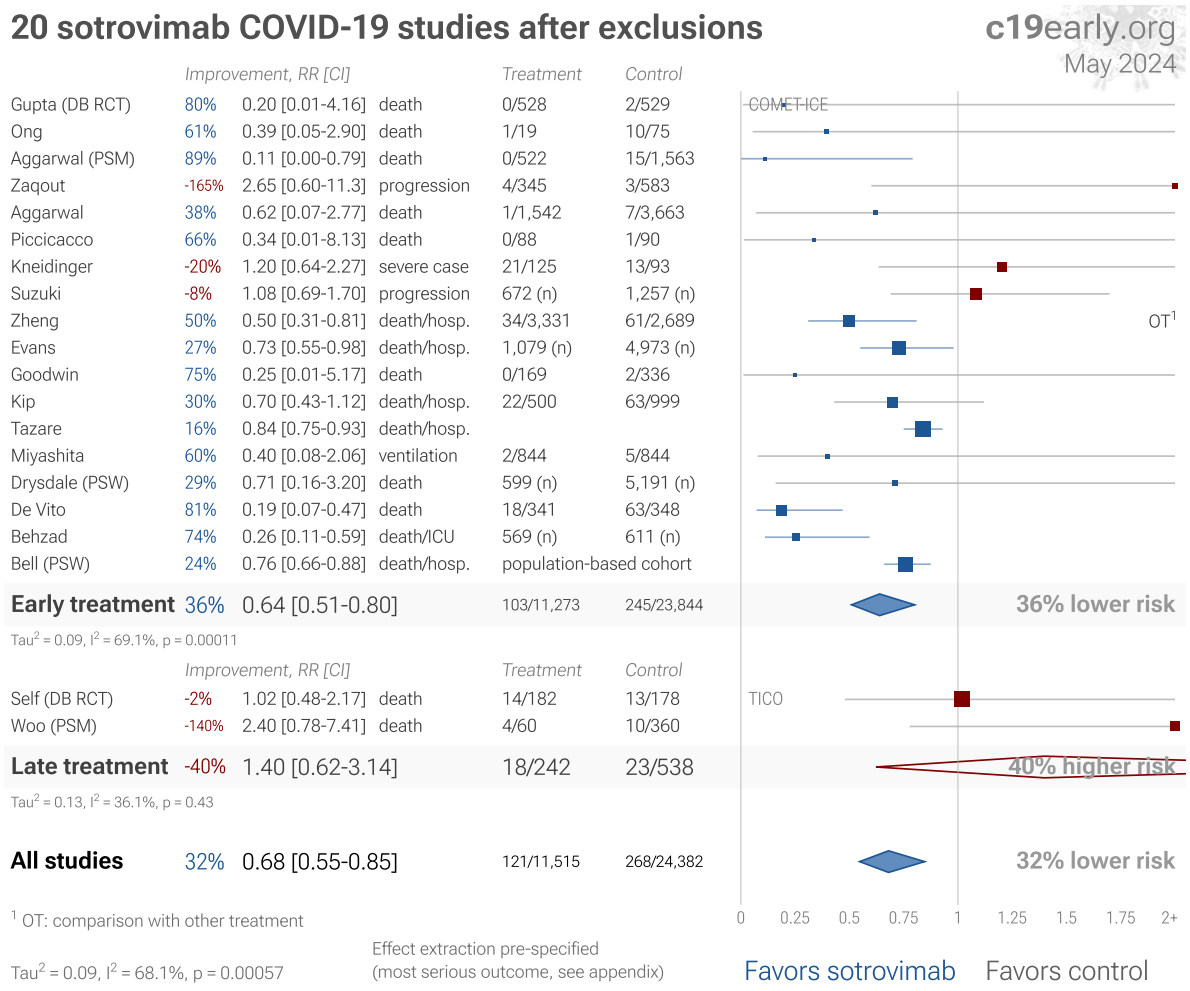


Figure 14. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome 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 4. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 15 shows a mixed-effects meta-regression of efficacy as a function of treatment delay in COVID-19 sotrovimab studies, with group estimates for different stages when a specific value is not provided. For comparison, Figure 16 shows a meta-regression for all studies providing specific values across 69 treatments. Efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

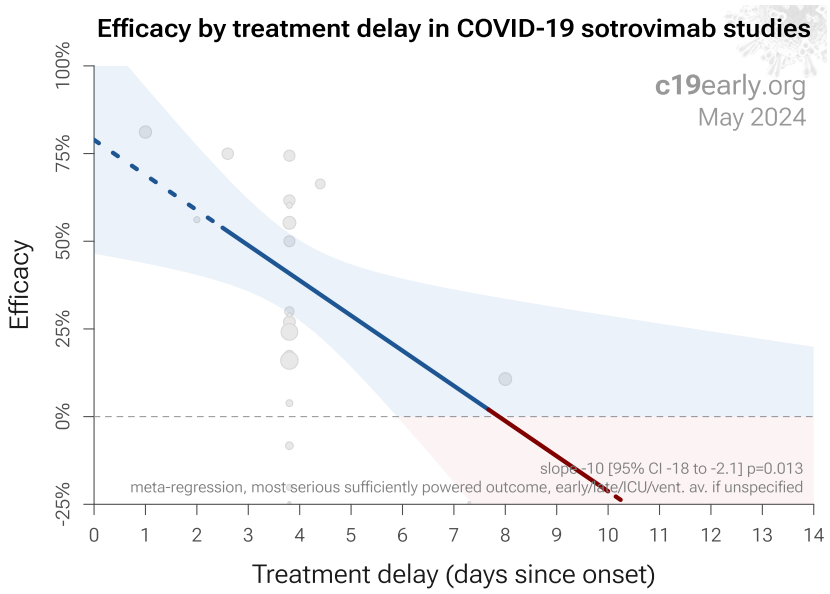


Figure 16. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 sotrovimab studies.

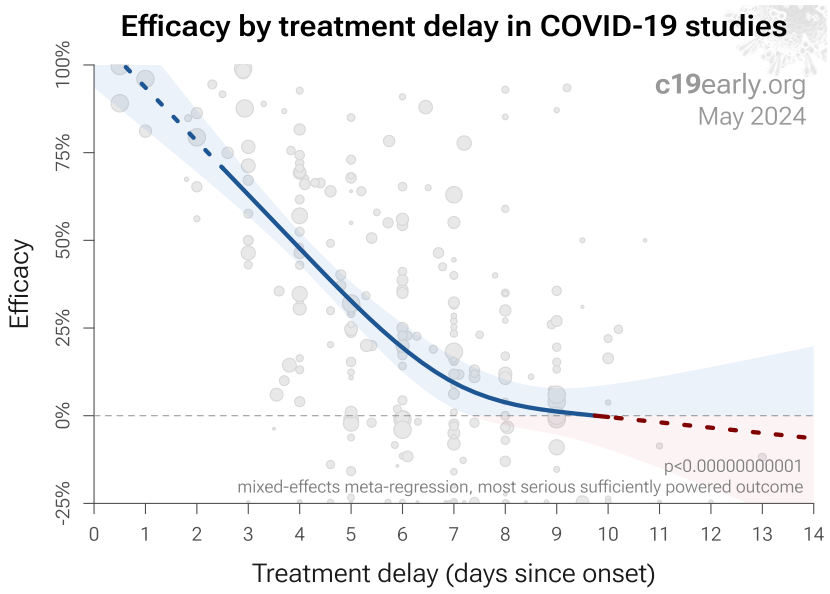


Figure 16. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 69 treatments.

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 17 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 18 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 19 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 $p = 0.0000031$ to $p = 0.0000000067$.

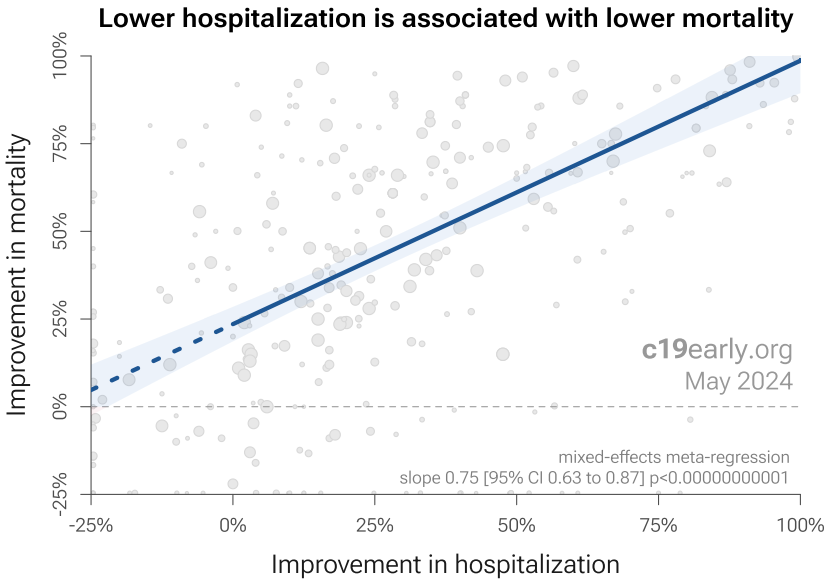


Figure 17. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

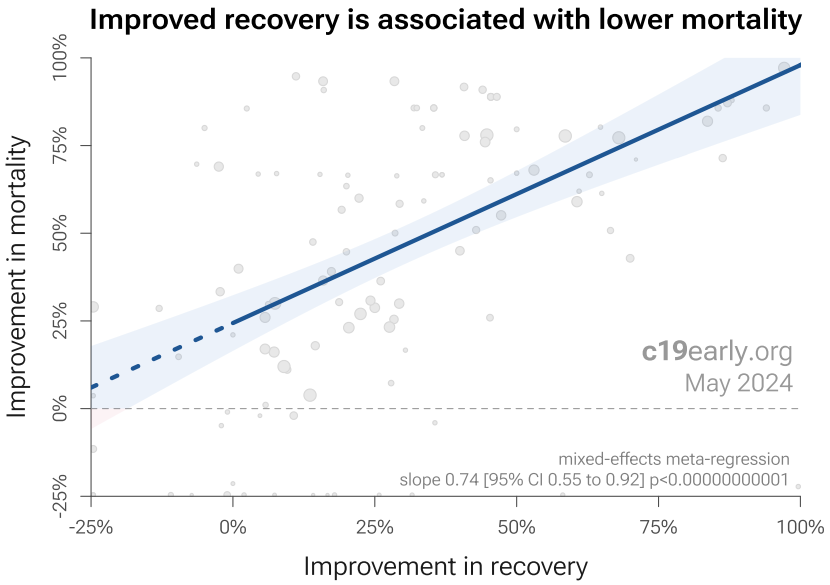


Figure 18. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

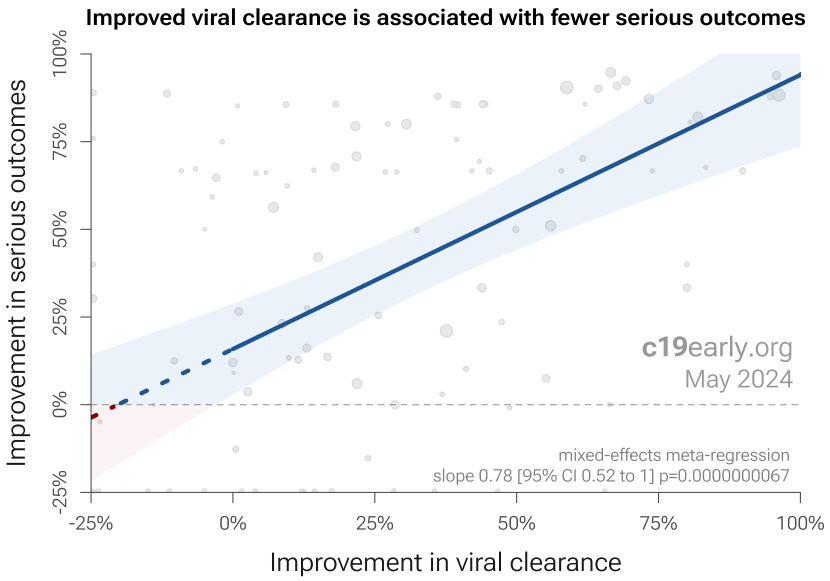


Figure 17. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 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. 88% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.7 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 5.5 months. Figure 20 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

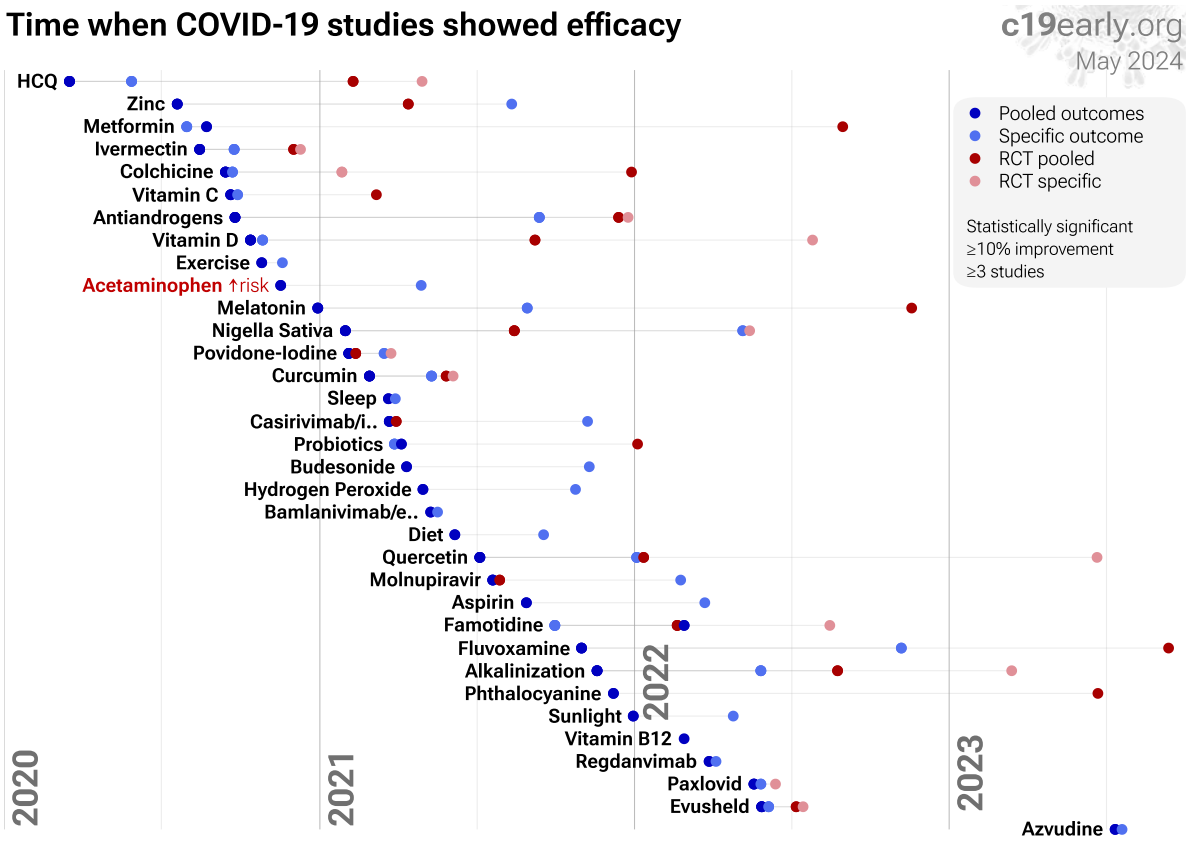


Figure 20. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

Retrospective studies may overestimate efficacy. *Wilcock et al.* show that COVID-19 prescription treatments have been preferentially used by patients at lower risk. Retrospective studies may overestimate efficacy, and data for accurate adjustment may not be available. For example, patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

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 sotrovimab, 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 21 shows a scatter plot of results for prospective and retrospective studies. 55% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 50% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 30% improvement, compared to 39% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

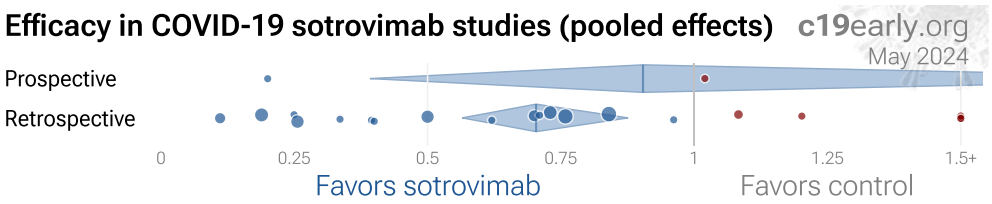


Figure 21. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Early treatment bias. Studies for sotrovimab were primarily for early treatment, in contrast with typical low cost treatments that were mostly tested with late treatment.

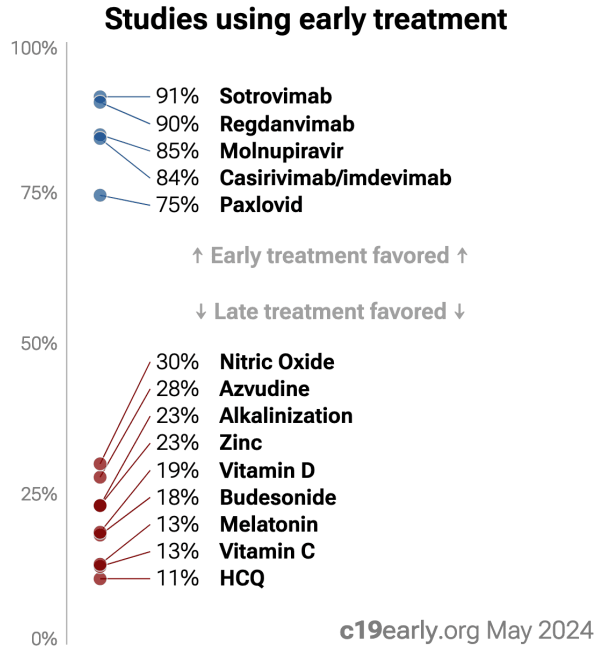


Figure 22. **Patented treatments received mostly early treatment studies, while low cost treatments were typically tested for late treatment.**

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 23 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.

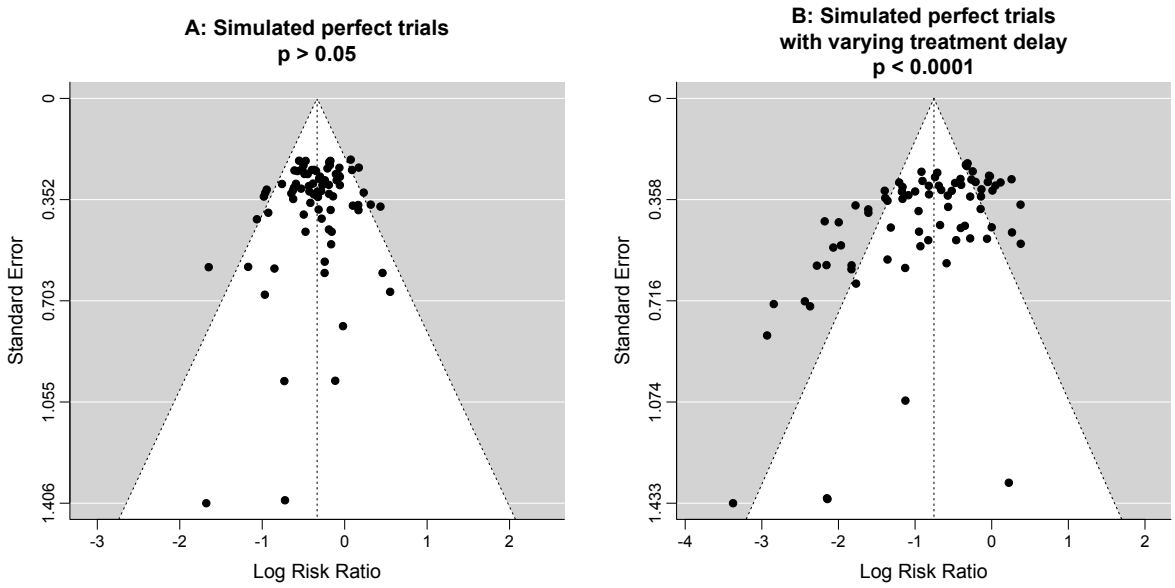


Figure 23. **Example funnel plot analysis for simulated perfect trials.**

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 22 studies compare against other treatments, which may reduce the effect seen.

Reviews. *Focosi (B) et al.* present a review covering sotrovimab for COVID-19.

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 24 shows an overview of the results for sotrovimab in the context of multiple COVID-19 treatments, and Figure 25 shows a plot of efficacy vs. cost for COVID-19 treatments.

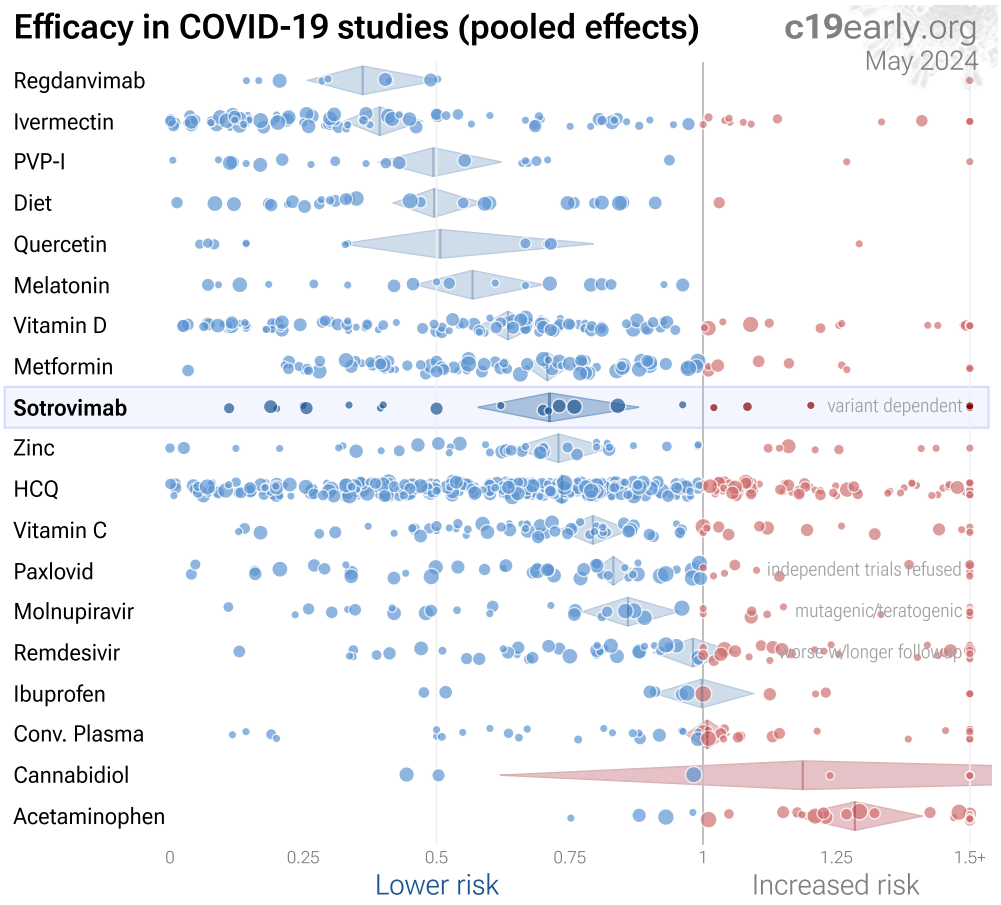


Figure 24. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy *c19early.org (B)*.

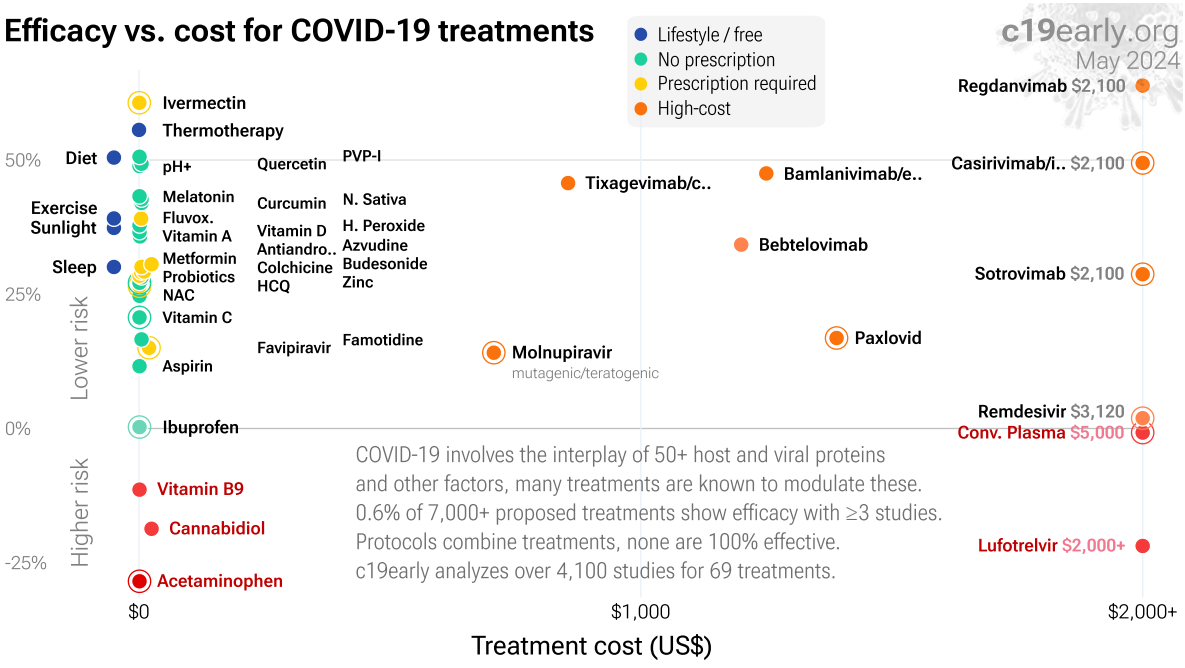


Figure 25. Efficacy vs. cost for COVID-19 treatments.

Conclusion

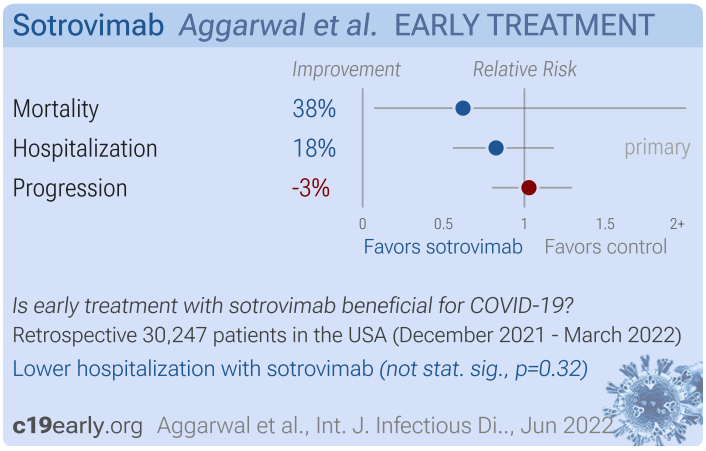
Sotrovimab is an effective treatment for COVID-19. Statistically significant lower risk is seen for hospitalization. 12 studies from 12 independent teams in 6 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 29% [12-42%] lower risk. Results are similar for higher quality and peer-reviewed studies and worse for Randomized Controlled Trials. Early treatment shows efficacy while late treatment does not, consistent with expectations for an antiviral treatment. Results are robust — in exclusion sensitivity analysis 12 of 22 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Efficacy is variant dependent. *In Vitro* studies suggest lower efficacy for omicron BA.1 *Liu, Sheward, VanBlargan*, BA.4, BA.5 *Haars*, XBB.1.9.3, XBB.1.5.24, XBB.2.9, CH.1.1 *Pochtovyi*, and no efficacy for BA.2 *Zhou*, XBB.1.9.1, XBB.1.16, BQ.1.1.45, and CL.1 *Pochtovyi*. US EUA has been revoked. mAb use may create new variants that spread globally *Focosi, Leducq*, and may be associated with prolonged viral loads, clinical deterioration, and immune escape *Choudhary, Günther, Leducq*.

Prescription treatments have been preferentially used by patients at lower risk *Wilcock*. Retrospective studies may overestimate efficacy, for example patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

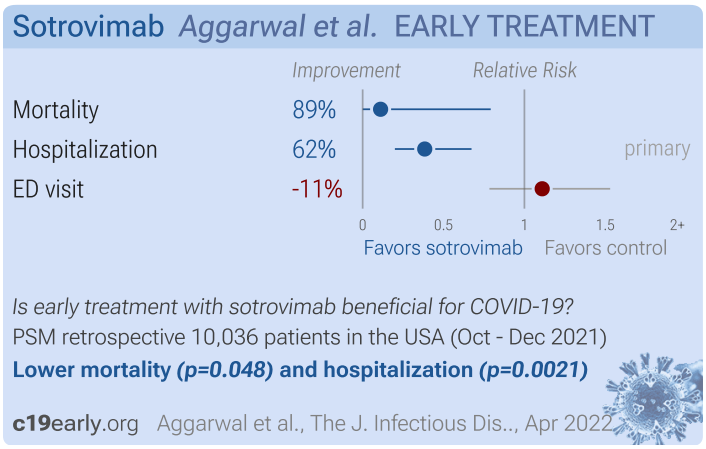
Study Notes

Aggarwal



Aggarwal: Retrospective 30,247 outpatients in the USA, showing no significant differences with sotrovimab with omicron BA.1.

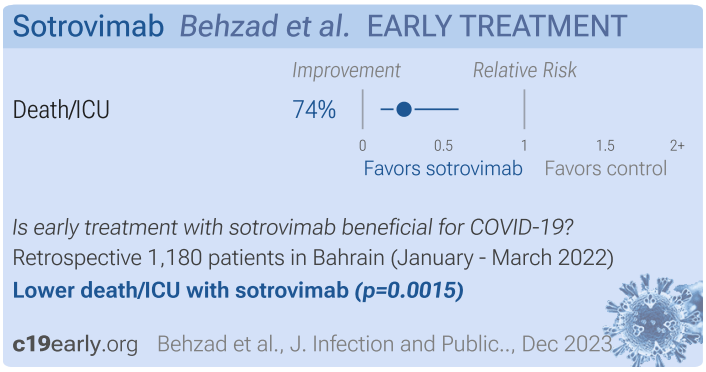
Aggarwal



Aggarwal (B): PSM retrospective 10,036 outpatients, 522 treated with sotrovimab, showing lower mortality and hospitalization with treatment.

Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene *c19early.org (C), c19early.org (D)*, vitamin D *c19early.org (E)*, etc.) — either because the physician recommending sotrovimab also recommended them, or because the patient seeking out sotrovimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

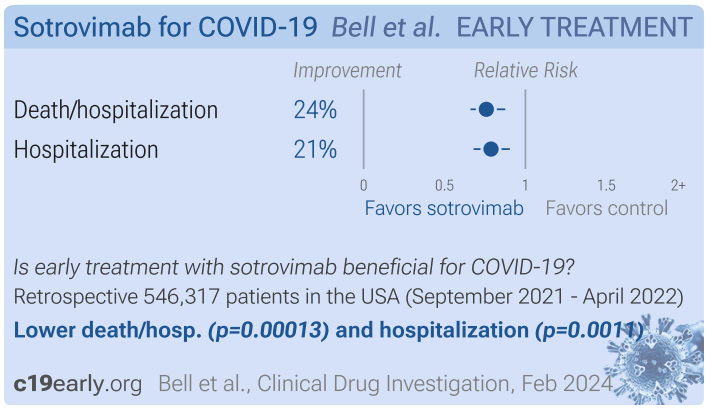
Behzad



Behzad: Analysis of 1,180 high-risk COVID-19 outpatients infected with Omicron BA.2 showing lower risk of death or ICU admission with sotrovimab treatment.

Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene *c19early.org (C), c19early.org (D)*, vitamin D *c19early.org (E)*, etc.) — either because the physician recommending sotrovimab also recommended them, or because the patient seeking out sotrovimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

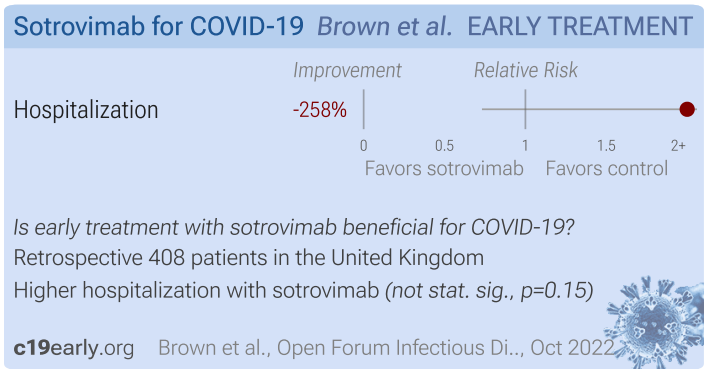
Bell



Bell: N3C retrospective 4,992 high-risk outpatients with mild-to-moderate COVID-19 showing reduced risk of hospitalization or death with sotrovimab treatment compared to 541,325 untreated controls during periods of Delta and Omicron BA.2 variant predominance in the US (September 2021-April 2022).

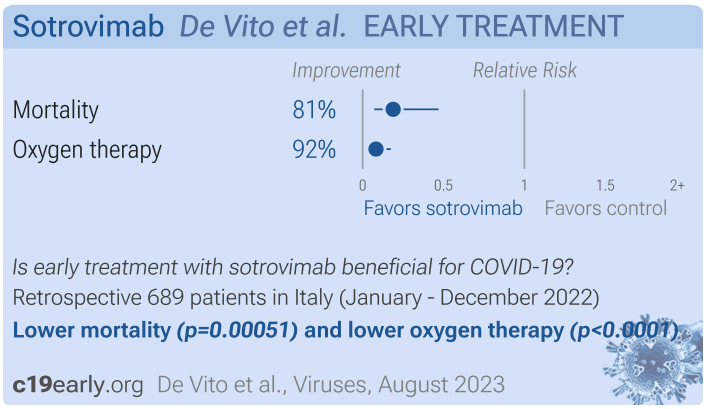
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene [c19early.org (C), c19early.org (D)], vitamin D [c19early.org (E)], etc.) — either because the physician recommending sotrovimab also recommended them, or because the patient seeking out sotrovimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

Brown



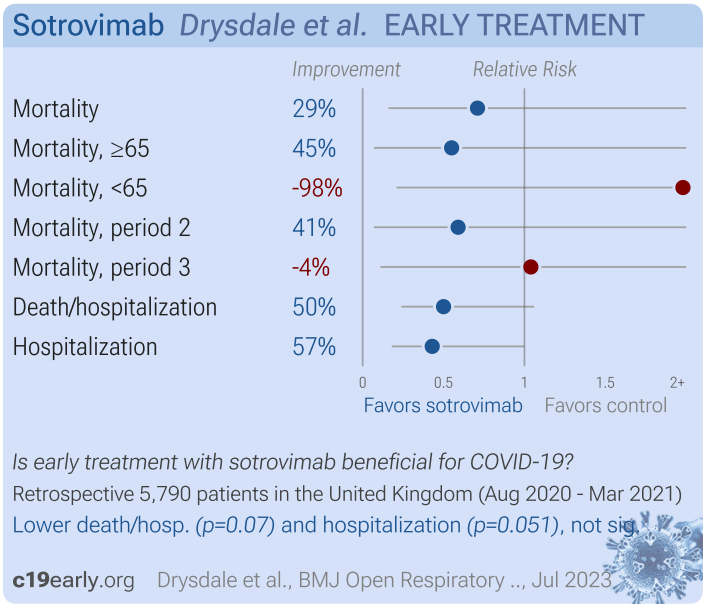
Brown: Retrospective 186 patients in the UK treated with sotrovimab, and 222 eligible but declining treatment, showing no significant difference in hospitalization. No group details are provided and the results are subject to confounding by indication.

De Vito



De Vito: Retrospective 689 COVID-19 patients in Italy, showing lower mortality with sotrovimab treatment.

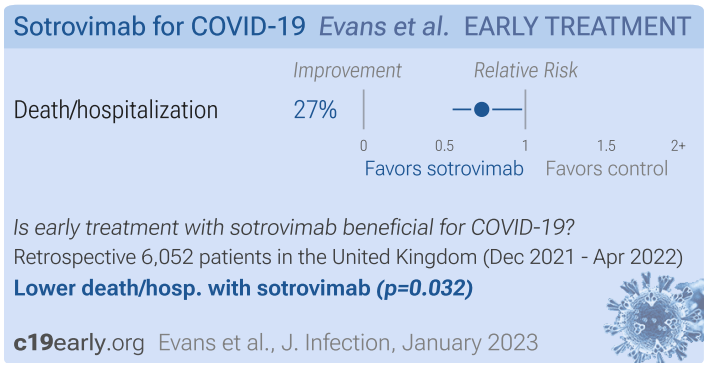
Drysdale



Drysdale: Retrospective 599 high-risk sotrovimab patients and 5,191 untreated controls, showing lower hospitalization/mortality with treatment, without statistical significance in the overall cohort. Efficacy was better for those ≥65, and efficacy was lower in later time periods.

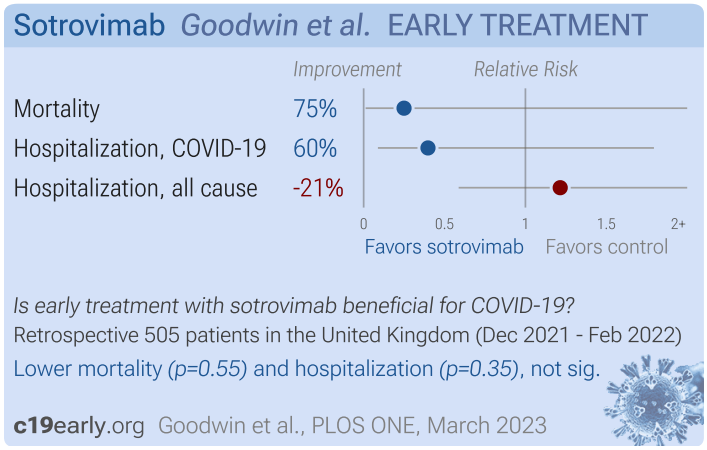
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene *c19early.org (C), c19early.org (D)*, vitamin D *c19early.org (E)*, etc.) — either because the physician recommending sotrovimab also recommended them, or because the patient seeking out sotrovimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

Evans



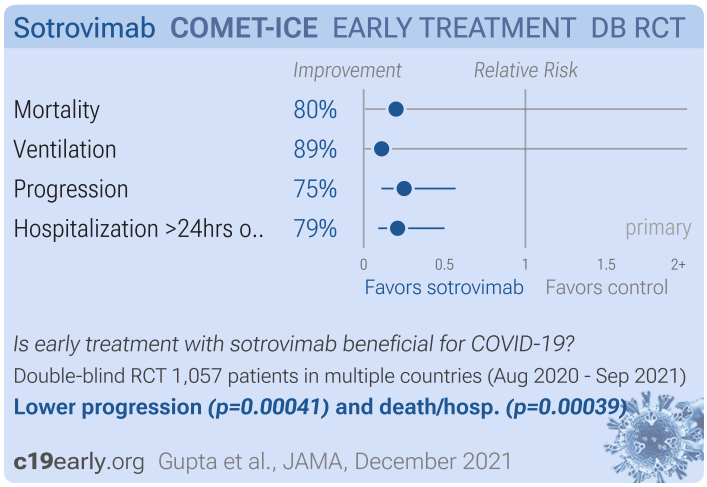
Evans: Retrospective high risk outpatients in the UK, showing lower hospitalization/death with sotrovimab treatment. Residual confounding is likely with adjustments having no detail on specific comorbidities.

Goodwin



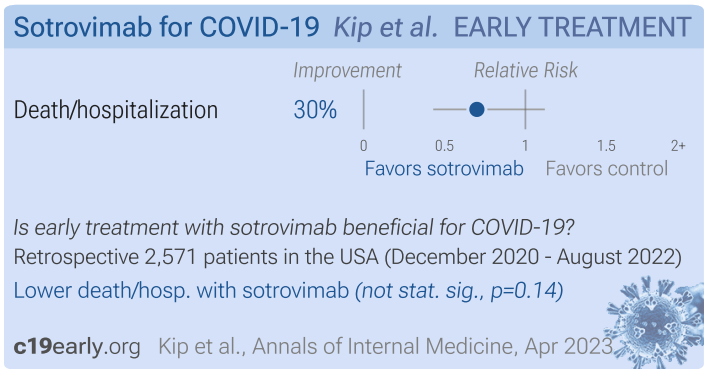
Goodwin: Retrospective 604 outpatients in the UK, showing lower risk of hospitalization with sotrovimab treatment, without statistical significance due to the small number of hospitalizations.

Gupta



Gupta: RCT 1,057 outpatients, 529 treated with sotrovimab, showing significantly lower hospitalization >24h or mortality with treatment.

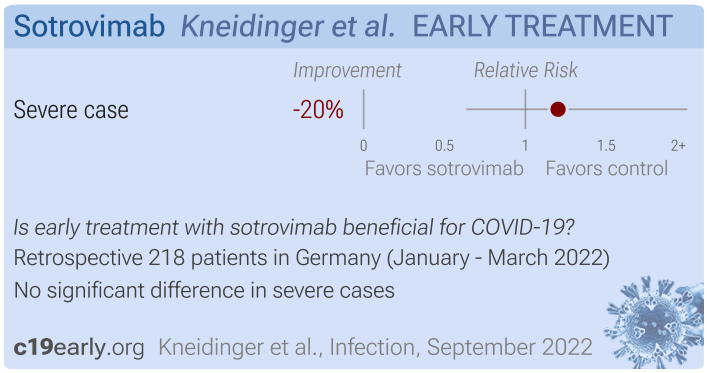
Kip



Kip: Retrospective 2,571 patients treated with mAbs in the USA, and 5,135 control patients, showing lower combined mortality/hospitalization for bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and bebtelovimab, with statistical significance only for casirivimab/imdevimab.

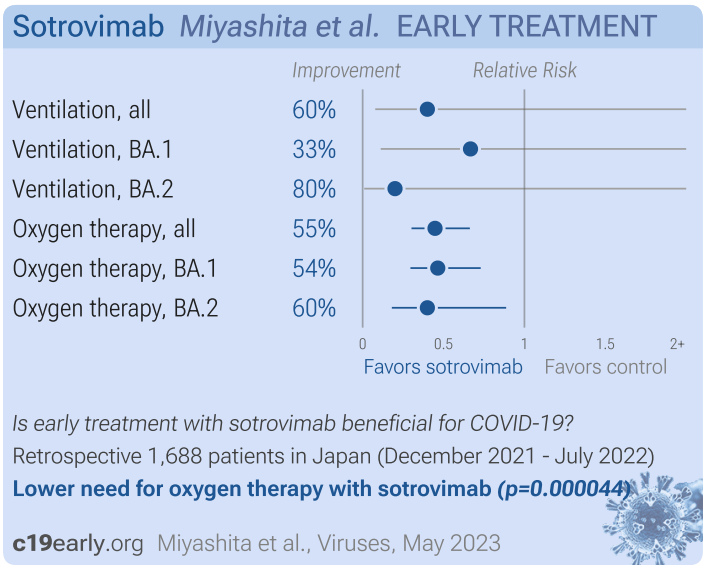
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene *c19early.org (C), c19early.org (D)*, vitamin D *c19early.org (E)*, etc.) — either because the physician recommending sotrovimab also recommended them, or because the patient seeking out sotrovimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

Kneidinger



Kneidinger: Retrospective 218 COVID+ lung transplant patients in Germany, showing no significant difference in severe cases with early sotrovimab use.

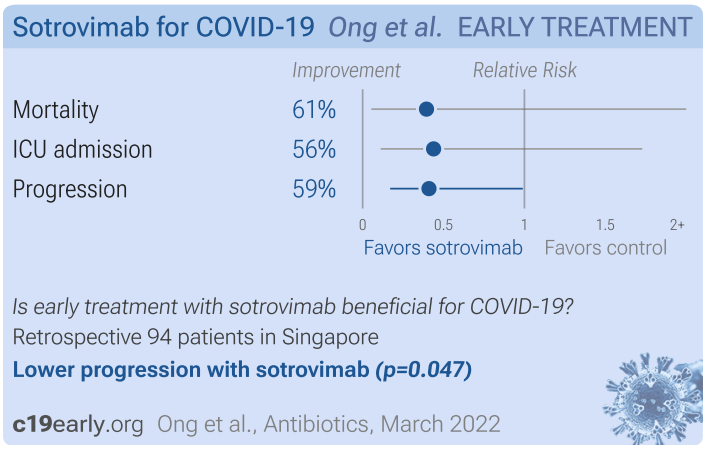
Miyashita



Miyashita: Retrospective 844 patients treated with sotrovimab and matched controls in Japan, showing lower risk of oxygen therapy with treatment.

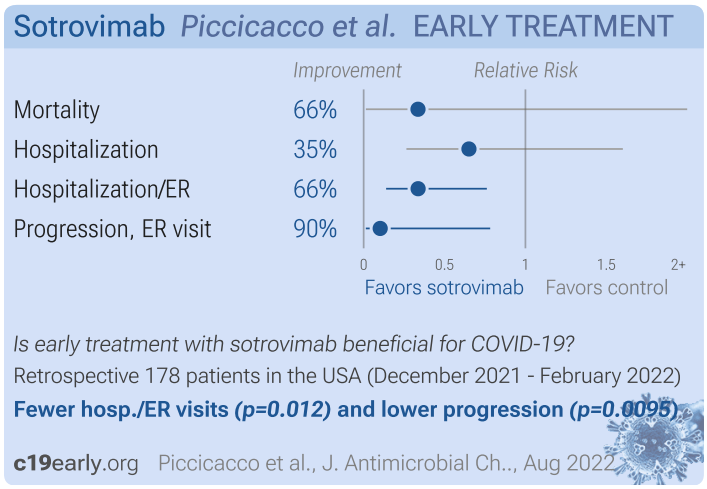
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene *c19early.org (C), c19early.org (D)*, vitamin D *c19early.org (E)*, etc.) — either because the physician recommending sotrovimab also recommended them, or because the patient seeking out sotrovimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

Ong



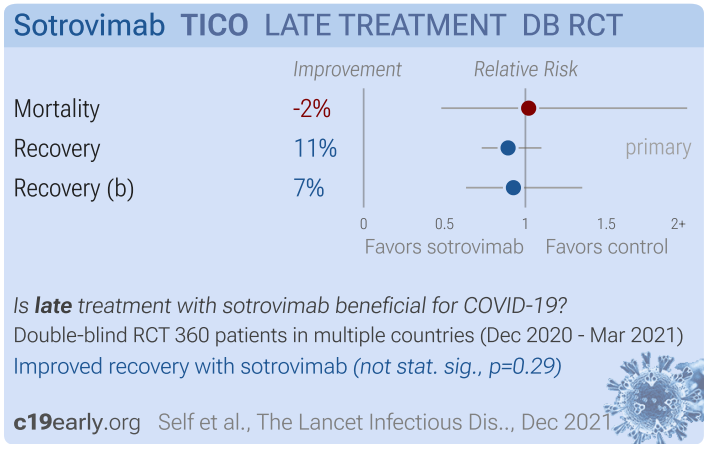
Ong: Retrospective 19 sotrovimab patients and 75 controls is Singapore, showing lower progression with treatment.

Piccicacco



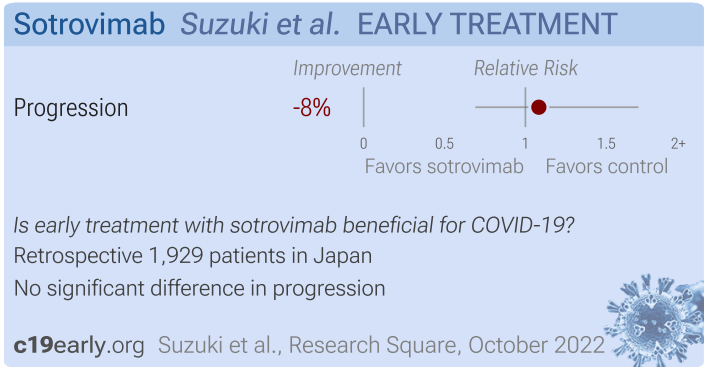
Piccicacco: Retrospective high-risk outpatients in the USA, 82 treated with remdesivir, 88 with sotrovimab, and 90 control patients, showing significantly lower combined hospitalization/ER visits with both treatments in unadjusted results. The dominant variant was omicron B.1.1.529.

Self



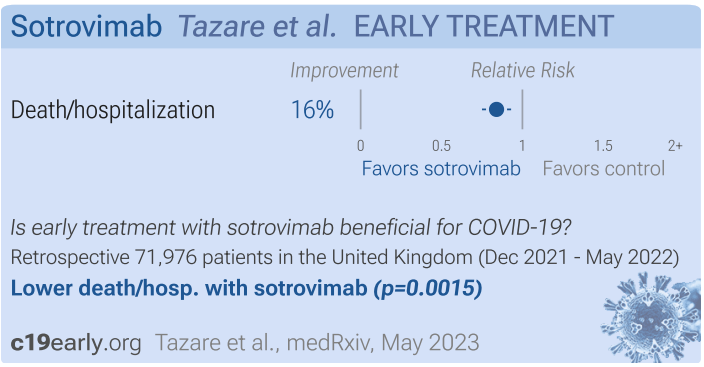
Self: RCT with 182 sotrovimab patients and 178 control patients, median 8 days from symptom onset, showing no significant differences and terminated early due to futility.

Suzuki



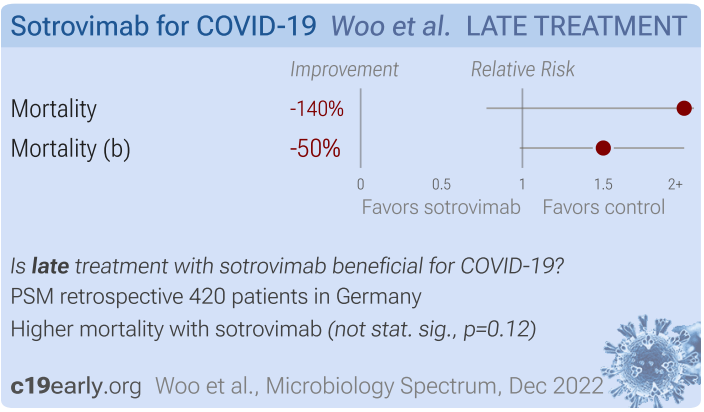
Suzuki: Retrospective 1,921 patients in Japan, showing no significant difference in progression with sotrovimab use.

Tazare



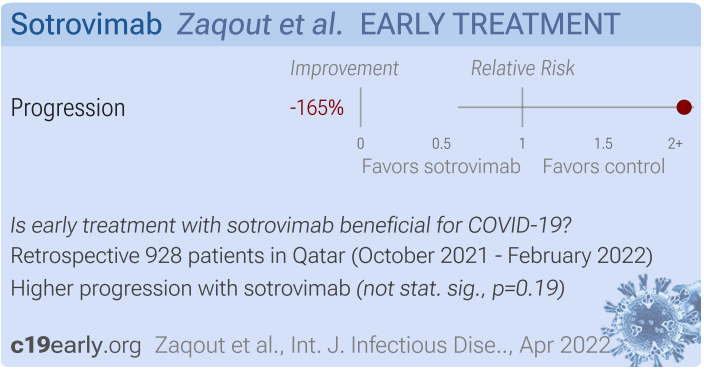
Tazare: OpenSAFELY retrospective 75,048 outpatients in the UK, using the clone-censor-weight approach to address immortal time bias, showing lower combined mortality/hospitalization with sotrovimab treatment.

Woo



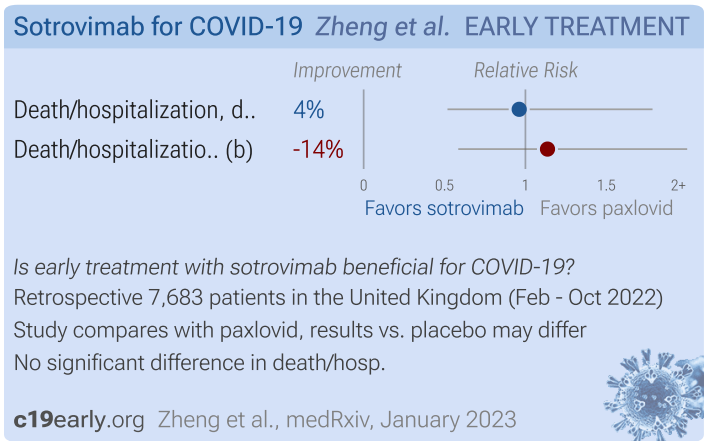
Woo: PSM retrospective 1,254 hospitalized patients in Germany, 147 treated with sotrovimab, showing higher mortality with sotrovimab, without statistical significance.

Zaqout



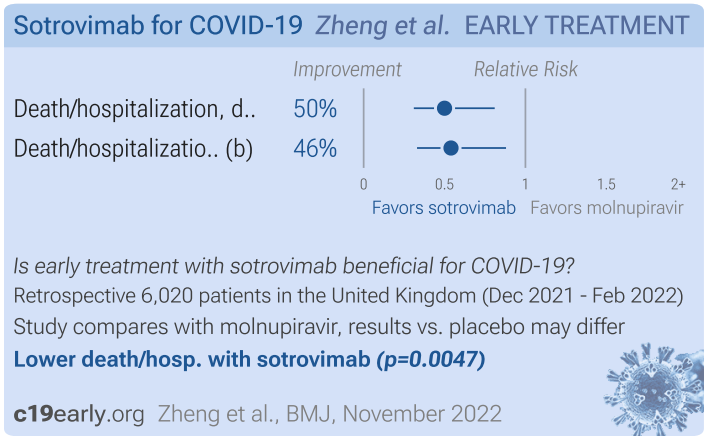
Zaqout: Retrospective 345 sotrovimab treated patients in Qatar matched with 583 patients that opted not to receive treatment, showing higher progression with treatment, without statistical significance.

Zheng



Zheng: OpenSAFELY retrospective 7,683 outpatients in the UK, showing no significant difference in hospitalization/death between paxlovid and sotrovimab.

Zheng



Zheng (B): Retrospective 3,331 sotrovimab and 2,689 molnupiravir patients in the UK, showing lower risk of combined hospitalization/death with sotrovimab.

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 sotrovimab 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 sotrovimab 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 (3.12.3) with scipy (1.13.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.2), and plotly (5.21.0).

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/vmeta.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.

Aggarwal, 6/18/2022, retrospective, USA, peer-reviewed, 10 authors, study period 26 December, 2021 - 10 March, 2022.	risk of death, 38.0% lower, RR 0.62, *p* = 0.62, treatment 1 of 1,542 (0.1%), control 7 of 3,663 (0.2%), odds ratio converted to relative risk.
	risk of hospitalization, 17.5% lower, RR 0.82, *p* = 0.32, treatment 39 of 1,542 (2.5%), control 116 of 3,663 (3.2%), NNT 157, odds ratio converted to relative risk, primary outcome.

	risk of progression, 2.8% higher, RR 1.03, p = 0.83, treatment 93 of 1,542 (6.0%), control 224 of 3,663 (6.1%), NNT 1189, odds ratio converted to relative risk, ED visit.
Aggarwal (B), 4/5/2022, retrospective, USA, peer-reviewed, 14 authors, study period 1 October, 2021 - 11 December, 2021.	**risk of death, 88.9% lower, RR 0.11, p = 0.048**, treatment 0 of 522 (0.0%), control 15 of 1,563 (1.0%), NNT 104, adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable, day 28.
	risk of hospitalization, 61.6% lower, RR 0.38, p = 0.002, treatment 11 of 522 (2.1%), control 89 of 1,563 (5.7%), NNT 28, adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable, day 28, primary outcome.
	ED visit, 11.0% higher, RR 1.11, p = 0.55, treatment 44 of 522 (8.4%), control 119 of 1,563 (7.6%), adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable, day 28.
Behzad, 12/4/2023, retrospective, Bahrain, peer-reviewed, 6 authors, study period 1 January, 2022 - 31 March, 2022.	**risk of death/ICU, 74.4% lower, HR 0.26, p = 0.001**, treatment 569, control 611.
Bell, 2/20/2024, retrospective, USA, peer-reviewed, 12 authors, study period 27 September, 2021 - 30 April, 2022.	**risk of death/hospitalization, 24.2% lower, RR 0.76, p < 0.001**, NNT 107, odds ratio converted to relative risk, propensity score weighting, day 29.
	risk of hospitalization, 21.3% lower, RR 0.79, p = 0.001, NNT 121, odds ratio converted to relative risk, propensity score weighting, day 29.
Brown, 10/6/2022, retrospective, United Kingdom, peer-reviewed, 17 authors, excluded in exclusion analyses: unadjusted results with no group details; significant unadjusted confounding possible.	**risk of hospitalization, 258.1% higher, RR 3.58, p = 0.15**, treatment 6 of 186 (3.2%), control 2 of 222 (0.9%).
De Vito, 8/17/2023, retrospective, Italy, peer-reviewed, 12 authors, study period 1 January, 2022 - 31 December, 2022, average treatment delay 1.0 days.	**risk of death, 81.1% lower, RR 0.19, p < 0.001**, treatment 18 of 341 (5.3%), control 63 of 348 (18.1%), NNT 7.8, odds ratio converted to relative risk.
	risk of oxygen therapy, 91.8% lower, RR 0.08, p < 0.001, treatment 17 of 341 (5.0%), control 144 of 348 (41.4%), NNT 2.7, odds ratio converted to relative risk.
Drysdale, 7/27/2023, retrospective, United Kingdom, peer-reviewed, 14 authors, study period August 2020 - March 2021.	**risk of death, 29.0% lower, HR 0.71, p = 0.65**, treatment 599, control 5,191, propensity score weighting, Cox proportional hazards.
	risk of death/hospitalization, 50.0% lower, HR 0.50, p = 0.07, treatment 599, control 5,191, propensity score weighting, Cox proportional hazards.
	risk of hospitalization, 57.0% lower, HR 0.43, p = 0.05, treatment 599, control 5,191, propensity score weighting, Cox proportional hazards.

Evans, 1/25/2023, retrospective, United Kingdom, peer-reviewed, 11 authors, study period 16 December, 2021 - 22 April, 2022.	risk of death/hospitalization, 27.0% lower, HR 0.73, $p = 0.03$, treatment 1,079, control 4,973, Cox proportional hazards.
Goodwin, 3/15/2023, retrospective, United Kingdom, peer-reviewed, 3 authors, study period 22 December, 2021 - 20 February, 2022.	risk of death, 75.0% lower, RR 0.25, $p = 0.55$, treatment 0 of 169 (0.0%), control 2 of 336 (0.6%), NNT 168, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 60.2% lower, RR 0.40, $p = 0.35$, treatment 2 of 169 (1.2%), control 10 of 336 (3.0%), NNT 56, COVID-19 related.
	risk of hospitalization, 21.5% higher, RR 1.21, $p = 0.69$, treatment 11 of 169 (6.5%), control 18 of 336 (5.4%), all cause.
Gupta, 12/4/2021, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, 68 authors, study period 27 August, 2020 - 2 September, 2021, average treatment delay 2.6 days, trial NCT04545060 (history) (COMET-ICE), conflicts of interest: research funding from the drug patent holder, employee of the drug patent holder.	risk of death, 80.0% lower, RR 0.20, $p = 0.50$, treatment 0 of 528 (0.0%), control 2 of 529 (0.4%), NNT 264, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 29.
	risk of mechanical ventilation, 88.9% lower, RR 0.11, $p = 0.12$, treatment 0 of 528 (0.0%), control 4 of 529 (0.8%), NNT 132, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 29.
	risk of progression, 75.0% lower, RR 0.25, $p < 0.001$, treatment 7 of 528 (1.3%), control 28 of 529 (5.3%), NNT 25, day 29.
	risk of hospitalization >24hrs or death, 79.0% lower, RR 0.21, $p < 0.001$, treatment 6 of 528 (1.1%), control 30 of 529 (5.7%), NNT 22, day 29, ITT, primary outcome.
Kip, 4/4/2023, retrospective, USA, peer-reviewed, 16 authors, study period 8 December, 2020 - 31 August, 2022.	risk of death/hospitalization, 30.0% lower, RR 0.70, $p = 0.14$, treatment 22 of 500 (4.4%), control 63 of 999 (6.3%), NNT 52, delta and omicron variants, day 28.
Kneidinger, 9/9/2022, retrospective, Germany, peer-reviewed, 11 authors, study period 1 January, 2022 - 20 March, 2022, lung transplant patients.	risk of severe case, 20.2% higher, RR 1.20, $p = 0.79$, treatment 21 of 125 (16.8%), control 13 of 93 (14.0%).
Miyashita, 5/31/2023, retrospective, Japan, peer-reviewed, 7 authors, study period December 2021 - July 2022.	risk of mechanical ventilation, 60.0% lower, RR 0.40, $p = 0.45$, treatment 2 of 844 (0.2%), control 5 of 844 (0.6%), NNT 281, all.
	risk of mechanical ventilation, 33.3% lower, RR 0.67, $p = 1.00$, treatment 2 of 642 (0.3%), control 3 of 642 (0.5%), NNT 642, BA.1.
	risk of mechanical ventilation, 80.0% lower, RR 0.20, $p = 0.50$, treatment 0 of 202 (0.0%), control 2 of 202 (1.0%), NNT 101, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), BA.2.
	risk of oxygen therapy, 55.3% lower, RR 0.45, $p < 0.001$, treatment 34 of 844 (4.0%), control 76 of 844 (9.0%), NNT 20, all.

	risk of oxygen therapy, 53.6% lower, RR 0.46, $p < 0.001$, treatment 26 of 642 (4.0%), control 56 of 642 (8.7%), NNT 21, BA.1.
	risk of oxygen therapy, 60.0% lower, RR 0.40, $p = 0.03$, treatment 8 of 202 (4.0%), control 20 of 202 (9.9%), NNT 17, BA.2.
Ong, 3/5/2022, retrospective, Singapore, peer-reviewed, 10 authors, average treatment delay 2.0 days.	risk of death, 60.5% lower, RR 0.39, $p = 0.45$, treatment 1 of 19 (5.3%), control 10 of 75 (13.3%), NNT 12.
	risk of ICU admission, 56.1% lower, RR 0.44, $p = 0.35$, treatment 2 of 19 (10.5%), control 18 of 75 (24.0%), NNT 7.4.
	risk of progression, 59.0% lower, HR 0.41, $p = 0.047$, treatment 19, control 75, Cox proportional hazards.
Piccicacco, 8/1/2022, retrospective, USA, peer-reviewed, 7 authors, study period 27 December, 2021 - 4 February, 2022, average treatment delay 4.4 days.	risk of death, 66.4% lower, RR 0.34, $p = 1.00$, treatment 0 of 88 (0.0%), control 1 of 90 (1.1%), NNT 90, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 29.
	risk of hospitalization, 34.9% lower, RR 0.65, $p = 0.46$, treatment 7 of 88 (8.0%), control 11 of 90 (12.2%), NNT 23, day 29.
	risk of hospitalization/ER, 66.3% lower, RR 0.34, $p = 0.01$, treatment 7 of 88 (8.0%), control 21 of 90 (23.3%), NNT 6.5, odds ratio converted to relative risk, day 29.
	risk of progression, 89.8% lower, RR 0.10, $p = 0.009$, treatment 1 of 88 (1.1%), control 10 of 90 (11.1%), NNT 10, ER visit, day 29.
Suzuki, 10/5/2022, retrospective, Japan, preprint, 53 authors.	risk of progression, 8.3% higher, OR 1.08, $p = 0.73$, treatment 672, control 1,257, adjusted per study, multivariable, RR approximated with OR.
Tazare, 5/16/2023, retrospective, United Kingdom, preprint, 31 authors, study period 16 December, 2021 - 21 May, 2022.	risk of death/hospitalization, 16.0% lower, HR 0.84, $p = 0.002$, treatment 6,408, control 65,568.
Zaqout, 4/21/2022, retrospective, Qatar, peer-reviewed, median age 40.0, 17 authors, study period 20 October, 2021 - 28 February, 2022.	risk of progression, 164.7% higher, RR 2.65, $p = 0.19$, treatment 4 of 345 (1.2%), control 3 of 583 (0.5%), adjusted per study, odds ratio converted to relative risk, progression to severe/critical disease or mortality.
Zheng, 1/22/2023, retrospective, United Kingdom, preprint, mean age 54.3, 9 authors, study period 11 February, 2022 - 1 October, 2022, this trial compares with another treatment - results may be better when compared to placebo, excluded in exclusion analyses: study compares against another treatment showing significant efficacy.	risk of death/hospitalization, 3.8% lower, HR 0.96, $p = 0.91$, treatment 2,847, control 4,836, inverted to make HR<1 favor treatment, COVID-19 related, propensity score weighting, Cox proportional hazards, day 60, model 4.
	risk of death/hospitalization, 13.6% higher, HR 1.14, $p = 0.70$, treatment 19 of 2,847 (0.7%), control 33 of 4,836 (0.7%), inverted to make HR<1 favor treatment, COVID-19 related, propensity score weighting, Cox proportional hazards, day 28, model 4.

Zheng (B), 11/16/2022, retrospective, United Kingdom, peer-reviewed, mean age 52.0, 33 authors, study period 16 December, 2021 - 10 February, 2022, this trial compares with another treatment - results may be better when compared to placebo.	risk of death/hospitalization, 50.0% lower, HR 0.50, $p = 0.005$, treatment 34 of 3,331 (1.0%), control 61 of 2,689 (2.3%), NNT 80, adjusted per study, multivariable, Cox proportional hazards, day 60, model 4.
	risk of death/hospitalization, 46.0% lower, HR 0.54, $p = 0.01$, treatment 32 of 3,331 (1.0%), control 55 of 2,689 (2.0%), NNT 92, adjusted per study, multivariable, Cox proportional hazards, day 28, model 4.

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.

Self, 12/23/2021, Double Blind Randomized Controlled Trial, multiple countries, peer-reviewed, 67 authors, study period 16 December, 2020 - 1 March, 2021, average treatment delay 8.0 days, trial NCT04501978 (history) (TICO).	risk of death, 2.0% higher, RR 1.02, $p = 0.96$, treatment 14 of 182 (7.7%), control 13 of 178 (7.3%), day 90.
	risk of no recovery, 10.7% lower, RR 0.89, $p = 0.29$, treatment 22 of 160 (13.8%), control 27 of 178 (15.2%), NNT 70, inverted to make RR<1 favor treatment, day 90, primary outcome.
	risk of no recovery, 7.4% lower, RR 0.93, $p = 0.69$, treatment 160, control 178, inverted to make RR<1 favor treatment, pulmonary-plus ordinal outcome @day 5.
Woo, 12/8/2022, retrospective, Germany, peer-reviewed, 13 authors.	risk of death, 140.0% higher, RR 2.40, $p = 0.12$, treatment 4 of 60 (6.7%), control 10 of 360 (2.8%), non-ICU, propensity score matching.
	risk of death, 50.0% higher, RR 1.50, $p = 0.08$, treatment 36 of 87 (41.4%), control 24 of 87 (27.6%), ICU, propensity score matching.

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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