Camostat for COVID-19: real-time meta analysis of 15 studies

@CovidAnalysis, September 2024, Version 5
https://c19early.org/cmmeta.html

Abstract

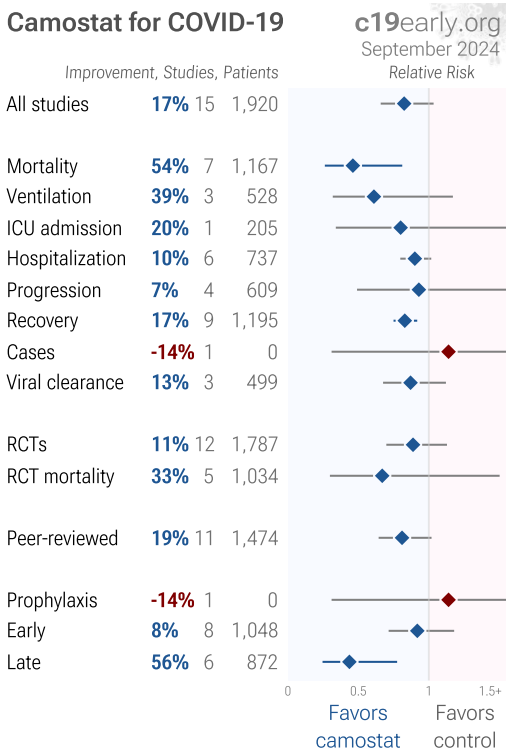
Statistically significant lower risk is seen for mortality and recovery. 3 studies from 3 independent teams in 3 countries show significant improvements.

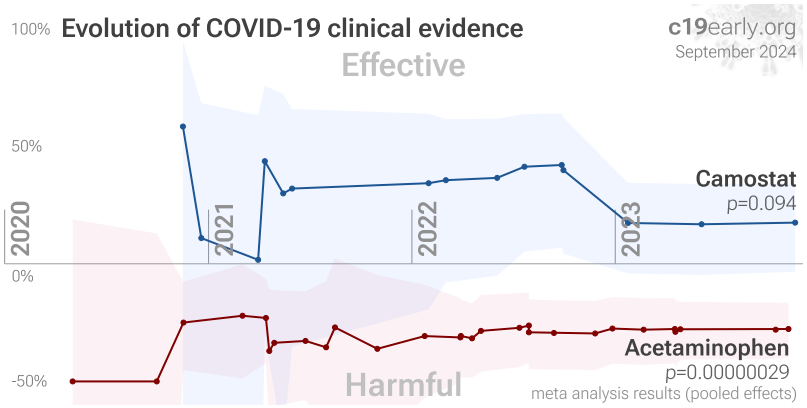
Meta analysis using the most serious outcome reported shows 17% [-3-34%] lower risk, without reaching statistical significance. Results are similar for peer-reviewed studies and worse for Randomized Controlled Trials.

6 RCTs with 1,092 patients have not reported results (up to 3 years late).

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 significantly more effective.

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





CAMOSTAT FOR COVID-19 — HIGHLIGHTS

Camostat reduces risk with very high confidence for mortality and recovery, low confidence for hospitalization and in pooled analysis, and very low confidence for ventilation, however increased risk is seen with very low confidence for cases.

Outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 92 treatments.

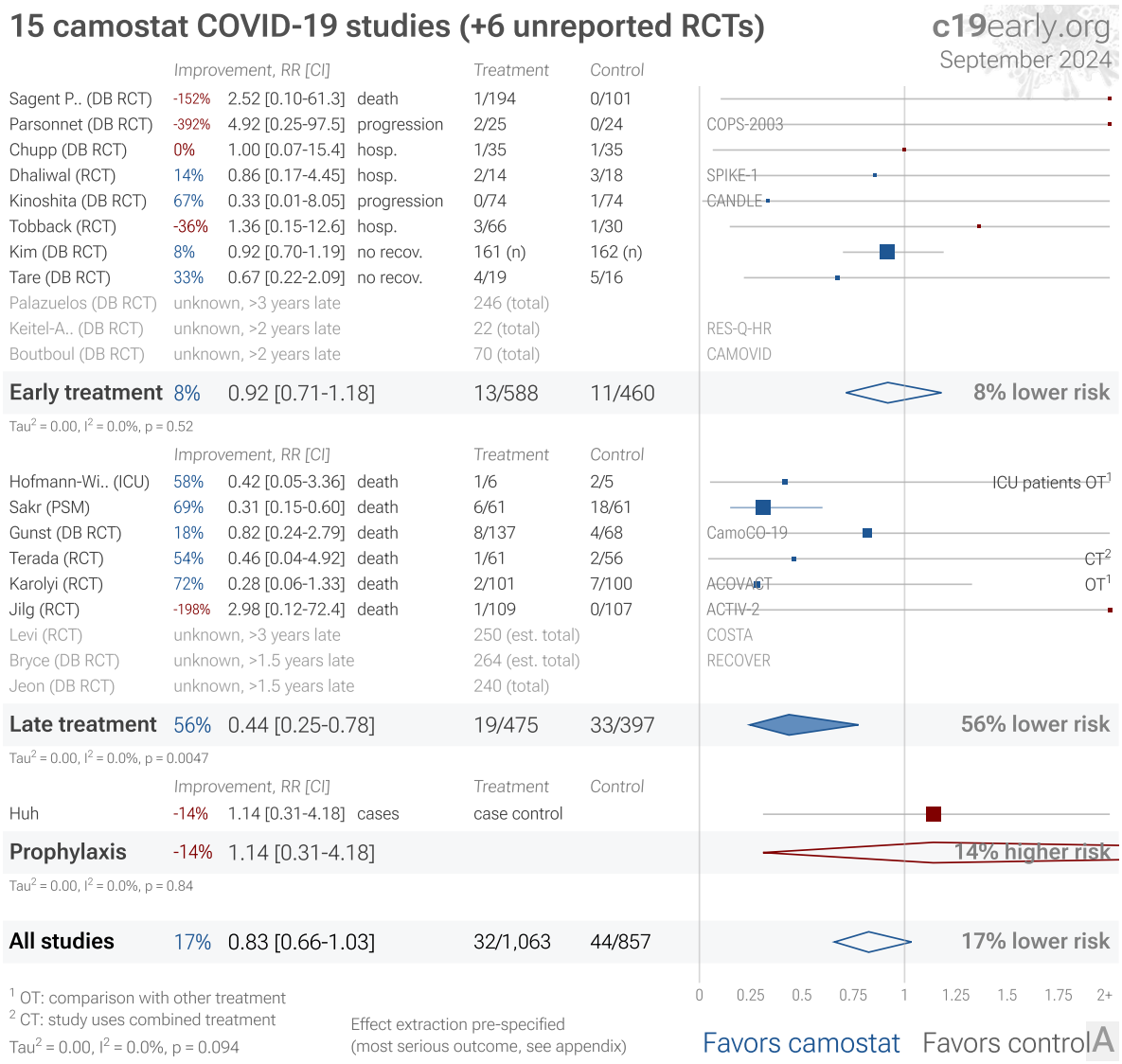


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in camostat studies.**

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 injury [1-9] and cognitive deficits [3,8], cardiovascular complications [10-12], 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[A,13-17], 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[18], 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 camostat 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, and Randomized Controlled Trials (RCTs).

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.

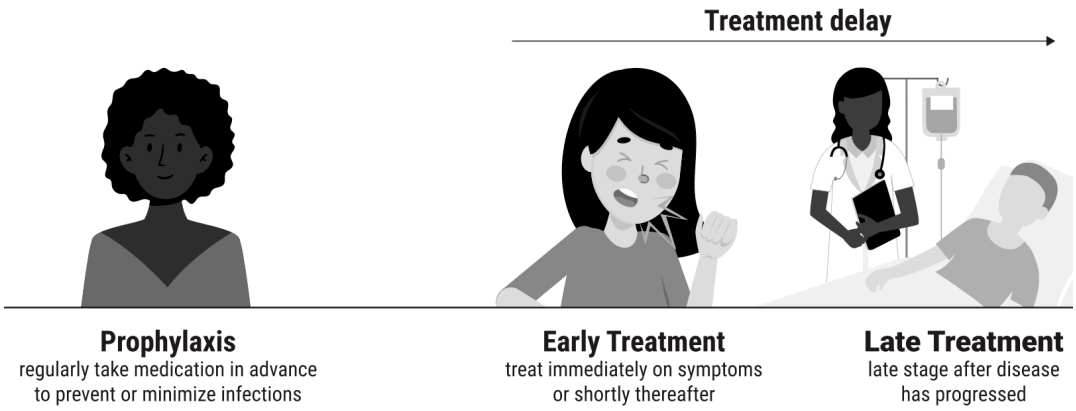


Figure 2. Treatment stages.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, 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, 12, and 13 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**17%** [-3-34%]	15	1,920	247
Peer-reviewed studies	**19%** [-2-36%]	11	1,474	220
Randomized Controlled Trials	**11%** [-13-30%]	12	1,787	209
Mortality	**54%** [19-74%] **	7	1,167	141
Ventilation	**39%** [-17-68%]	3	528	71
Hospitalization	**10%** [-2-20%]	6	737	109
Recovery	**17%** [8-25%] ***	9	1,195	168
Viral	**13%** [-12-32%]	3	499	16
RCT mortality	**33%** [-50-70%]	5	1,034	111
RCT hospitalization	**14%** [2-24%] *	5	615	98

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

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	**8%** [-18-29%]	**56%** [22-75%] **	**-14%** [-318-69%]
Peer-reviewed studies	**10%** [-17-30%]	**56%** [22-75%] **	**-14%** [-318-69%]
Randomized Controlled Trials	**8%** [-18-29%]	**39%** [-41-74%]	
Mortality	**-152%** [-6033-90%]	**56%** [22-75%] **	
Ventilation		**39%** [-17-68%]	
Hospitalization	**-1%** [-232-69%]	**4%** [-21-24%]	
Recovery	**12%** [-5-26%]	**19%** [9-29%] ***	
Viral	**13%** [-12-32%]		
RCT mortality	**-152%** [-6033-90%]	**39%** [-41-74%]	
RCT hospitalization	**-1%** [-232-69%]	**14%** [2-25%] *	

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

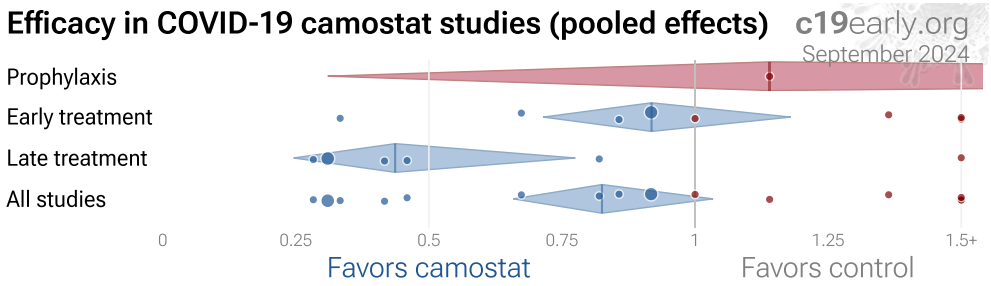


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

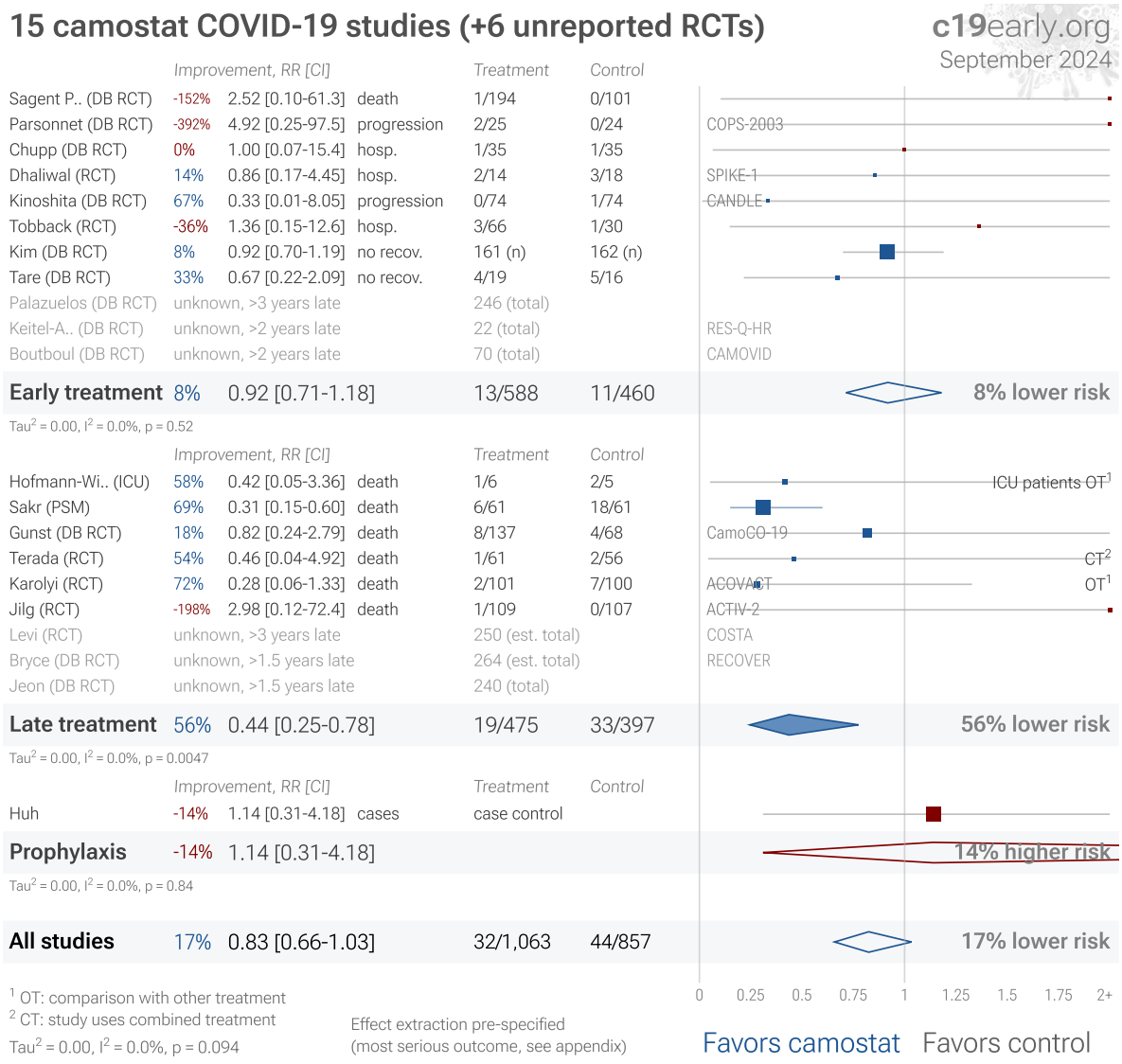


Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

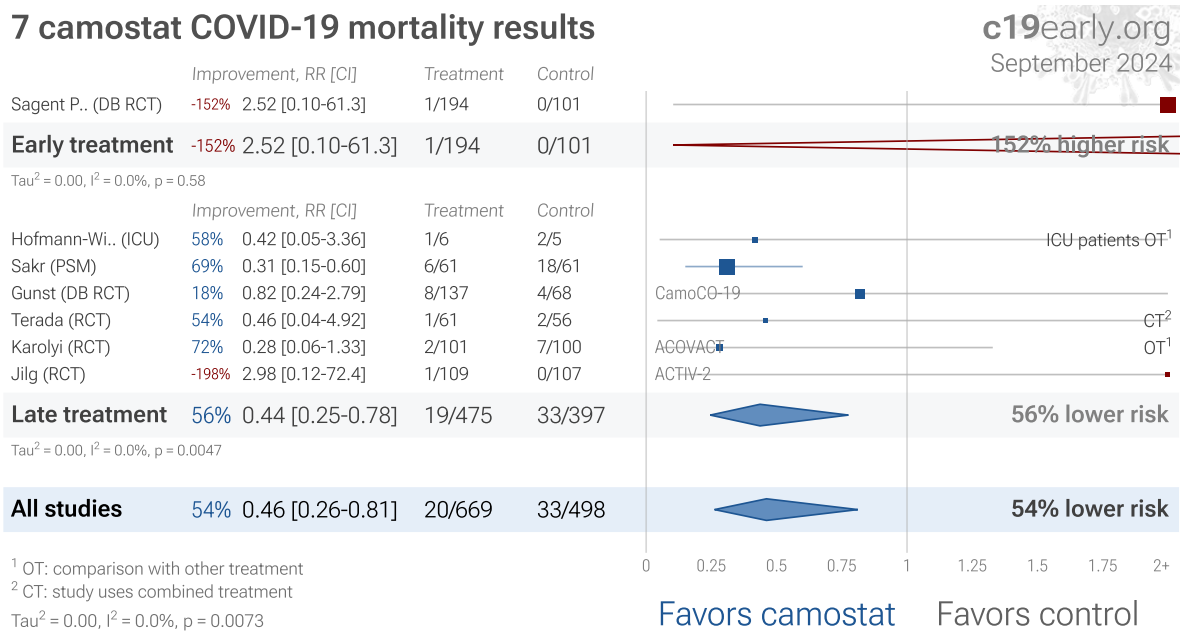


Figure 5. Random effects meta-analysis for mortality results.

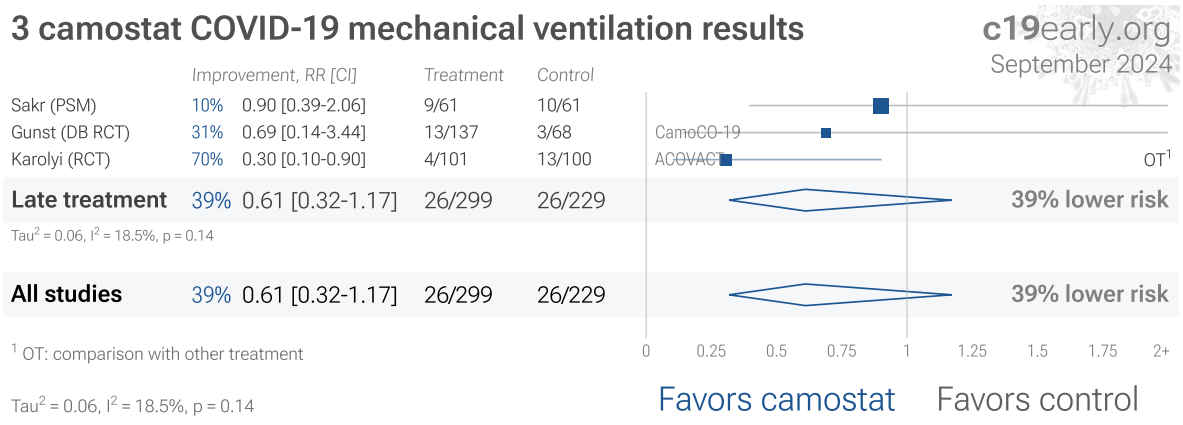


Figure 6. Random effects meta-analysis for ventilation.

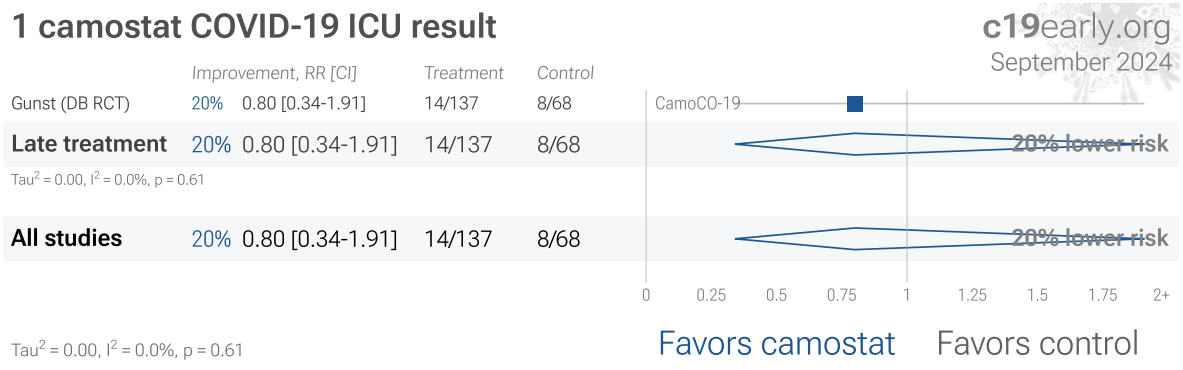


Figure 7. Random effects meta-analysis for ICU admission.

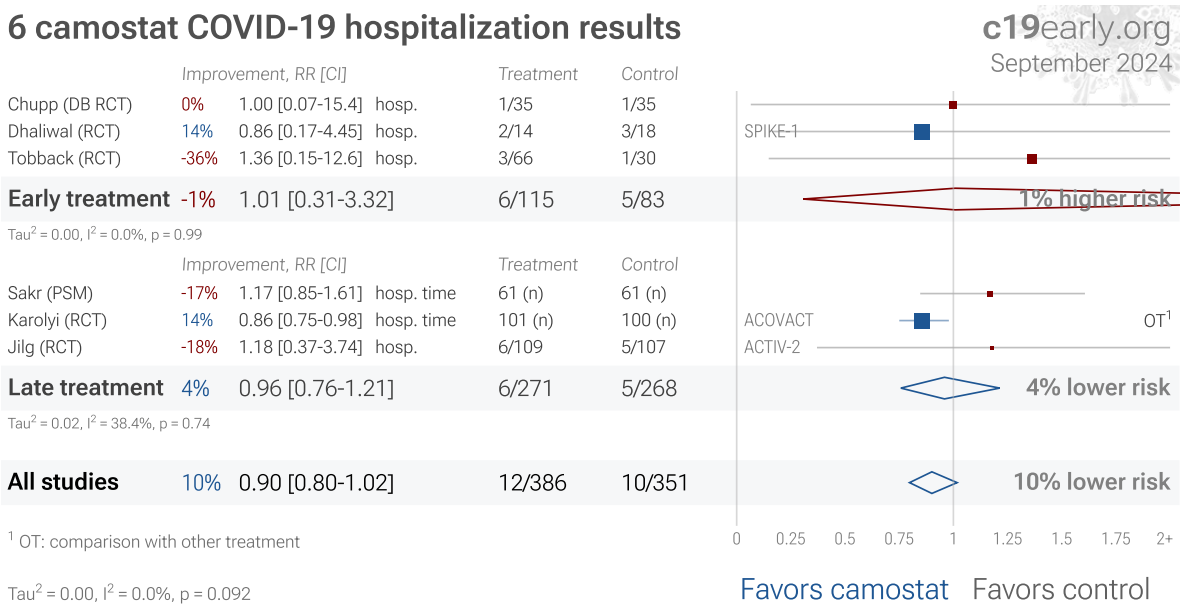


Figure 8. Random effects meta-analysis for hospitalization.

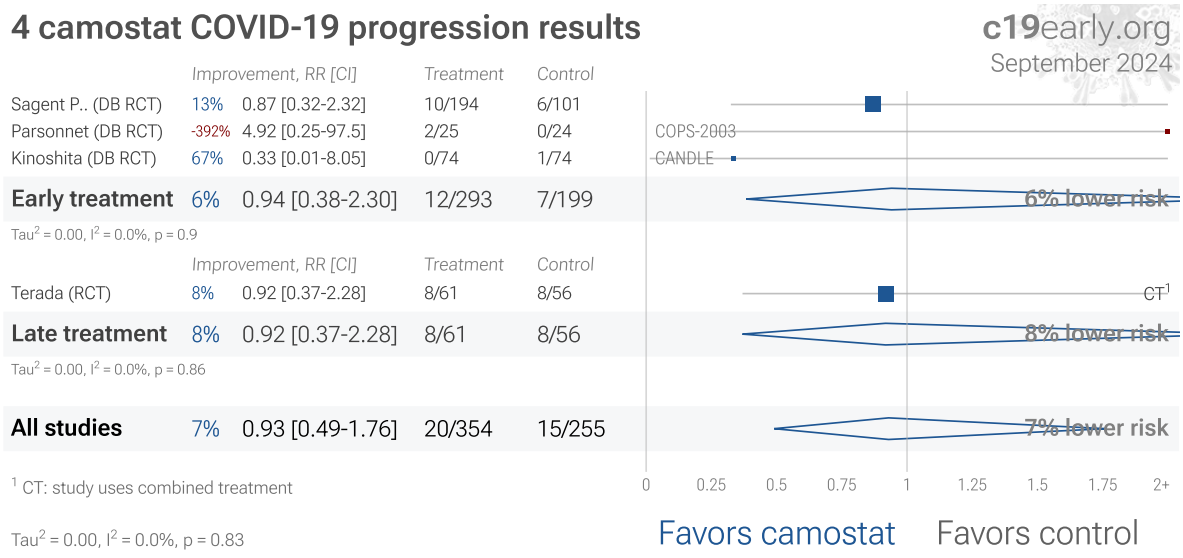


Figure 9. Random effects meta-analysis for progression.

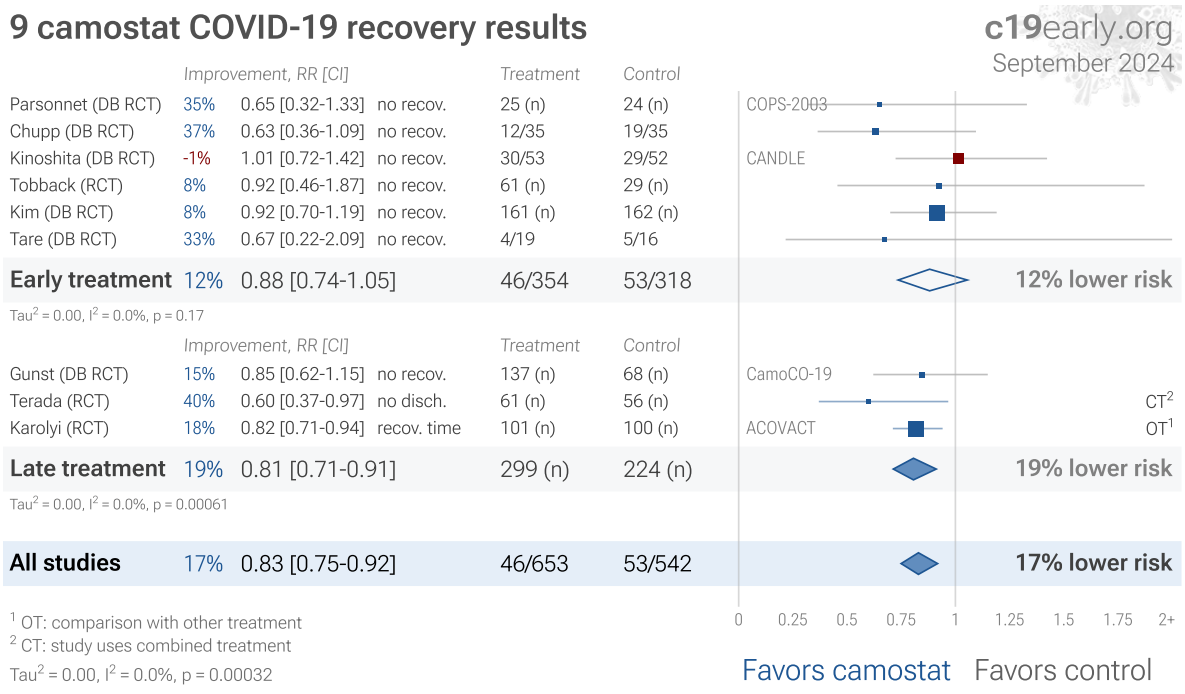


Figure 10. Random effects meta-analysis for recovery.

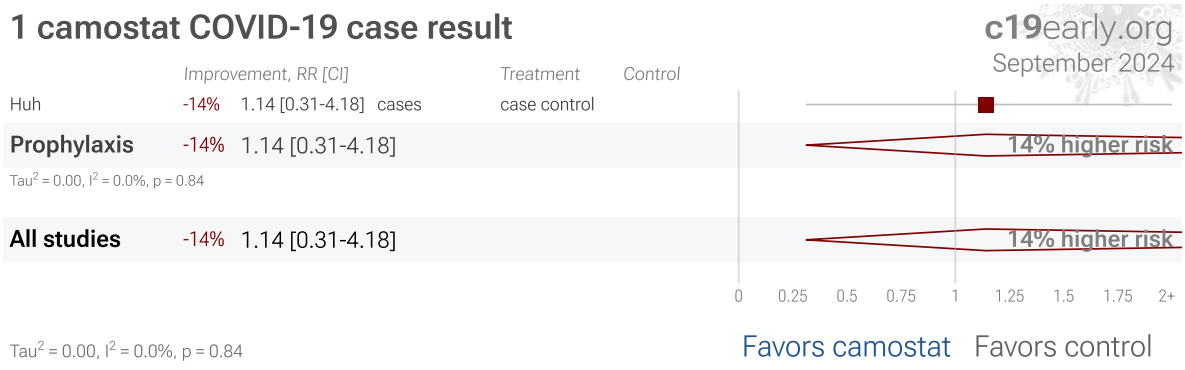


Figure 11. Random effects meta-analysis for cases.

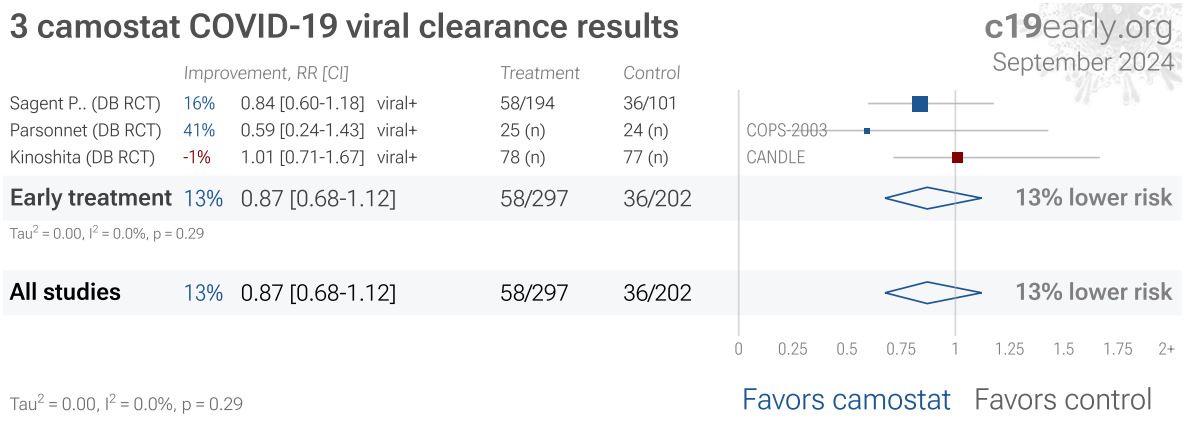


Figure 12. Random effects meta-analysis for viral clearance.

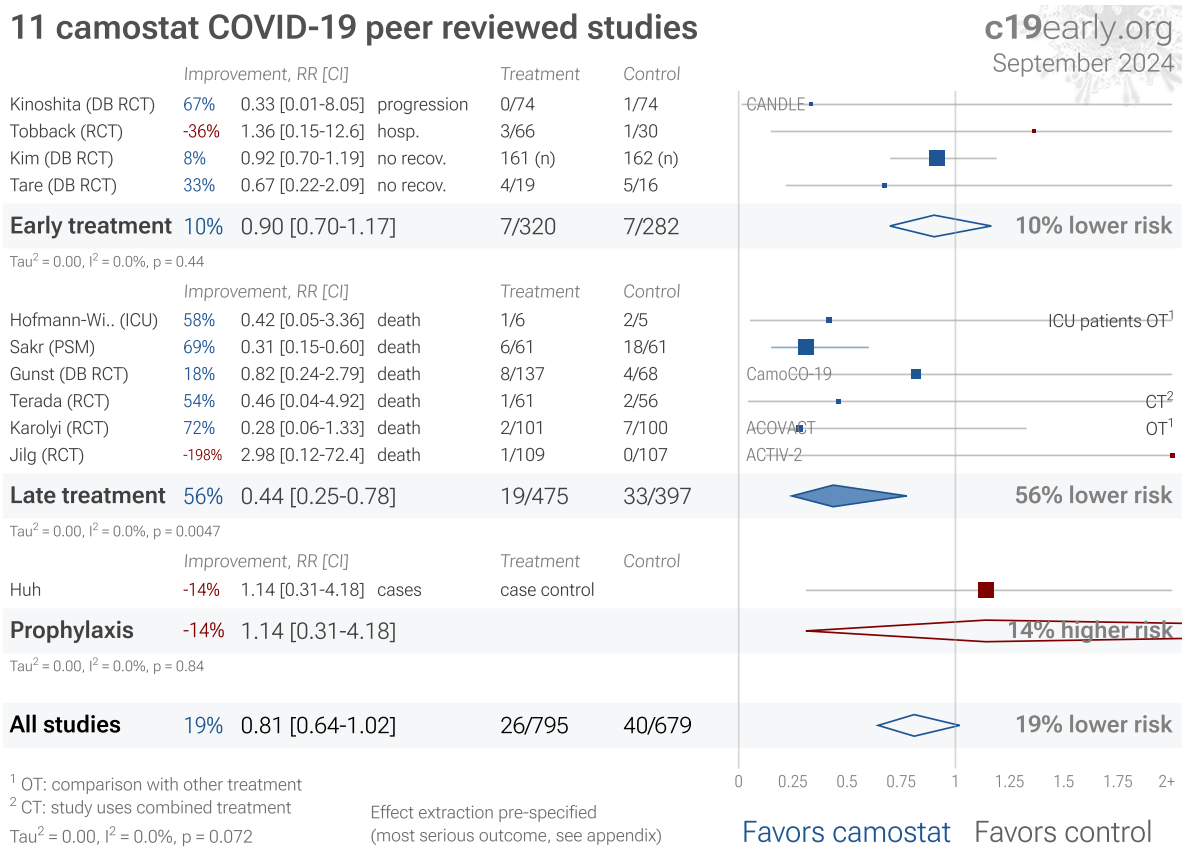


Figure 13. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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 14 shows a comparison of results for RCTs and non-RCT studies. Figure 15, 16, and 17 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

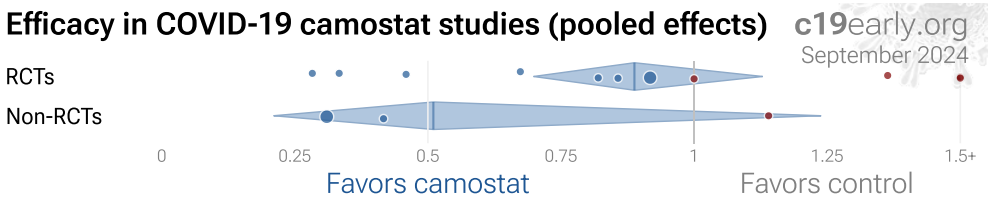


Figure 14. **Results for RCTs and non-RCT studies.**

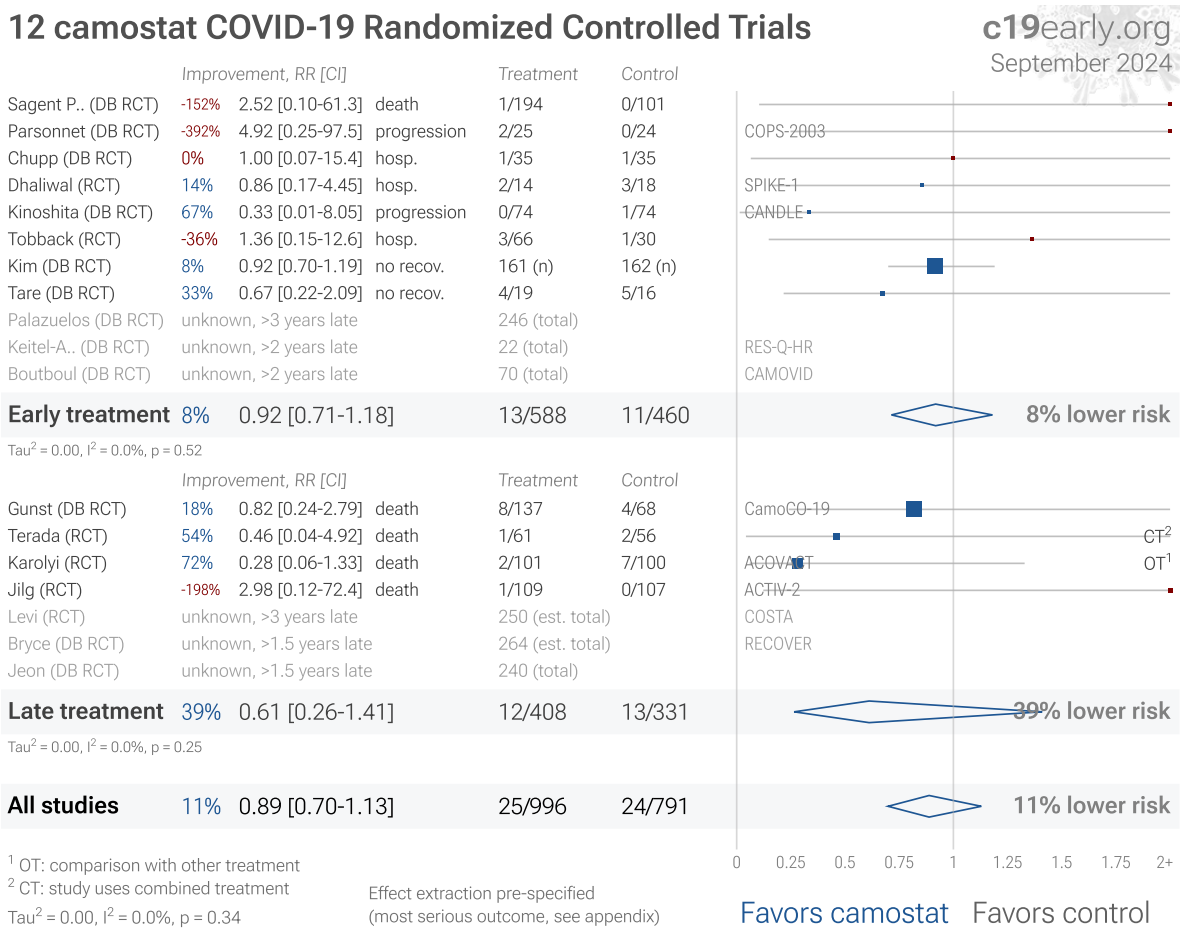


Figure 15. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

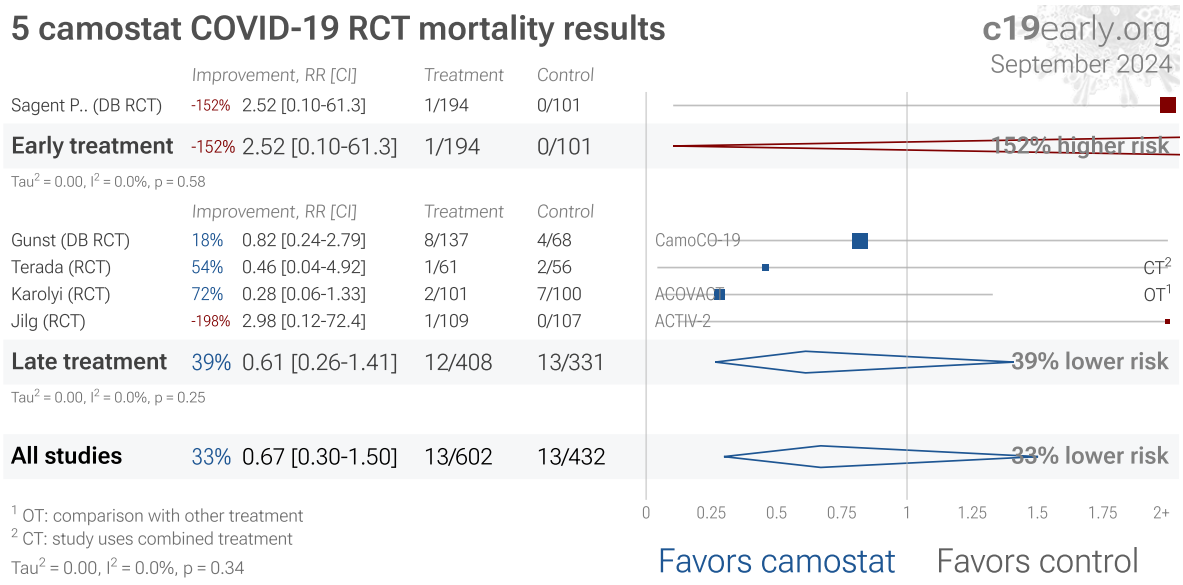


Figure 16. Random effects meta-analysis for RCT mortality results.

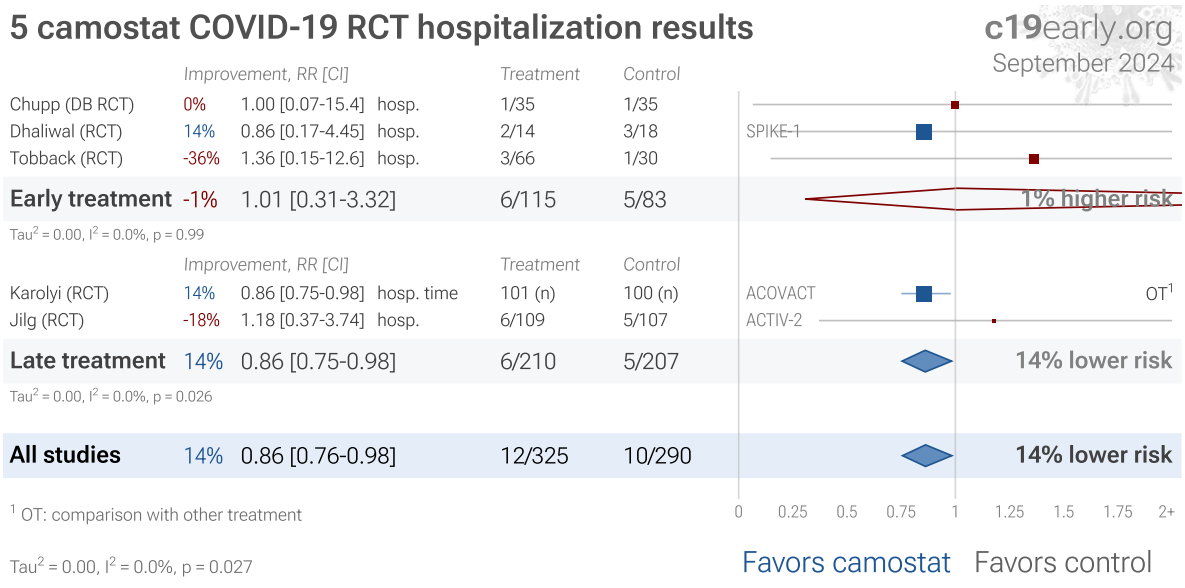


Figure 17. **Random effects meta-analysis for RCT hospitalization results.**

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[21], and analysis of double-blind RCTs has identified extreme levels of bias[22]. 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 92 treatments we have analyzed, 64% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

RCT bias for widely available treatments. RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for camostat are more likely to enroll low-risk participants that do not need treatment to recover,

making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT 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 [27,28].

Using all studies identifies efficacy 7+ months faster (8+ months for low-cost treatments). Currently, 48 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, 30 have been confirmed in RCTs, with a mean delay of 6.9 months. When considering only low cost treatments, 25 have been confirmed with a delay of 8.2 months. For the 18 unconfirmed treatments, 4 have zero RCTs to date. The point estimates for the remaining 14 are all consistent with the overall results (benefit or harm), with 12 showing >20%. The only treatment showing >10% efficacy for all studies, but <10% for RCTs is sotrovimab.

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.

Unreported RCTs

6 camostat RCTs have not reported results [29-34]. The trials report a total of 1,092 patients, with 4 trials having actual enrollment of 578, and the remainder estimated. The results are delayed from 1.5 years to over 3 years.

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 [35,36]. Baloxavir marboxil 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 [37]
<24 hours	-33 hours symptoms [38]
24-48 hours	-13 hours symptoms [38]
Inpatients	-2.5 hours to improvement [39]

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

Figure 18 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 92 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

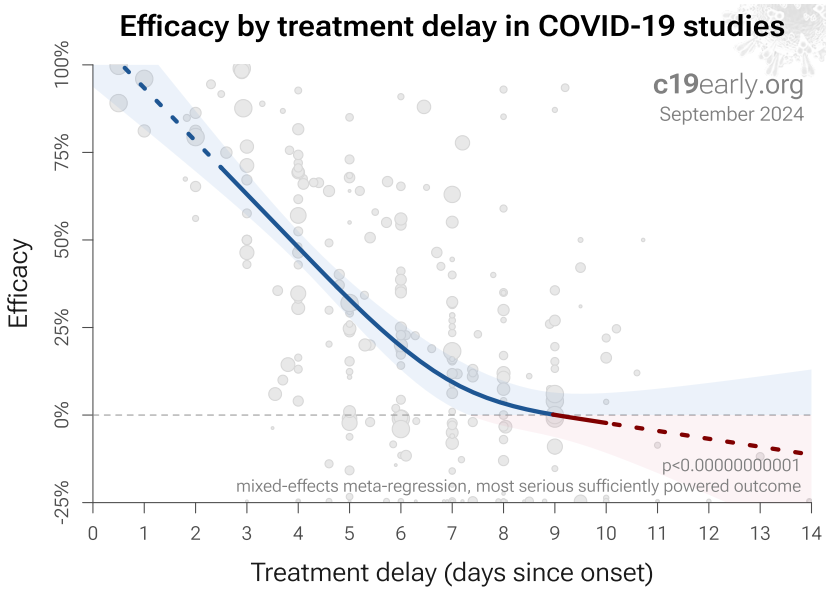


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 92 treatments.

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 [41], for example the Gamma variant shows significantly different characteristics [42-45]. 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 [46,47].

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 [48-58], 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 92 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 19 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly,

Figure 20 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 21 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 $p = 0.0000013$ to $p = 0.000000015$.

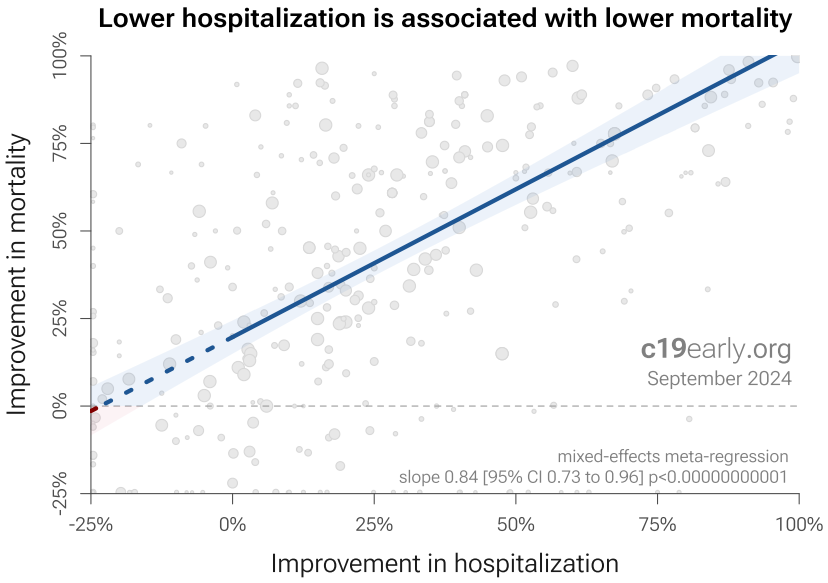


Figure 19. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

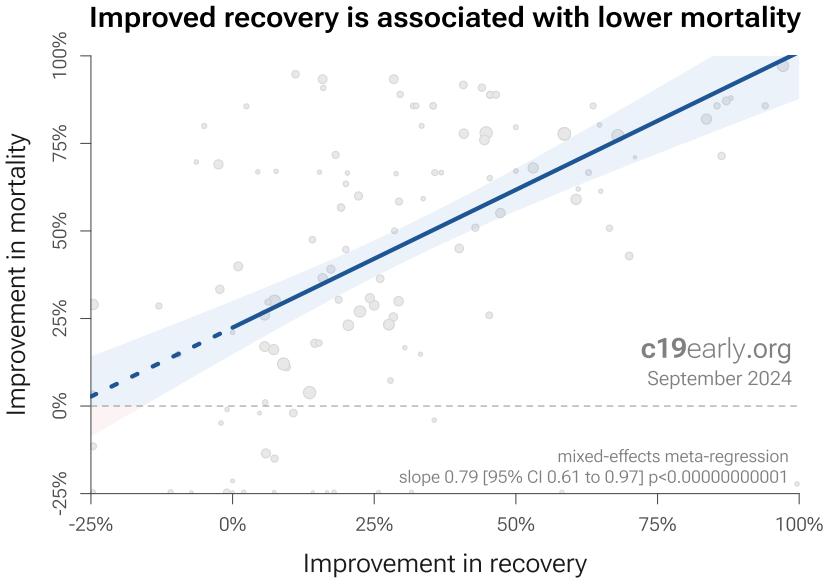


Figure 20. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

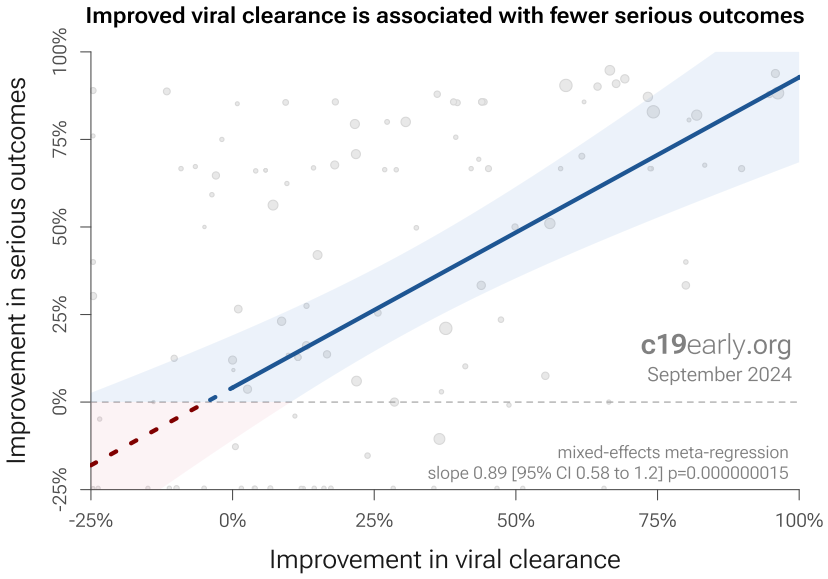


Figure 19. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (6 months for RCTs). Currently, 48 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 89% of these have been confirmed with one or more specific outcomes, with a mean delay of 5.1 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 6.4 months. Figure 22 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

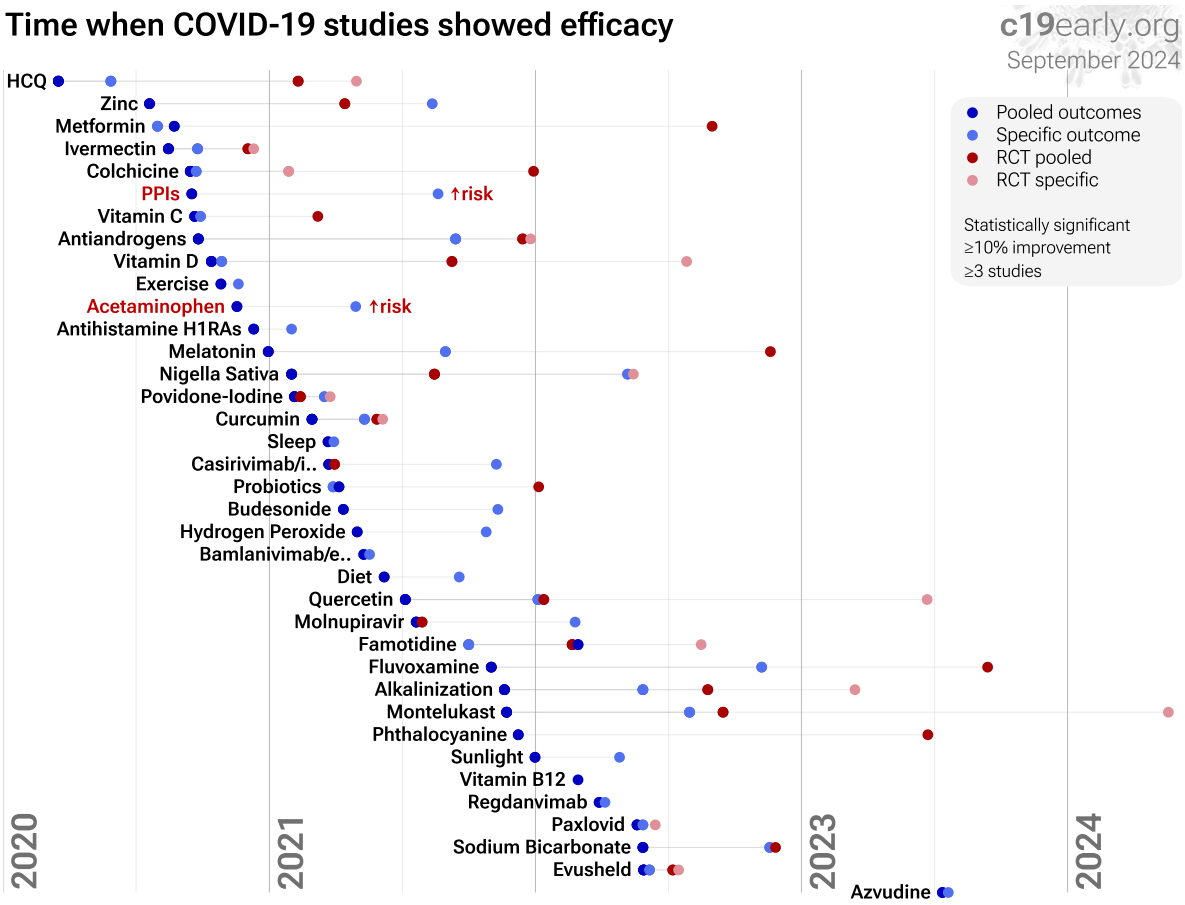


Figure 22. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results[62-65]. For camostat, 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 23 shows a scatter plot of results for prospective and retrospective studies. 67% of retrospective studies report positive effects, compared to 58% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 58% improvement, compared to 11% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.

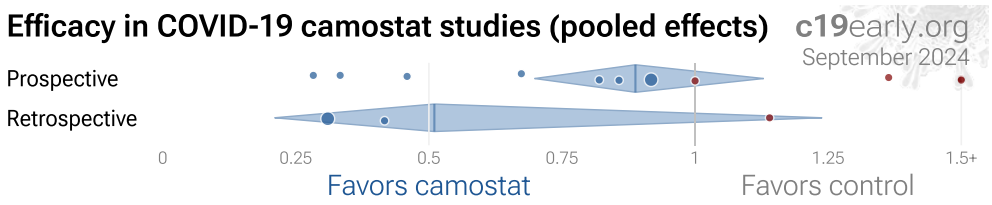


Figure 23. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 24 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 $p < 0.05$[66-73]. 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.

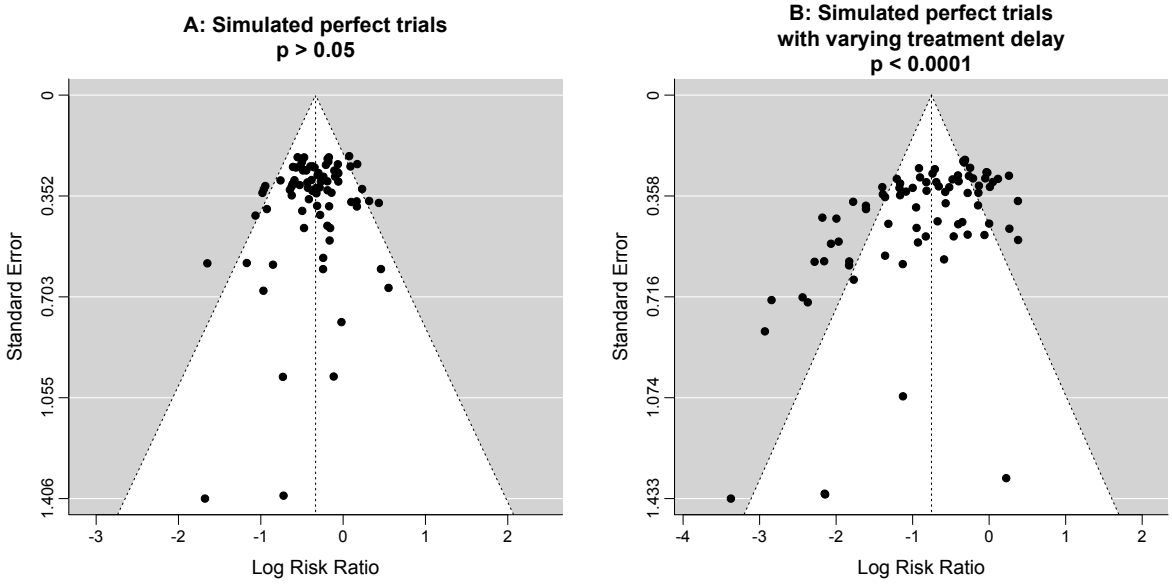


Figure 24. **Example funnel plot analysis for simulated perfect trials.**

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Camostat for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 camostat trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for

example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all camostat trials represent the optimal conditions for efficacy.

Limitations. Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses 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[48-58]. 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 15 studies compare against other treatments, which may reduce the effect seen. 1 of 15 studies combine treatments. The results of camostat alone may differ. 1 of 12 RCTs use combined treatment.

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[13-17], providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk[18], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 25 shows an overview of the results for camostat in the context of multiple COVID-19 treatments, and Figure 26 shows a plot of efficacy vs. cost for COVID-19 treatments.

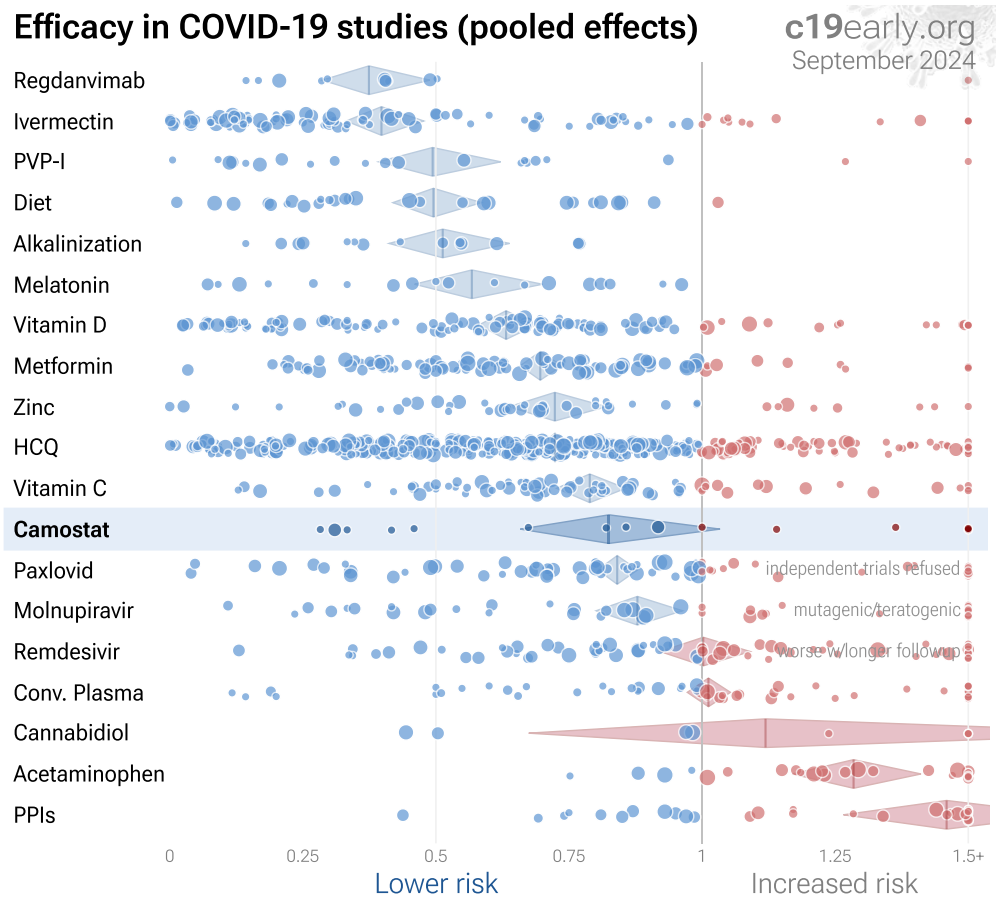


Figure 25. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy[74].

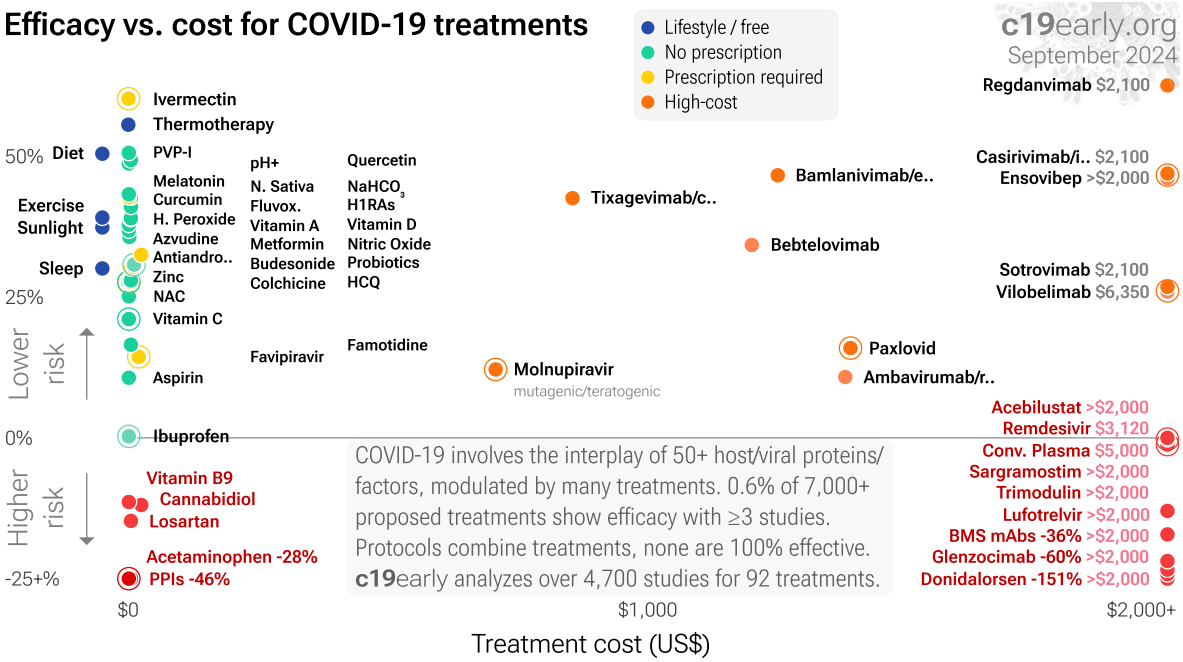


Figure 26. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Statistically significant lower risk is seen for mortality and recovery. 3 studies from 3 independent teams in 3 countries show significant improvements. Meta analysis using the most serious outcome reported shows 17% [-3-34%] lower risk, without reaching statistical significance. Results are similar for peer-reviewed studies and worse for Randomized Controlled Trials.

Study Notes

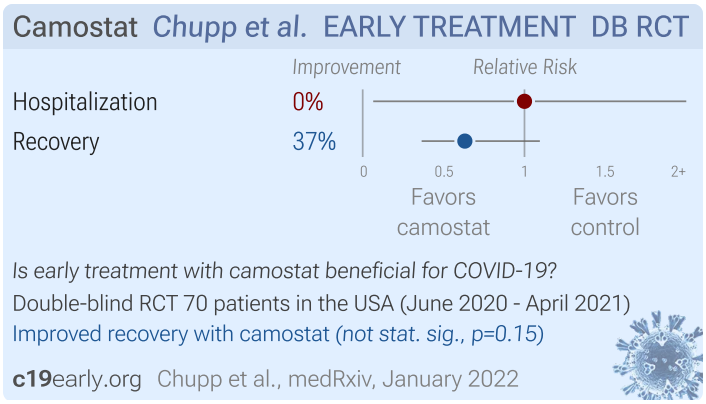
Boutboul

Boutboul: 70 patient camostat early treatment RCT with results not reported over 2 years after completion.

Bryce

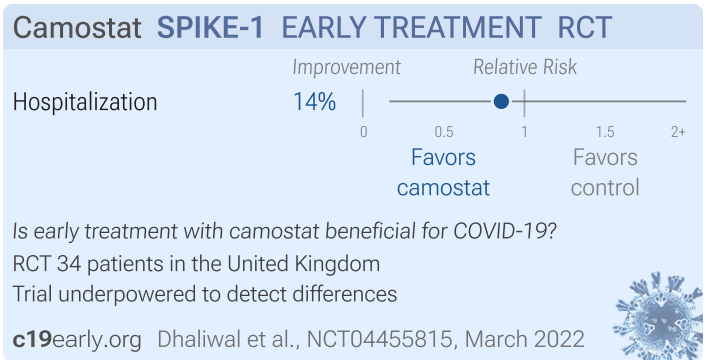
Bryce: RCT 100 patients showing no significant difference with camostat. Results are currently unclear - different mortality numbers are provided for all-cause mortality and mortality rate. The main outcome measures appear to be different due to only including "patients that submitted day 28 outcome data".

Chupp



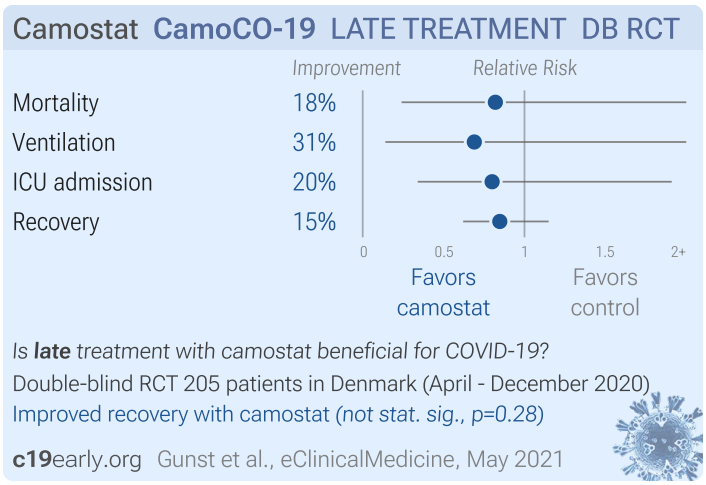
Chupp: RCT 70 outpatients showing significantly lower symptom scores at day 6, faster recovery, and improved taste/smell, and fatigue with camostat treatment. There was no significant difference for viral load. The recovery result is from [76].

Dhaliwal



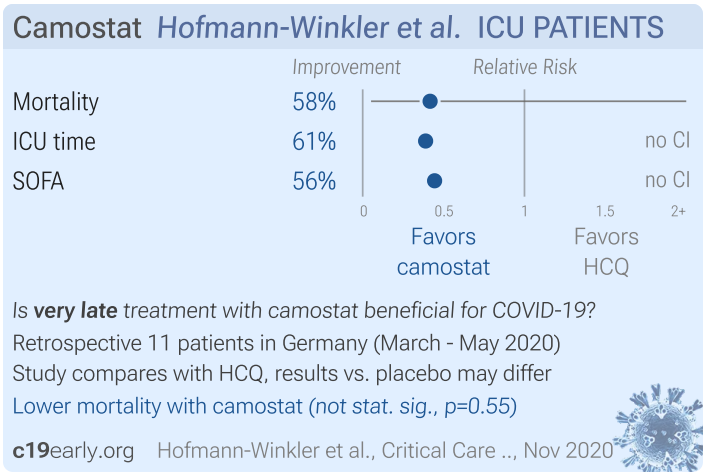
Dhaliwal: Early terminated RCT with 34 patients showing no significant differences with camostat treatment.

Gunst



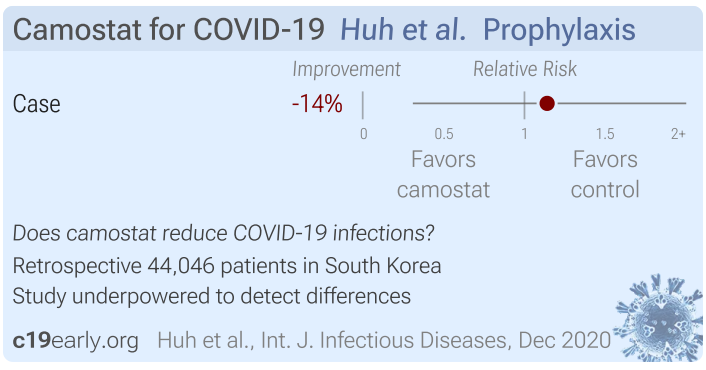
Gunst: RCT 205 hospitalized patients showing no significant benefit with camostat. There was a trend towards lower risk of ICU admission or death in the camostat group (10% vs. 18% for placebo), but the study was not powered for this endpoint. Viral load and inflammatory markers were not significantly different between groups. The study was underpowered due to faster than expected clinical improvement.

Hofmann-Winkler



Hofmann-Winkler: Retrospective 11 critically ill COVID-19 ICU patients with organ failure treated with camostat mesylate (6 patients) or HCQ (5 patients). Over an 8 day period, the severity of COVID-19 decreased in the camostat group as measured by a decline in the SOFA score, inflammatory markers, and improvement in oxygenation. A similar effect was not seen in the HCQ group.

Huh

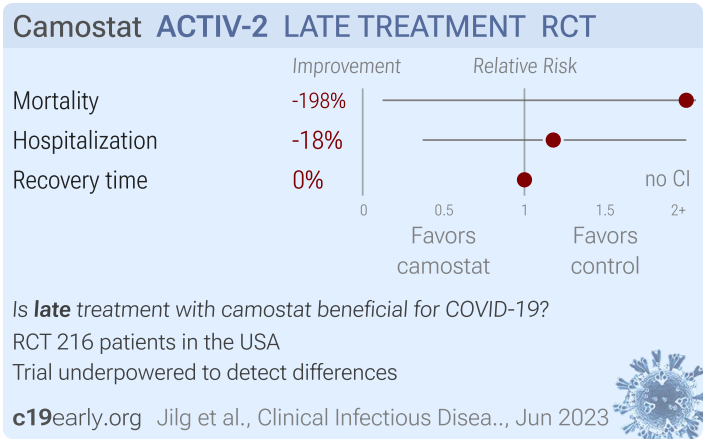


Huh: Retrospective database analysis showing no significant differences with camostat use.

Jeon

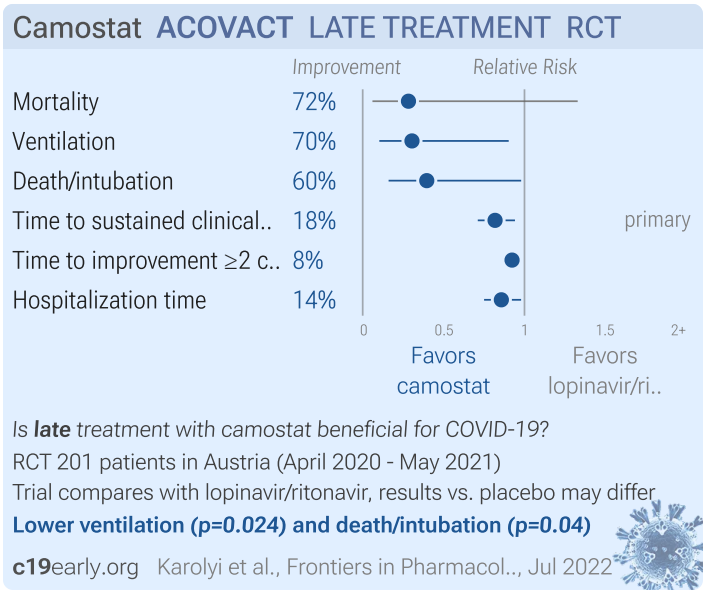
Jeon: 240 patient camostat late treatment RCT with results not reported over 1.5 years after completion.

Jilg



Jilg: RCT 216 patients, 55% >5 days from symptom onset, showing no significant difference with camostat treatment.

Karolyi

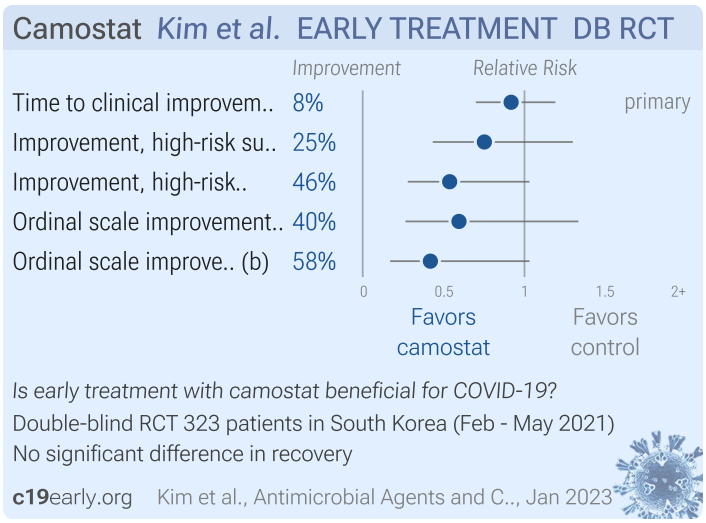


Karolyi: RCT 201 hospitalized COVID-19 patients showing faster clinical improvement, less progression to mechanical ventilation or death, and shorter hospital stay with camostat mesylate compared to lopinavir/ritonavir. There was also a trend towards lower 29-day mortality with camostat. Authors note that the lopinavir/ritonavir dose likely did not reach effective levels, so it may be considered similar to a placebo group.

Keitel-Anselmino

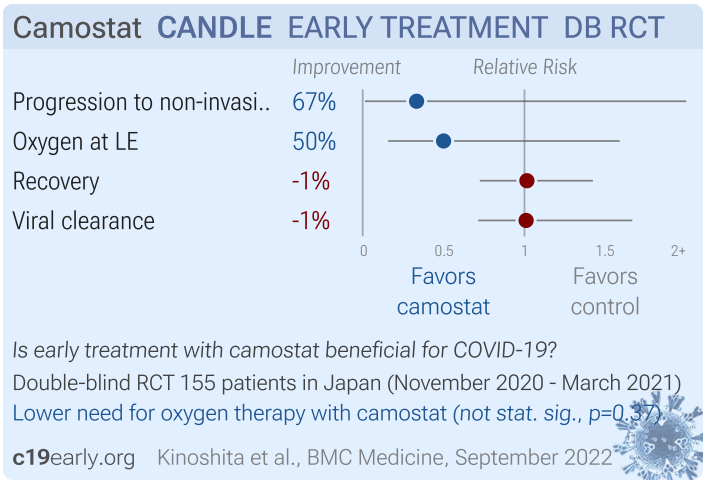
Keitel-Anselmino: 22 patient camostat early treatment RCT with results not reported over 2 years after completion.

Kim



Kim: Double-blind RCT with 342 mild to moderate COVID-19 outpatients in South Korea, showing no significant difference in time to clinical improvement with camostat mesylate. In a post-hoc subgroup analysis of high-risk patients, there were non-statistically significant trends towards faster improvement in ordinal scale scores and subjective symptom scores at day 7 with treatment. Viral cultures suggested faster viral clearance with treatment, without statistical significance.

Kinoshita



Kinoshita: RCT 155 hospitalized patients showing no significant differences with camostat.

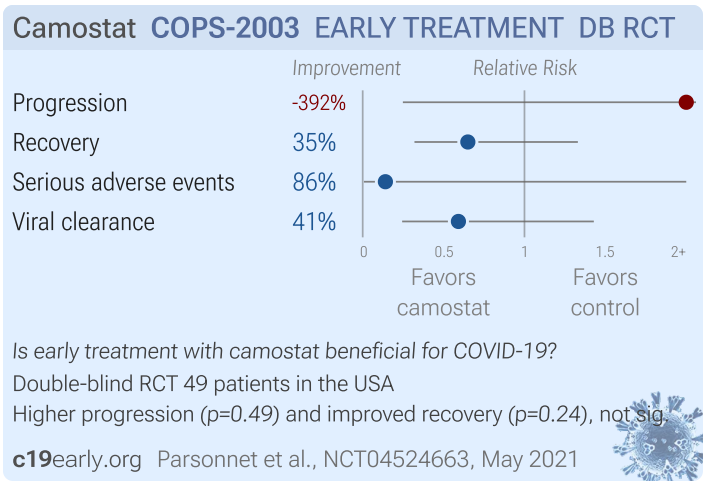
Levi

Levi: Estimated 250 patient camostat late treatment RCT with results not reported over 3 years after estimated completion.

Palazuelos

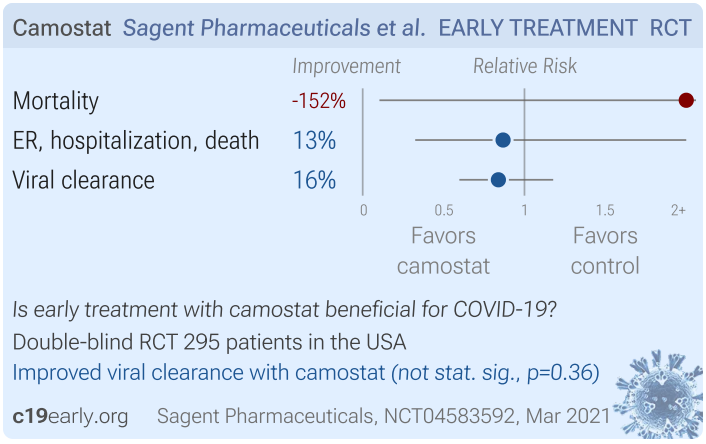
Palazuelos: 246 patient camostat early treatment RCT with results not reported over 3 years after completion.

Parsonnet



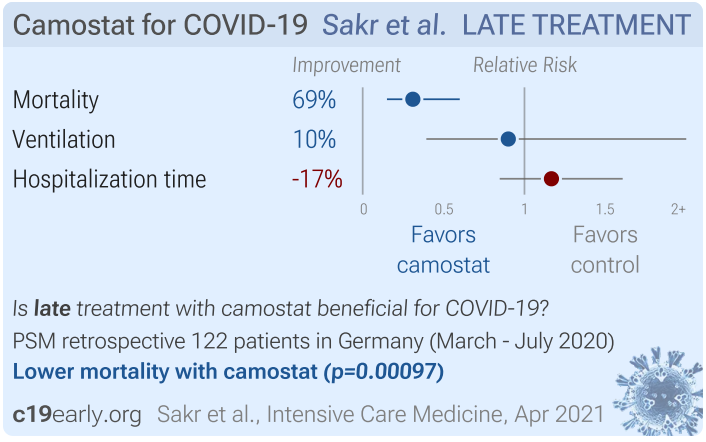
Parsonnet: RCT 49 outpatients in the USA, showing no significant differences with camostat treatment.

Sagent Pharmaceuticals



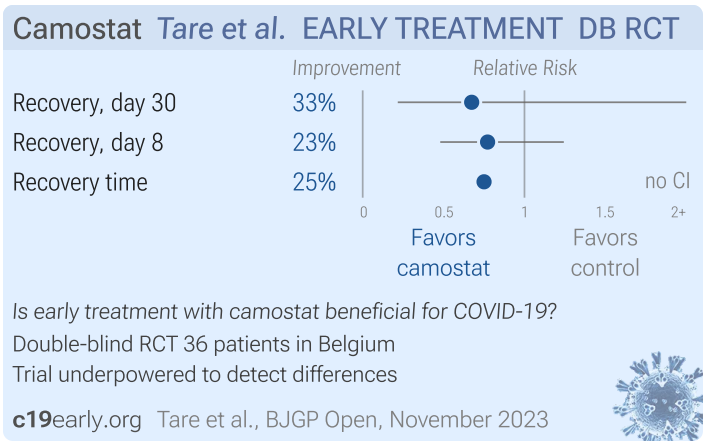
Sagent Pharmaceuticals: RCT 295 outpatients in the USA, showing no significant differences with camostat.

Sakr



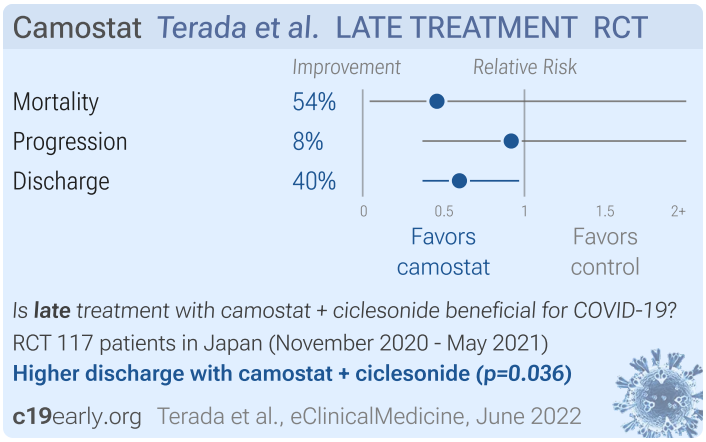
Sakr: Retrospective 371 critically ill COVID-19 patients showing lower mortality with camostat mesylate treatment.

Tare



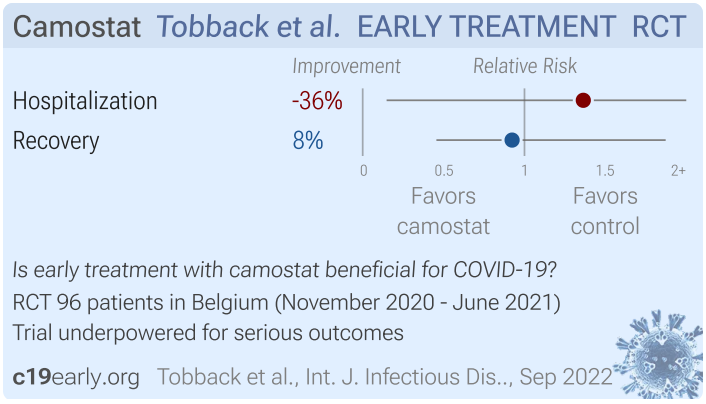
Tare: Small early terminated RCT showing better recovery with camostat treatment, without statistical significance.

Terada



Terada: RCT 117 hospitalized patients with moderate COVID-19 pneumonia in Japan, showing a shorter time to discharge with favipiravir, camostat, and ciclesonide combination therapy compared to favipiravir monotherapy. Subgroup analysis showed greater benefit in patients ≤60 years old and those with less severe disease not requiring oxygen. There were no significant differences between groups in clinical findings, laboratory values, or adverse events. The mortality numbers in the main results table and the text are different, without explanation.

Tobback



Tobback: RCT 90 outpatients showing no significant difference in viral load or time to clinical improvement with camostat mesylate. The trial was discontinued early and did not reach the intended sample size. Authors note that combining camostat with a cathepsin inhibitor may improve efficacy.

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 camostat 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 camostat for COVID-19 that report a comparison with a control group are included in the main analysis. 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 [91]. 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 [94]. 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 (3.12.5) with scipy (1.14.1), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.2), and plotly (5.23.0).

Forest plots are computed using PythonMeta [95] 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 (4.4.0) using the metafor (4.6-0) and rms (6.8-0) 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 [35,36].

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/cmmeta.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.

Boutboul, 12/2/2021, Double Blind Randomized Controlled Trial, placebo-controlled, France, trial NCT04608266 (history) (CAMOVID).	70 patient RCT with results unknown and over 2 years late.
Chupp, 1/31/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 24 authors, study period June 2020 - April 2021, trial NCT04353284 (history).	risk of hospitalization, no change, RR 1.00, $p = 1.00$, treatment 1 of 35 (2.9%), control 1 of 35 (2.9%).
	risk of no recovery, 36.8% lower, RR 0.63, $p = 0.15$, treatment 12 of 35 (34.3%), control 19 of 35 (54.3%), NNT 5.0.
Dhaliwal, 3/3/2022, Randomized Controlled Trial, United Kingdom, preprint, 1 author, trial NCT04455815 (history) (SPIKE-1).	risk of hospitalization, 14.3% lower, RR 0.86, $p = 1.00$, treatment 2 of 14 (14.3%), control 3 of 18 (16.7%), NNT 42.
Keitel-Anselmino, 10/29/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Germany, trial NCT04681430 (history) (RES-Q-HR).	22 patient RCT with results unknown and over 2 years late.
Kim, 1/24/2023, Double Blind Randomized Controlled Trial, placebo-controlled, South Korea, peer-reviewed, median age 53.0, mean age 51.4, 34 authors, study period February 2021 - May 2021, trial NCT04521296 (history).	time to clinical improvement, 8.3% lower, HR 0.92, $p = 0.54$, treatment 161, control 162, inverted to make HR<1 favor treatment, primary outcome.
	improvement, 24.8% lower, HR 0.75, $p = 0.31$, treatment 109, control 104, inverted to make HR<1 favor treatment, high-risk subgroup, day 7.
	improvement, 46.2% lower, HR 0.54, $p = 0.06$, treatment 77, control 78, inverted to make HR<1 favor treatment, high-risk subgroup, mFAS, day 7.
	ordinal scale improvement, 40.5% lower, HR 0.60, $p = 0.21$, treatment 109, control 104, inverted to make HR<1 favor treatment, high-risk subgroup, day 7.
	ordinal scale improvement, 58.2% lower, HR 0.42, $p = 0.06$, treatment 77, control 78, inverted to make HR<1 favor treatment, high-risk subgroup, mFAS, day 7.
Kinoshita, 9/27/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Japan, peer-reviewed, 14 authors, study period November 2020 - March 2021, trial NCT04657497 (history) (CANDLE).	progression to non-invasive ventilation or high-flow oxygen, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 74 (0.0%), control 1 of 74 (1.4%), NNT 74, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), Figure 4.

	oxygen at LE, 50.0% lower, RR 0.50, *p* = 0.37, treatment 4 of 74 (5.4%), control 8 of 74 (10.8%), NNT 18, Figure 4.
	risk of no recovery, 1.5% higher, RR 1.01, *p* = 1.00, treatment 30 of 53 (56.6%), control 29 of 52 (55.8%).
	risk of no viral clearance, 1.0% higher, HR 1.01, *p* = 0.97, treatment 78, control 77, inverted to make HR<1 favor treatment.
Palazuelos, 6/10/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, trial NCT04530617 (history).	246 patient RCT with results unknown and over 3 years late.
Parsonnet, 5/15/2021, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 1 author, trial NCT04524663 (history) (COPS-2003).	risk of progression, 392.0% higher, RR 4.92, *p* = 0.49, treatment 2 of 25 (8.0%), control 0 of 24 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of no recovery, 35.0% lower, HR 0.65, *p* = 0.24, treatment 25, control 24, Cox proportional hazards.
	serious adverse events, 86.0% lower, RR 0.14, *p* = 0.11, treatment 0 of 25 (0.0%), control 3 of 24 (12.5%), NNT 8.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no viral clearance, 40.8% lower, HR 0.59, *p* = 0.24, treatment 25, control 24, inverted to make HR<1 favor treatment, Cox proportional hazards.
Sagent Pharmaceuticals, 3/31/2021, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 1 author, trial NCT04583592 (history).	risk of death, 152.1% higher, RR 2.52, *p* = 1.00, treatment 1 of 194 (0.5%), control 0 of 101 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 28.
	ER, hospitalization, death, 13.2% lower, RR 0.87, *p* = 0.79, treatment 10 of 194 (5.2%), control 6 of 101 (5.9%), NNT 127.
	risk of no viral clearance, 16.1% lower, RR 0.84, *p* = 0.36, treatment 58 of 194 (29.9%), control 36 of 101 (35.6%), NNT 17, day 15.
Tare, 11/20/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Belgium, peer-reviewed, median age 55.0, 11 authors, trial NCT04730206 (history).	risk of no recovery, 32.6% lower, RR 0.67, *p* = 0.70, treatment 4 of 19 (21.1%), control 5 of 16 (31.2%), NNT 9.8, day 30.
	risk of no recovery, 22.8% lower, RR 0.77, *p* = 0.48, treatment 11 of 19 (57.9%), control 12 of 16 (75.0%), NNT 5.8, day 8.
Tobback, 9/30/2022, Randomized Controlled Trial, placebo-controlled, Belgium, peer-reviewed, median age 40.0, 13 authors, study period November 2020 - June 2021, trial NCT04625114 (history).	risk of hospitalization, 36.4% higher, RR 1.36, *p* = 1.00, treatment 3 of 66 (4.5%), control 1 of 30 (3.3%).
	risk of no recovery, 7.7% lower, HR 0.92, *p* = 0.84, treatment 61, control 29, adjusted per study, inverted to make HR<1 favor treatment, multivariable, Cox proportional hazards.

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.

Bryce, 9/15/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, trial NCT04470544 (history) (RECOVER).	Estimated 264 patient RCT with results unknown and over 1.5 years late.
Gunst, 5/31/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Denmark, peer-reviewed, median age 61.0, 39 authors, study period 4 April, 2020 - 31 December, 2020, trial NCT04321096 (history) (CamoCO-19).	risk of death, 18.0% lower, HR 0.82, $p = 0.75$, treatment 8 of 137 (5.8%), control 4 of 68 (5.9%), Cox proportional hazards.
	risk of mechanical ventilation, 31.0% lower, HR 0.69, $p = 0.65$, treatment 13 of 137 (9.5%), control 3 of 68 (4.4%), Cox proportional hazards.
	risk of ICU admission, 20.0% lower, HR 0.80, $p = 0.61$, treatment 14 of 137 (10.2%), control 8 of 68 (11.8%), NNT 65, adjusted per study, multivariable, Cox proportional hazards.
	risk of no recovery, 15.3% lower, HR 0.85, $p = 0.28$, treatment 137, control 68, adjusted per study, inverted to make HR<1 favor treatment, multivariable, Cox proportional hazards.
Hofmann-Winkler, 11/16/2020, retrospective, Germany, peer-reviewed, 19 authors, study period March 2020 - May 2020, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 58.3% lower, RR 0.42, $p = 0.55$, treatment 1 of 6 (16.7%), control 2 of 5 (40.0%), NNT 4.3.
Jeon, 12/9/2022, Double Blind Randomized Controlled Trial, placebo-controlled, South Korea, trial NCT04713176 (history).	240 patient RCT with results unknown and over 1.5 years late.
Jilg, 6/5/2023, Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, median age 37.0, 39 authors, trial NCT04518410 (history) (ACTIV-2).	risk of death, 198.2% higher, RR 2.98, $p = 1.00$, treatment 1 of 109 (0.9%), control 0 of 107 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 17.8% higher, RR 1.18, $p = 1.00$, treatment 6 of 109 (5.5%), control 5 of 107 (4.7%).
Karolyi, 7/22/2022, Randomized Controlled Trial, Austria, peer-reviewed, mean age 58.6, 21 authors, study period 20 April, 2020 - 14 May, 2021, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04351724 (history) (ACOVACT).	risk of death, 71.7% lower, RR 0.28, $p = 0.10$, treatment 2 of 101 (2.0%), control 7 of 100 (7.0%), NNT 20.
	risk of mechanical ventilation, 69.5% lower, RR 0.30, $p = 0.02$, treatment 4 of 101 (4.0%), control 13 of 100 (13.0%), NNT 11.
	risk of death/intubation, 60.4% lower, RR 0.40, $p = 0.04$, treatment 6 of 101 (5.9%), control 15 of 100 (15.0%), NNT 11.
	relative time to sustained clinical improvement, 18.2% lower, relative time 0.82, $p = 0.005$, treatment 101, control 100, primary outcome.

	relative time to improvement ≥2 categories, 7.7% lower, relative time 0.92, $p = 0.02$, treatment 101, control 100.
	hospitalization time, 14.3% lower, relative time 0.86, $p = 0.02$, treatment 101, control 100.
Levi, 12/11/2020, Randomized Controlled Trial, placebo-controlled, trial NCT04355052 (history) (COSTA).	Estimated 250 patient RCT with results unknown and over 3 years late.
Sakr, 4/12/2021, retrospective, Germany, peer-reviewed, 11 authors, study period 16 March, 2020 - 19 July, 2020.	risk of death, 69.0% lower, HR 0.31, $p < 0.001$, treatment 6 of 61 (9.8%), control 18 of 61 (29.5%), NNT 5.1, adjusted per study, propensity score matching, multivariable, Cox proportional hazards.
	risk of mechanical ventilation, 10.0% lower, RR 0.90, $p = 1.00$, treatment 9 of 61 (14.8%), control 10 of 61 (16.4%), NNT 61, propensity score matching.
	hospitalization time, 16.7% higher, relative time 1.17, $p = 0.35$, treatment 61, control 61, propensity score matching.
Terada, 6/3/2022, Randomized Controlled Trial, Japan, peer-reviewed, mean age 57.0, 11 authors, study period 11 November, 2020 - 31 May, 2021, this trial uses multiple treatments in the treatment arm (combined with ciclesonide) - results of individual treatments may vary, trial jRCTs031200196.	risk of death, 54.1% lower, RR 0.46, $p = 0.61$, treatment 1 of 61 (1.6%), control 2 of 56 (3.6%), NNT 52.
	risk of progression, 8.2% lower, RR 0.92, $p = 1.00$, treatment 8 of 61 (13.1%), control 8 of 56 (14.3%), NNT 85.
	risk of no hospital discharge, 40.2% lower, HR 0.60, $p = 0.04$, treatment 61, control 56, inverted to make HR<1 favor treatment.

Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Huh, 12/19/2020, retrospective, database analysis, South Korea, peer-reviewed, 8 authors.	risk of case, 14.0% higher, OR 1.14, $p = 0.84$, treatment 3 of 7,341 (0.0%) cases, 29 of 36,705 (0.1%) controls, adjusted per study, case control OR, multivariable.

Supplementary Data

Supplementary Data

Footnotes

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

References

1. ***Yang*** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.
2. ***Scardua-Silva*** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.
3. ***Hampshire*** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.
4. ***Duloquin*** et al., *Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2*, Journal of Clinical Medicine, doi:10.3390/jcm13051397.
5. ***Sodagar*** et al., *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, Biomolecules, doi:10.3390/biom12070971.
6. ***Sagar*** et al., *COVID-19-associated cerebral microbleeds in the general population*, Brain Communications, doi:10.1093/braincomms/fcae127.
7. ***Verma*** et al., *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, bioRxiv, doi:10.1101/2024.06.02.596989.
8. ***Panagea*** et al., *Neurocognitive Impairment in Long COVID: A Systematic Review*, Archives of Clinical Neuropsychology, doi:10.1093/arclin/acae042.
9. ***Ariza*** et al., *COVID-19: Unveiling the Neuropsychiatric Maze—From Acute to Long-Term Manifestations*, Biomedicines, doi:10.3390/biomedicines12061147.
10. ***Eberhardt*** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.
11. ***Van Tin*** et al., *Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF-κB Signaling*, Cells, doi:10.3390/cells13161331.
12. ***Borka Balas*** et al., *COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice*, Reviews in Cardiovascular Medicine, doi:10.31083/j.rcm2405125.
13. ***Malone*** et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, Nature Reviews Molecular Cell Biology, doi:10.1038/s41580-021-00432-z.
14. ***Murigneux*** et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.
15. ***Lv*** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.
16. ***Lui*** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.
17. ***Niarakis*** et al., *Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1282859.
18. ***c19early.org***, c19early.org/treatments.html.
19. ***Zeraatkar*** et al., *Consistency of covid-19 trial preprints with published reports and impact for decision making: retrospective review*, BMJ Medicine, doi:10.1136/bmjmed-2022-0003091.

20. **Davidson** et al., *No evidence of important difference in summary treatment effects between COVID-19 preprints and peer-reviewed publications: a meta-epidemiological study*, Journal of Clinical Epidemiology, doi:10.1016/j.jclinepi.2023.08.011.

21. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings, Second Edition*, doi:10.1002/9780470691922.

22. **Gøtzsche**, P., *Bias in double-blind trials*, Doctoral Thesis, University of Copenhagen, www.scientificfreedom.dk/2023/05/16/bias-in-double-blind-trials-doctoral-thesis/.

23. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.

24. **Concato** et al., NEJM, 342:1887-1892, doi:10.1056/NEJM200006223422507.

25. **Anglemyer** et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews 2014, Issue 4, doi:10.1002/14651858.MR000034.pub2.

26. **Lee** et al., *Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines*, Arch Intern Med., 2011, 171:1, 18-22, doi:10.1001/archinternmed.2010.482.

27. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.

28. **Nichol** et al., *Challenging issues in randomised controlled trials*, Injury, 2010, doi: 10.1016/j.injury.2010.03.033, www.injuryjournal.com/article/S0020-1383(10)00233-0/fulltext.

29. **Bryce** et al., *RECOVER: Phase 2 Randomized, Double-Blind Trial TREating Hospitalized Patients With COVID-19 With Camostat MesilatE, a TMPRSS2 Inhibitor*, NCT04470544, clinicaltrials.gov/study/NCT04470544.

30. **Jeon** et al., *A Double-blind, Randomized, Placebo-controlled, Multi-center, Phase III Study to Evaluate the Efficacy and Safety of DW1248 With Remdesivir in Severe COVID-19 Patients*, NCT04713176, clinicaltrials.gov/study/NCT04713176.

31. **Boutboul** et al., *A Multicenter Randomized Trial to Evaluate the Efficacy and Safety of Camostat Mesylate for the Treatment of SARS-CoV-2 Infection - COVID-19 in Ambulatory Adult Patients (CAMOVID)*, NCT04608266, clinicaltrials.gov/study/NCT04608266.

32. **Keitel-Anselmino** et al., *Reconvalescent Plasma / Camostat Mesylate Early in Sars-CoV-2 Q-PCR (COVID-19) Positive High-risk Individuals*, NCT04681430, clinicaltrials.gov/study/NCT04681430.

33. **Palazuelos** et al., *Randomized, Double-blind, Placebo-controlled, Multicenter, Multi-arm, Phase II Trial of Novel Agents for the Treatment of Mild to Moderate COVID-19 Positive Outpatients*, NCT04530617, clinicaltrials.gov/study/NCT04530617.

34. **Levi** et al., *Open Label Study to Compare Efficacy, Safety and Tolerability of Hydroxychloroquine Combined With Azithromycin Compared to Hydroxychloroquine Combined With Camostat Mesylate and to "no Treatment" in SARS CoV 2 Virus (COSTA)*, NCT04355052, clinicaltrials.gov/study/NCT04355052.

35. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.

36. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.

37. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.

38. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.

39. **Kumar** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, The Lancet Infectious Diseases, doi:10.1016/S1473-3099(21)00469-2.

40. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.3071.

41. **Korves** et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, medRxiv, doi:10.1101/2024.03.08.24303818.

42. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.

43. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.

44. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, medRxiv, doi:10.1101/2021.08.27.21262754.

45. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, Research Square, doi:10.21203/rs.3.rs-910467/v1.

46. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.

47. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.

48. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.

49. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.

50. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.

51. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.

52. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.

53. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.

54. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.

55. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.

56. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.

57. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.

58. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.

59. **Williams**, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.

60. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, Rapid Communications in Mass Spectrometry, doi:10.1002/rcm.9358.

61. **Singh** et al., *The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis*, Journal of Antimicrobial Chemotherapy, doi:10.1093/jac/dkae045.

62. **Meneguesso**, A., *Médica defende tratamento precoce da Covid-19*, www.youtube.com/watch?v=X5FCrIm_19U.

63. **Boulware**, D., *Comments regarding paper rejection*, twitter.com/boulware_dr/status/1311331372884205570.

64. **Meeus**, G., *Online Comment*, twitter.com/gertmeeus_MD/status/1386636373889781761.

65. **twitter.com**, twitter.com/KashPrime/status/1768487878454124914.

66. **Rothstein**, H., *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*, www.wiley.com/en-ae/Publication+Bias+in+Meta+Analysis:+Prevention,+Assessment+and+Adjustments-p-9780470870143.

67. **Stanley** et al., *Meta-regression approximations to reduce publication selection bias*, Research Synthesis Methods, doi:10.1002/jrsm.1095.

68. **Rücker** et al., *Arcsine test for publication bias in meta-analyses with binary outcomes*, Statistics in Medicine, doi:10.1002/sim.2971.

69. **Peters**, J., *Comparison of Two Methods to Detect Publication Bias in Meta-analysis*, JAMA, doi:10.1001/jama.295.6.676.

70. **Moreno** et al., *Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study*, BMC Medical Research Methodology, doi:10.1186/1471-2288-9-2.

71. **Macaskill** et al., *A comparison of methods to detect publication bias in meta-analysis*, Statistics in Medicine, doi:10.1002/sim.698.

72. **Egger** et al., *Bias in meta-analysis detected by a simple, graphical test*, BMJ, doi:10.1136/bmj.315.7109.629.

73. **Harbord** et al., *A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints*, Statistics in Medicine, doi:10.1002/sim.2380.

74. **c19early.org (B)**, c19early.org/timeline.html.

75. **Chupp** et al., *A Phase 2 Randomized, Double-Blind, Placebo-controlled Trial of Oral Camostat Mesylate for Early Treatment of COVID-19 Outpatients Showed Shorter Illness Course and Attenuation of Loss of Smell and Taste*, medRxiv, doi:10.1101/2022.01.28.22270035.

76. **bmcinfectdis.biomedcentral.com**, bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-024-09468-w.

77. **Dhaliwal** et al., *A Randomised Phase II Trial in Early COVID-19, Assessing Use of Camostat by Blocking SARS-CoV-2 Spike Protein-initiated Membrane Fusion*, NCT04455815, clinicaltrials.gov/study/NCT04455815.

78. **Gunst** et al., *Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial*, eClinicalMedicine, doi:10.1016/j.eclinm.2021.100849.

79. **Hofmann-Winkler** et al., *Camostat Mesylate May Reduce Severity of Coronavirus Disease 2019 Sepsis: A First Observation*, Critical Care Explorations, doi:10.1097/CCE.0000000000000284.

80. **Huh** et al., *Association of prescribed medications with the risk of COVID-19 infection and severity among adults in South Korea*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2020.12.041.

81. **Jilg** et al., *One Week of Oral Camostat Versus Placebo in Nonhospitalized Adults With Mild-to-Moderate Coronavirus Disease 2019 (COVID-19): A Randomized Controlled Phase 2 Trial*, Clinical Infectious Diseases, doi:10.1093/cid/ciad342.

82. **Karolyi** et al., *Camostat Mesylate Versus Lopinavir/Ritonavir in Hospitalized Patients With COVID-19—Results From a Randomized, Controlled, Open Label, Platform Trial (ACOVACT)*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.870493.

83. **Kim** et al., *A Double-Blind, Randomized, Placebo-Controlled, Phase II Clinical Study To Evaluate the Efficacy and Safety of Camostat Mesylate (DWJ1248) in Adult Patients with Mild to Moderate COVID-19*, Antimicrobial Agents and Chemotherapy, doi:10.1128/aac.00452-22.

84. **Kinoshita** et al., *A multicenter, double-blind, randomized, parallel-group, placebo-controlled study to evaluate the efficacy and safety of camostat mesilate in patients with COVID-19 (CANDLE study)*, BMC Medicine, doi:10.1186/s12916-022-02518-7.

85. **Parsonnet** et al., *A Phase 2 Randomized, Double Blinded, Placebo Controlled Study of Oral Camostat Mesilate Compared to Standard of Care in Subjects With Mild-Moderate COVID-19*, NCT04524663, clinicaltrials.gov/study/NCT04524663.

86. **Sagent Pharmaceuticals**, *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy of Camostat Mesilate for Treatment of COVID-19 in Outpatients*, NCT04583592, clinicaltrials.gov/study/NCT04583592.

87. **Sakr** et al., *Camostat mesylate therapy in critically ill patients with COVID-19 pneumonia*, Intensive Care Medicine, doi:10.1007/s00134-021-06395-1.

88. **Tare** et al., *The DAWN antivirals trial: process evaluation of a COVID-19 trial in general practice*, BJGP Open, doi:10.3399/bjgpo.2023.0109.

89. **Terada** et al., *Favipiravir, camostat, and ciclesonide combination therapy in patients with moderate COVID-19 pneumonia with/without oxygen therapy: An open-label, single-center phase 3 randomized clinical trial*, eClinicalMedicine, doi:10.1016/j.eclinm.2022.101484.

90. **Tobback** et al., *Efficacy and safety of camostat mesylate in early COVID-19 disease in an ambulatory setting: a randomized placebo-controlled phase II trial*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2022.06.054.

91. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.

92. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.

93. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.

94. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.

95. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.