

Sargramostim for COVID-19: real-time meta-analysis of 4 studies

@CovidAnalysis, April 2026, Version 1, c19early.org/gmmeta.html

Abstract

Meta-analysis using the most serious outcome reported shows 13% [-31-85%] higher risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 870 patients and only 18 control events for the most serious outcome in trials to date.

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

SARGRAMOSTIM FOR COVID-19 — HIGHLIGHTS

Sargramostim reduces risk with low confidence for viral clearance, however increased risk is seen with very low confidence for progression, recovery, and in pooled analysis.

Real-time updates and corrections with a consistent protocol for 216 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

Serious Outcome Risk



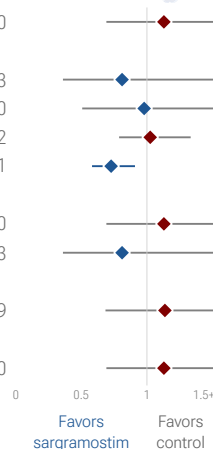
Sargramostim for COVID-19

Improvement, Studies, Patients

All studies	-13%	4	870
Mortality	19%	2	203
Ventilation	2%	3	270
Hospitalization	-3%	1	122
Viral clearance	27%	1	101
RCTs	-13%	4	870
RCT mortality	19%	2	203
Peer-reviewed	-14%	3	789
Late	-13%	4	870

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Relative Risk



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,

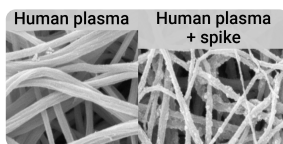


Fig. 1. SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from ¹.

ARDS, neurological injury²⁻¹⁷ and cognitive deficits^{5,10}, cardiovascular complications¹⁸⁻²⁴, DNA damage²⁵⁻²⁷, organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits²⁸—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. 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 400+ host and viral proteins and other factors^{A,29-36}, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 11,000 compounds may reduce COVID-19 risk³⁷, 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 sargramostim 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, individual outcomes, peer-reviewed studies, and Randomized Controlled Trials (RCTs).

Treatment timing

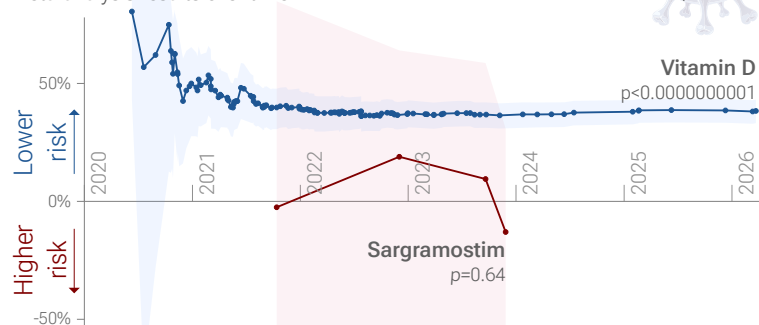
Fig. 2 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early treatment refers to treatment immediately or soon after symptoms appear, while late treatment refers to more delayed treatment. Currently all sargramostim studies use late treatment.

Results

Table 1 summarizes the results for all studies, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Fig. 3 shows a timeline of the results in sargramostim studies. Fig. 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, hospitalization, progression, recovery, viral clearance, and peer reviewed studies.

Evolution of COVID-19 clinical evidence

Meta-analysis results over time



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	Relative Risk	Studies	Patients
All studies	1.13 [0.69-1.85]	4	870
Peer-reviewed	1.14 [0.68-1.89]	3	789
RCTs	1.13 [0.69-1.85]	4	870
Mortality	0.81 [0.36-1.83]	2	203
Ventilation	0.98 [0.51-1.89]	3	270
RCT mortality	0.81 [0.36-1.83]	2	203

Table 1. Random-effects meta-analysis for all studies, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Results show the relative risk with treatment and the 95% confidence interval.

Timeline of COVID-19 sargramostim studies (pooled effects)

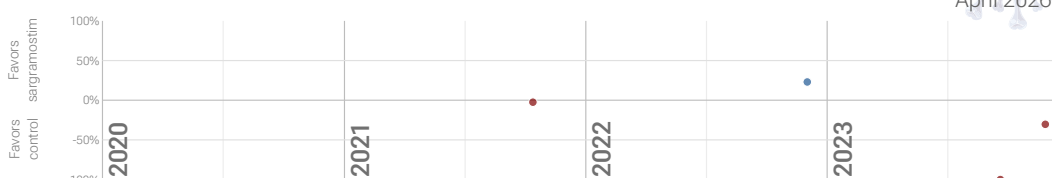


Fig. 3. Timeline of results in sargramostim studies.

4 sargramostim COVID-19 studies

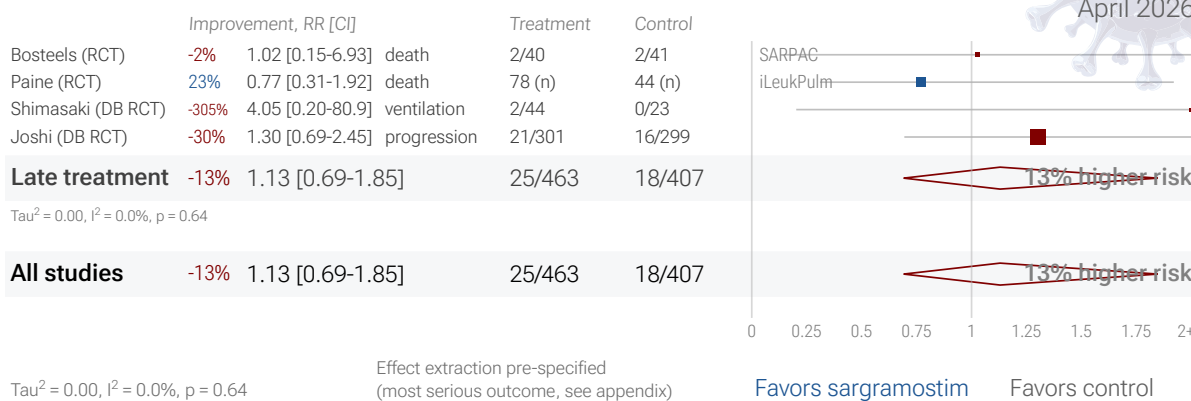


Fig. 4. Random-effects meta-analysis for all studies. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details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

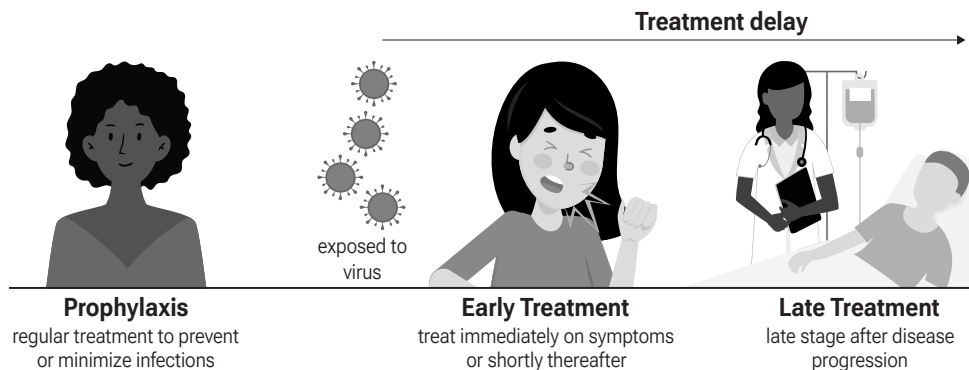


Fig. 2. Treatment stages.

2 sargramostim COVID-19 mortality results

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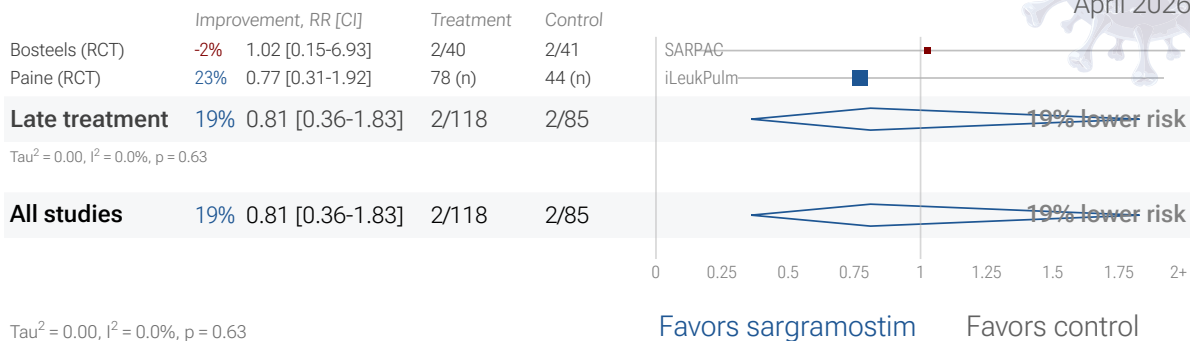


Fig. 5. Random-effects meta-analysis for mortality results.

3 sargramostim COVID-19 mechanical ventilation results

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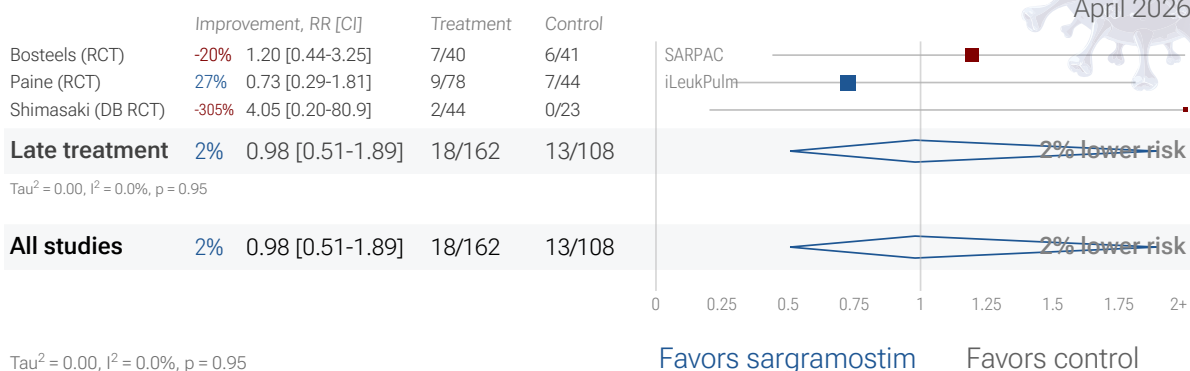


Fig. 6. Random-effects meta-analysis for ventilation.

1 sargramostim COVID-19 hospitalization result

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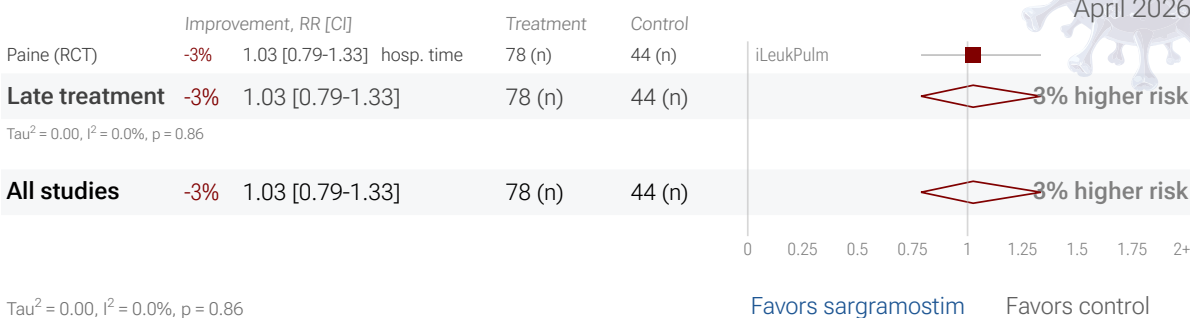


Fig. 7. Random-effects meta-analysis for hospitalization.

1 sargramostim COVID-19 progression result

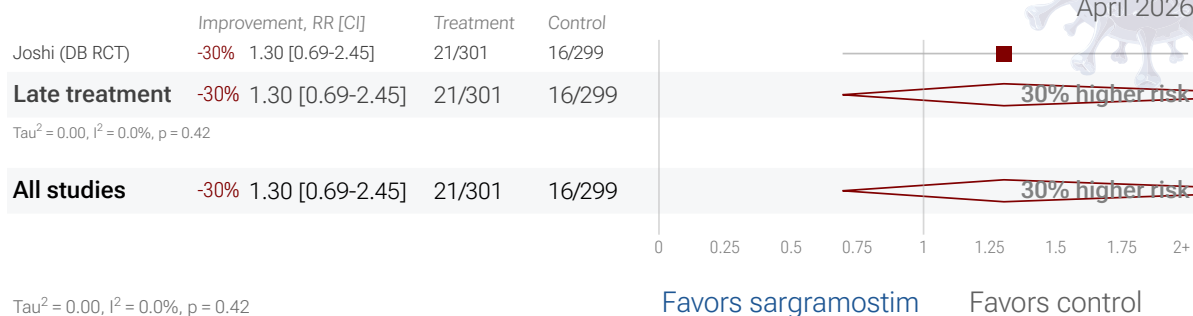


Fig. 8. Random-effects meta-analysis for progression.

1 sargramostim COVID-19 recovery result

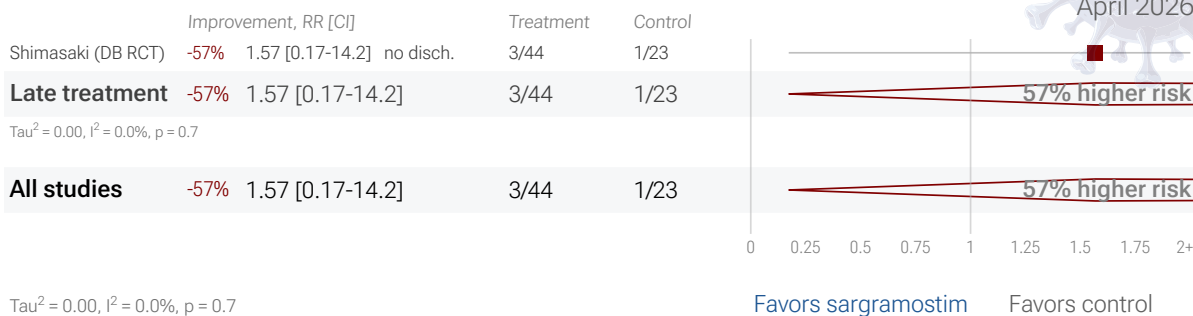


Fig. 9. Random-effects meta-analysis for recovery.

1 sargramostim COVID-19 viral clearance result

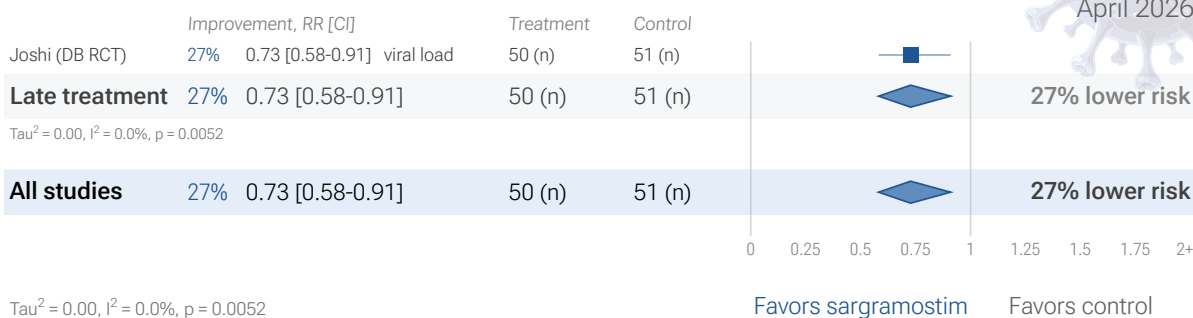


Fig. 10. Random-effects meta-analysis for viral clearance.

3 sargramostim COVID-19 peer reviewed studies

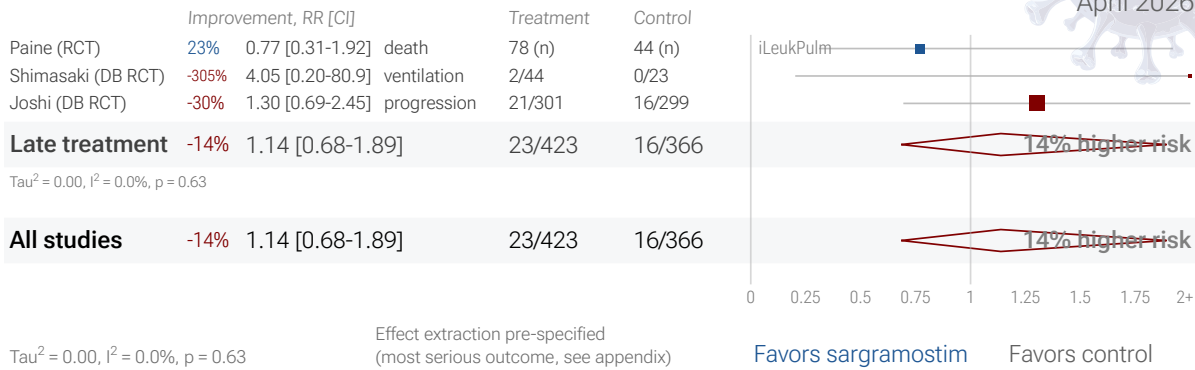


Fig. 11. Random-effects meta-analysis for peer reviewed studies. Zeraatkar et al. analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. 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. 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.

Randomized Controlled Trials (RCTs)

Currently all studies are RCTs.

Media Bias

Low-cost treatments were subject to bias and censorship during the pandemic. Scientific bias is seen in the design, analysis, presentation, and selective reporting of studies, which favored negative results. A similar bias is seen in the media coverage for low-cost treatments. However, the opposite is seen for high-profit treatments.

We analyze media coverage for the 216 treatments we cover using Altmetric⁴⁰, which reports the number of ~12,000 tracked news outlets that covered each study⁴¹. Studies are considered to have received significant media coverage if they were covered by at least 0.5% of the tracked news outlets. Fig. 12 and 13 show the bias toward positive results for high-profit treatments, in contrast to the opposite bias for low-cost treatments. This may result in widespread incorrect perceptions on the relative efficacy of high-profit and low-cost treatments. The impact is significant—increased cost limits the use of high-profit treatments and treatment equity, and high-profit treatments were also more difficult to access, especially for earlier treatment which improves efficacy and minimizes community transmission.

Media coverage for COVID-19 high-profit treatments c19early.org April 2026

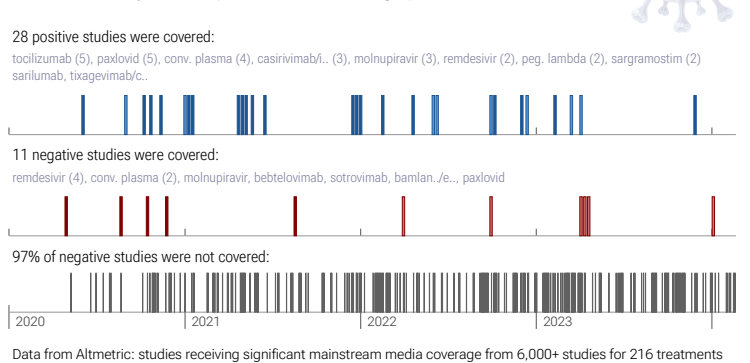


Fig. 12. Mainstream media was biased towards positive results for high-profit treatments.

Media censorship for COVID-19 low-cost treatments c19early.org April 2026

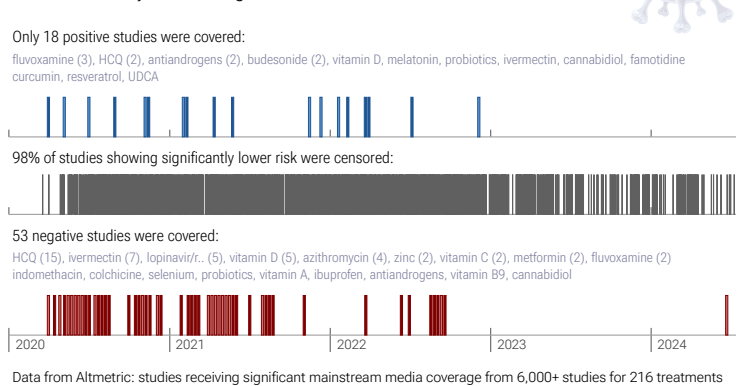


Fig. 13. In contrast to the results for high-profit treatments, mainstream media was biased against positive results for low-cost treatments.

A combination of factors may have led to the media's suppression of low-cost treatments:

- Politicization led to a media environment where coverage was often framed to support a political narrative rather than to provide objective scientific information. As Scott Alexander said: "if you say anything in favor of ivermectin you will be cast out of civilization and thrown into the circle of social hell reserved for Klan members and 1/6 insurrectionists. All the health officials in the world will shout 'horse dewormer!' at you and compare you to Josef Mengele." There was strong social pressure to discredit low-cost treatments.
- Censorship of information conflicting with selected authorities. For example, individuals and organizations presenting conflicting science were often banned on Twitter and YouTube.
- FDA requires "no adequate, approved, and available alternatives" in order to grant an EUA for novel high-profit interventions, creating a strong incentive for authorities to ignore or downplay existing low-cost treatments.
- Regulatory capture biases authorities towards high-profit interventions.
- Authorities ignored most evidence for low-cost treatments, for example the NIH references only 2% of studies in delayed, rarely-updated, biased commentaries with no quantitative analysis.
- Media coverage of science is often not very accurate, e.g., misunderstanding confounding issues. For example the media widely considered the RECOVERY HCQ RCT to be conclusive on efficacy, but very late treatment of late stage patients (mostly on oxygen already) with an excessive toxic dose (shown dangerous in a dose comparison RCT) provides no information on the recommended early/prophylactic treatment. With difficulty in understanding basic confounders like treatment delay and dose, the media may favor deferring to authorities. Many studies for low-cost treatments require greater expertise to analyze. Relatively few journalists have a strong ability to analyze clinical trials and are outnumbered by the rest.
- Substantial funding from pharmaceutical advertising biases editorial decisions towards high-profit interventions.
- PR power - companies/teams with strong PR presence are favored in the media, which correlates with high-profit and high conflict of interest studies.
- The media was very negative in general, inflating risk, fear, and anxieties. A negative bias may improve ratings and revenue, increasing motivation to continue watching coverage. A combination of low-cost treatments greatly reducing risk conflicts with the negative narrative.

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^{42,43}. 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 ⁴⁴
<24 hours	-33 hours symptoms ⁴⁵
24-48 hours	-13 hours symptoms ⁴⁵
Inpatients	-2.5 hours to improvement ⁴⁶

Table 2. Studies of baloxavir marboxil for influenza show that early treatment is more effective.

Fig. 14 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 216 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

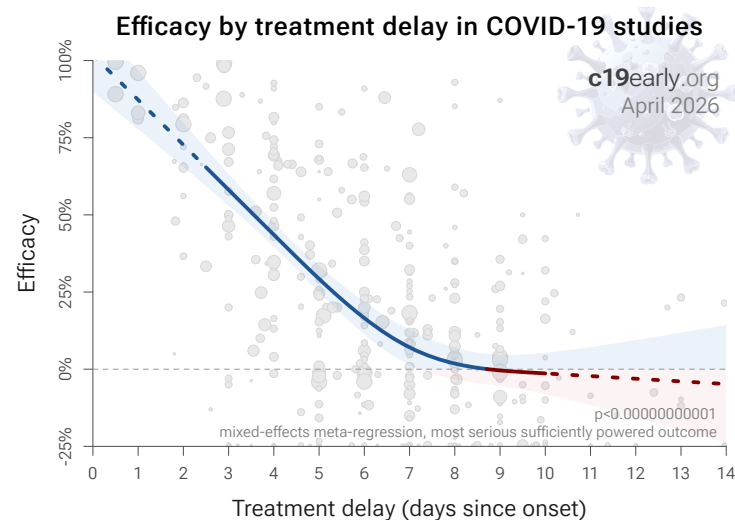


Fig. 14. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 216 treatments.

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.*

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants⁴⁸, for example the Gamma variant shows significantly different characteristics⁴⁹⁻⁵². 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^{53,54}.

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

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 anti-parasitic 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.

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 synergistic⁵⁷⁻⁷³, therefore efficacy may depend strongly on combined treatments.

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. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

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.

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 and safer collection of evidence.

Validating pooled outcome analysis for COVID-19

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.

Analysis of the the association between different outcomes across studies from all 216 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Fig. 15 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.00000000001$). Similarly, Fig. 16 shows that improved recovery is very strongly associated with lower mortality ($p < 0.00000000001$). 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. Fig. 17 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 $p = 0.000000019$ to $p = 0.0000000069$.

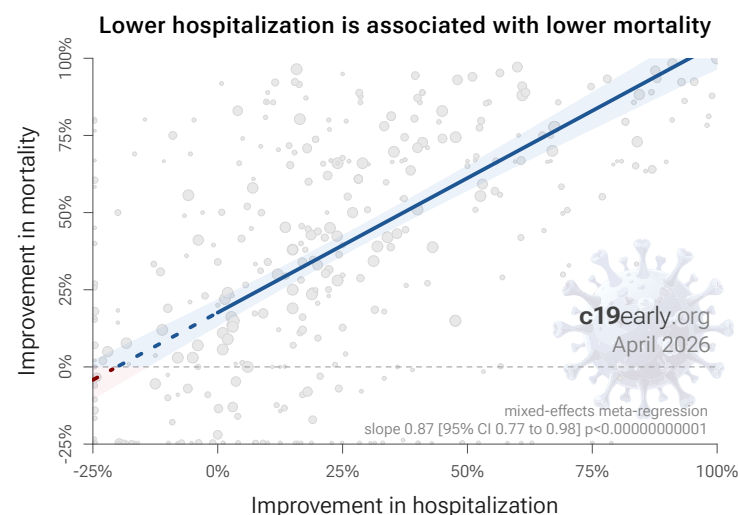


Fig. 15. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

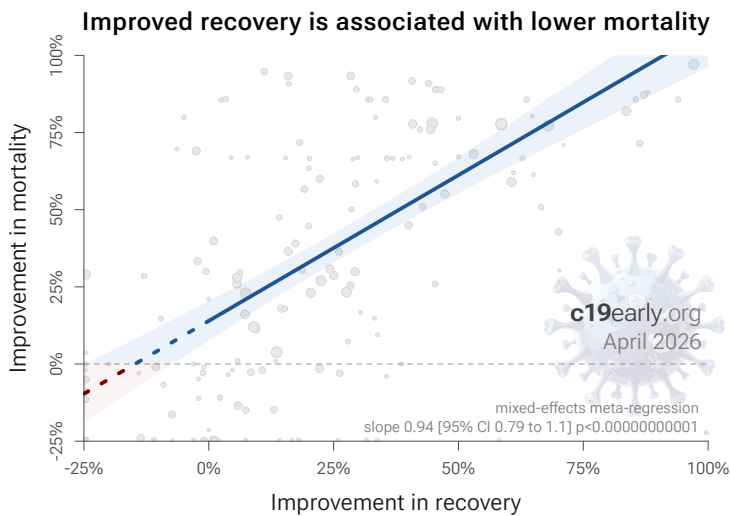


Fig. 16. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

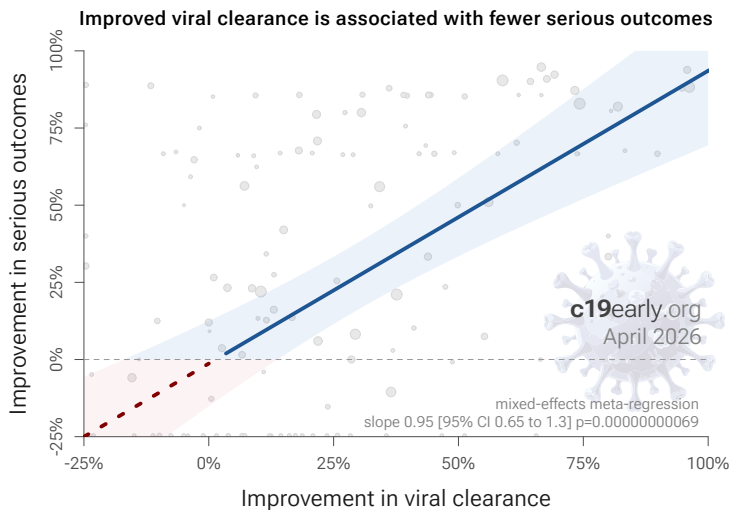


Fig. 15. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 59 of the treatments we analyze show statistically significant efficacy or harm, defined as $\geq 10\%$ decreased risk or $>0\%$ increased risk from ≥ 3 studies. 85% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.6 months. When restricting to RCTs only, 51% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.8 months. Fig. 18 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

Time when COVID-19 studies showed efficacy

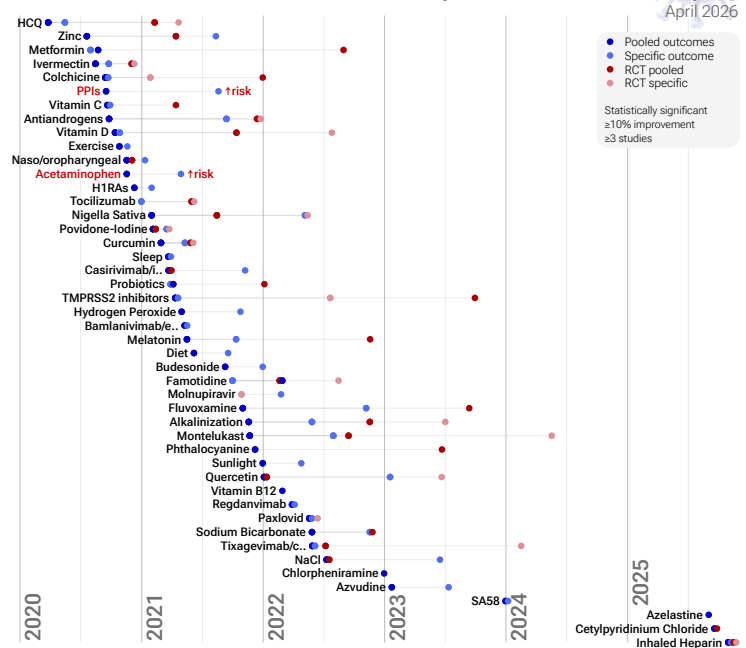


Fig. 18. The time when studies showed that treatments were effective, defined as statistically significant improvement of $\geq 10\%$ from ≥ 3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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 differences in treatment delay are more likely to hide efficacy.

Summary

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

Discussion

Publication bias

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

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 alone⁵⁷⁻⁷³. 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.

Other studies

Additional preclinical or review papers suggesting potential benefits of sargramostim for COVID-19 include⁷⁹⁻⁸³. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 400+ host and viral proteins and other factors²⁹⁻³⁶, providing many therapeutic targets. Over 11,000 compounds have been predicted to reduce COVID-19 risk³⁷, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Fig. 19 shows an overview of the results for sargramostim in the context of multiple COVID-19 treatments, and Fig. 20 shows a plot of efficacy vs. cost for COVID-19 treatments.

Efficacy in COVID-19 studies (pooled effects)

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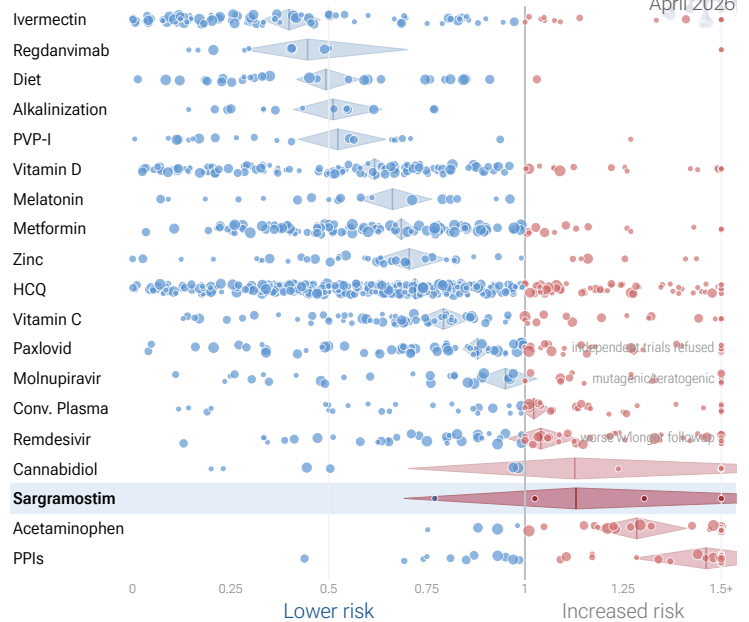


Fig. 19. Scatter plot showing results within the context of multiple COVID-19 treatments. Diamonds shows the results of random-effects meta-analysis. 0.5% of 11,000+ proposed treatments show efficacy⁸⁴.

Efficacy vs. cost for COVID-19 treatments

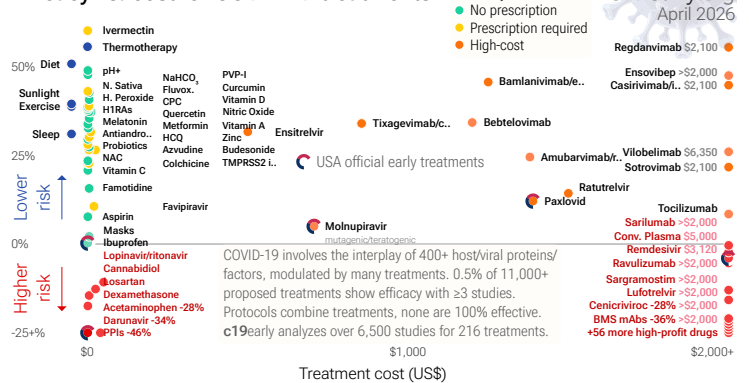


Fig. 20. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Meta-analysis using the most serious outcome reported shows 13% [-31-85%] higher risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 870 patients and only 18 control events for the most serious outcome in trials to date.

Contact. Contact us on X at @CovidAnalysis.

Funding. We have received no funding or compensation in any form, and do not accept donations. This is entirely volunteer work.

Conflicts of interest. We have no conflicts of interest. We have no affiliation with any pharmaceutical companies, supplement companies, governments, political parties, or advocacy organizations.

Disclaimer. We do not provide medical advice. No treatment is 100% effective, and all may have side effects. Protocols combine multiple treatments. Consult a qualified physician for personalized risk/benefit analysis.

AI. We use AI models (Gemini, Grok, Claude, and ChatGPT) tasked with functioning as additional peer-reviewers to check for errors, suggest improvements, and review spelling and grammar. Any corrections are verified and applied manually. Our preference for em dashes is independent of AI.

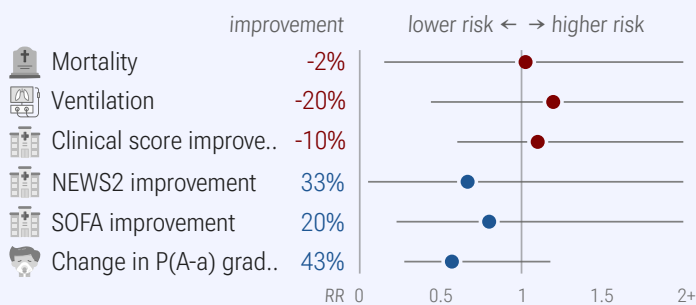
Dedication. This work is dedicated to those who risked their career to save lives under extreme censorship and persecution from authorities and media that have not even reviewed most of the science. In alphabetical order, those that paid the ultimate price: Dr. Thomas J. Borody, Dr. Jackie Stone, Dr. Vladimir (Zev) Zelenko; and those that continue to risk their careers to save lives: Dr. Mary Talley Bowden, Dr. Flavio Cadegiani, Dr. Shankara Chetty, Dr. Ryan Cole, Dr. George Fareed, Dr. Sabine Hazan, Dr. Pierre Kory, Dr. Tess Lawrie, Dr. Robert Malone, Dr. Paul Marik, Dr. Peter McCullough, Dr. Didier Raoult, Dr. Harvey Risch, Dr. Brian Tyson, Dr. Joseph Varon, and the estimated over one million physicians worldwide that prescribed one or more low-cost COVID-19 treatments known to reduce risk, contrary to authority beliefs.

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Study Notes

Bosteels

Sargramostim SARPAC LATE TREATMENT RCT



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

RCT 81 patients in Belgium

[Lower need for oxygen therapy with sargramostim \(not stat. sig., p=0.13\)](#)

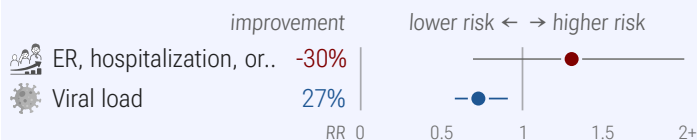
Bosteels et al., Research Square, October 2021

c19early.org

RCT 81 non-ventilated COVID-19 patients with hypoxemic respiratory failure showing improved oxygenation after 5 days of inhaled sargramostim (rh-GM-CSF) compared to standard of care. More patients in the sargramostim group experienced at least 25% improvement in oxygenation. Sargramostim treatment also increased circulating class-switched B cells and effector SARS-CoV-2 specific CD8 T cells. There were no significant differences in mortality or clinical scores.

Joshi

Sargramostim Joshi et al. LATE TREATMENT RCT



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

Double-blind RCT 600 patients in the USA (April 2021 - January 2022)

[Improved viral clearance with sargramostim \(p=0.0052\)](#)

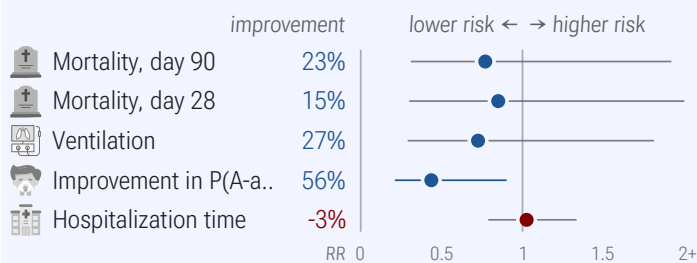
Joshi et al., Open Forum Infectious Di., Nov 2023

c19early.org

RCT 600 non-hospitalized COVID-19 patients at high risk for progression showing enhanced SARS-CoV-2 viral clearance by day 14 with inhaled sargramostim (rh GM-CSF) compared to placebo. There was no significant difference in the primary endpoint between groups. The sargramostim group had a different antibody response, with lower IgM titers at day 28 in vaccinated patients and higher IgG4 titers associated with isotype switching. Inflammatory cytokine levels did not increase with treatment.

Paine

Sargramostim iLeukPulm LATE TREATMENT RCT



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

RCT 122 patients in the USA (August 2020 - February 2021)

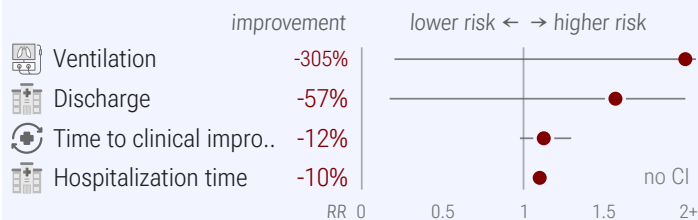
[Lower need for oxygen therapy with sargramostim \(p=0.039\)](#)

Paine et al., Military Medicine, December 2022

c19early.org

RCT 122 hospitalized COVID-19 patients showing improved oxygenation with inhaled sargramostim (GM-CSF) treatment. There was no significant difference in intubation rate, mortality, or adverse events.

Sargramostim Shimasaki et al. LATE TREATMENT RCT



Is **late** treatment with sargramostim beneficial for COVID-19?
 Double-blind RCT 70 patients in Japan (February - October 2021)
 Higher ventilation with sargramostim (not stat. sig., $p=0.54$)

Shimasaki et al., *Infectious Diseases*, Sep 2023

c19early.org

RCT 70 hospitalized COVID-19 patients with moderate pneumonia in Japan showing no significant difference in time to clinical improvement with inhaled sargramostim (GM-CSF) vs. placebo. Concomitant corticosteroid dose was not standardized. In a post-hoc analysis of patients who received ≤ 500 mg prednisolone-equivalent corticosteroids over 5 days, sargramostim improved oxygenation and clinical status compared to placebo. Higher corticosteroid doses were associated with delayed recovery. Authors hypothesize that high-dose corticosteroids may impair differentiation of monocytes into mature alveolar macrophages.

Appendix 1. Methods and Data

Search methods

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, which regularly receives notification of studies upon publication. Search terms are sargramostim 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 sargramostim for COVID-19 that report a comparison with a control group are included in the main analysis. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded.

Effect extraction

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 reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use 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

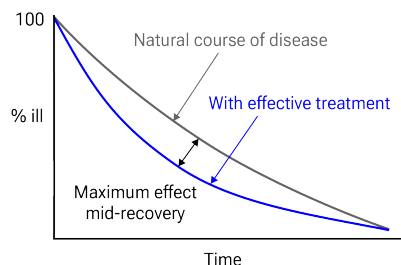


Fig. 21. Mid-recovery results can more accurately reflect efficacy when almost all patients recover. Mateja et al. confirm that intermediate viral load results more accurately reflect hospitalization/death.

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 outcomes. 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. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction⁸⁵. 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.

Statistical methods

Forest plots are computed using PythonMeta⁸⁶ 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. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to Zhang et al. Reported confidence intervals and p -values are used when available, and adjusted values are used 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 1⁹⁰. 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 (3.14.3) with scipy (1.17.1), pythonmeta (1.26), numpy (2.4.3), statsmodels (0.14.6), and plotly (6.6.0). 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 0.8.2 is used to parse PDF documents.

When evaluating potential effect modification across groups, we use an interaction test as described by Altman (C) et al. We compared the log-transformed relative risks using a z -test, deriving the standard error of the difference from the 95% confidence intervals. A two-sided interaction p -value of < 0.05 was considered a statistically significant difference in treatment effect between the groups.

Quality evaluation

Cochrane RoB 2/ROBINS-I are often used to evaluate studies, and have the advantage of providing standardized rules that can be applied with minimal understanding of the domain and study. However, the rules do not account for many real-world issues, often overemphasize or underemphasize others, and studies show low inter-rater reliability⁹⁸. Certain domains are more applicable for these tools, however the time-sensitive nature of a pandemic, with significant mortality for every day of delay in evidence assessment, and the characteristics of COVID-19 make them inappropriate for this domain. This can be demonstrated with examples where expert RoB 2/ROBINS-I ratings do not match reality for COVID-19. Popp et al. use RoB 2 to classify Reis et al. as low risk of bias, however this is the opposite of reality—the trial not only has very high risk of bias, but has very high actual known bias, refusing to release data despite pledging to, reporting multiple impossible numbers, having blinding and randomization failure, and many other issues¹⁰⁰. Axfors et al. use RoB 2 to classify Horby et al. as low risk of bias, however this is the opposite of real-

ty—the very late treatment and excessive dosage used produces results with no relevance to recommended usage. HCQ shows poor results with late treatment and excessive dosage, and the combination shows harm^B. *Hempenius et al.* use ROBINS-I to classify 33 studies for HCQ. The two rated as having the lowest risk of bias^{96,97} are far from the most informative. Both involve very late treatment, providing no information on recommended usage, and ROBINS-I does a very poor job of accounting for the impact of confounding factors^C.

Our quality evaluation focuses on known issues and bias, and the potential impact on outcomes, rather than just the risk of bias. The estimated potential impact of each confounding factor, and the direction of the impact is considered. For example, consider a study that shows significantly lower risk, the value of the study varies significantly if confounding points to an underestimate or an overestimate of efficacy. In one case, the real effect may be null, while the other case provides stronger evidence of efficacy (which may be greater than the study shows). Analysis focusing on the risk of bias, while simpler, may penalize studies for theoretical or technical issues that have no or minimal impact on outcomes. Analysis also depends on the outcome, for example certain issues are less relevant for objective outcomes such as mortality. Inaccurate penalization, and inaccurate high-quality evaluation in the face of known major issues affecting outcomes, increases in significance during a pandemic when immediate recognition of new evidence is critical, and when considering all global studies, as required during a pandemic. Investigators in other countries may have different customs for design, analysis, and reporting, and different English language skills, however they may not be less diligent or have greater bias. Investigators in lower-pharmaceutical-profit countries may have lower bias towards profitable interventions.

Treatment time

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^{42,43}.

Living analysis

This is a living analysis and is updated regularly. We received no funding, this research is done in our spare time. We have no affiliation with any pharmaceutical companies, supplement companies, governments, political parties, or advocacy organizations.

A summary of study results is below. Please submit updates and corrections at <https://c19early.org/gmmeta.html>.

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.

Bosteels, 10/13/2021, Randomized Controlled Trial, Belgium, preprint, median age 60.0, 31 authors, trial NCT04326920 (history) (SARPAC).

risk of death, 2.5% higher, RR 1.02, $p = 1.00$, treatment 2 of 40 (5.0%), control 2 of 41 (4.9%).

risk of mechanical ventilation, 19.6% higher, RR 1.20, $p = 0.77$, treatment 7 of 40 (17.5%), control 6 of 41 (14.6%).

relative clinical score improvement, 10.0% worse, RR 1.10, $p = 0.77$, treatment mean 2.0 (± 3.1) $n=40$, control mean 2.2 (± 3.0) $n=41$, day 6.

relative NEWS2 improvement, 33.3% better, RR 0.67, $p = 0.77$, treatment mean 0.6 (± 3.1) $n=40$, control mean 0.4 (± 3.0) $n=41$, day 6.

relative SOFA improvement, 20.0% better, RR 0.80, $p = 0.74$, treatment mean 0.5 (± 1.5) $n=40$, control mean 0.4 (± 1.2) $n=41$, day 6.

relative change in P(A-a) gradient, 43.0% better, RR 0.57, $p = 0.13$, treatment 40, control 41, day 6.

Joshi, 11/27/2023, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 10 authors, study period 28 April, 2021 - 31 January, 2022.

ER, hospitalization, or death, 30.4% higher, RR 1.30, $p = 0.50$, treatment 21 of 301 (7.0%), control 16 of 299 (5.4%).

viral load, 27.3% lower, relative load 0.73, $p = 0.005$, treatment mean 4.4 (± 2.06) $n=50$, control mean 3.2 (± 2.16) $n=51$.

Paine, 12/2/2022, Randomized Controlled Trial, USA, peer-reviewed, mean age 60.4, 14 authors, study period 19 August, 2020 - 17 February, 2021, trial NCT04411680 (history) (iLeukPulm).

risk of death, 23.0% lower, HR 0.77, $p = 0.58$, treatment 78, control 44, day 90.

risk of death, 15.0% lower, HR 0.85, $p = 0.76$, treatment 78, control 44, day 28.

risk of mechanical ventilation, 27.5% lower, RR 0.73, $p = 0.58$, treatment 9 of 78 (11.5%), control 7 of 44 (15.9%), NNT 23, day 14.

no improvement in P(A-a)O₂, 56.3% lower, RR 0.44, $p = 0.04$, treatment 10 of 63 (15.9%), control 12 of 33 (36.4%), NNT 4.9.

hospitalization time, 2.5% higher, relative time 1.03, $p = 0.86$, treatment mean 12.1 (± 9.4) $n=78$, control mean 11.8 (± 8.6) $n=44$.

Shimasaki, 9/20/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Japan, peer-reviewed, mean age 54.7, 26 authors, study period 8 February, 2021 - 25 October, 2021, trial NCT04642950 (history).

risk of mechanical ventilation, 304.5% higher, RR 4.05, $p = 0.54$, treatment 2 of 44 (4.5%), control 0 of 23 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).

risk of no hospital discharge, 56.8% higher, RR 1.57, $p = 1.00$, treatment 3 of 44 (6.8%), control 1 of 23 (4.3%).

time to clinical improvement, 12.5% higher, relative time 1.12, $p = 0.10$, treatment 47, control 23.

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.
- b. When administered late in infection, HCQ may enhance viral egress by further increasing lysosomal pH beyond the effect of ORF3a's water channel activity, thereby promoting lysosomal exocytosis, inactivating degradative enzymes, and facilitating the release of SARS-CoV-2 particles into the extracellular environment^{92,93}. Research also suggests potential cardioprotective effects at lower doses, but cardiotoxicity with excessive dosage⁹⁴. *Bobrowski et al.* also indicate negative effects if HCQ and remdesivir are combined.
- c. *Peters et al.* is subject to confounding by calendar-time (SOC evolved rapidly early in the pandemic, the linear covariate does not reflect non-linear SOC changes and hospital specific effects), hospital type (non-treatment hospitals were tertiary university centers), confounding by indication (4/7 hospitals initiated treatment on deterioration), immortal-time bias for as-treated (exposure assigned after baseline), significant differences for other experimental treatments, potential overadjustment from collider bias (steroid use and indication bias), limited baseline severity information, differences in hospice referral propensity across hospitals, unadjusted difference in time from onset to admission, difference in PCR positivity, and other factors. *Mahévas et al.* is subject to confounding by hospital (treatment highly dependent on the hospital, different SOC/ICU transfer practices, not included in PS), immortal time (only partly addressed in sensitivity analysis), co-treatment differences, calendar-time (SOC evolved rapidly early in the pandemic), binary coding for age (age ≥65 despite steep age-risk gradient), residual imbalance (variables dropped from PS), a composite outcome dependent on hospital triage/capacity, and other factors.

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