

Dornase alfa for COVID-19: real-time meta-analysis of 3 studies

@CovidAnalysis, April 2026, Version 2, c19early.org/dnasemeta.html

Abstract

Meta-analysis using the most serious outcome reported shows 12% [-34-87%] higher risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 242 patients and only 4 control events for the most serious outcome in trials to date. Studies to date are from only 3 different groups.

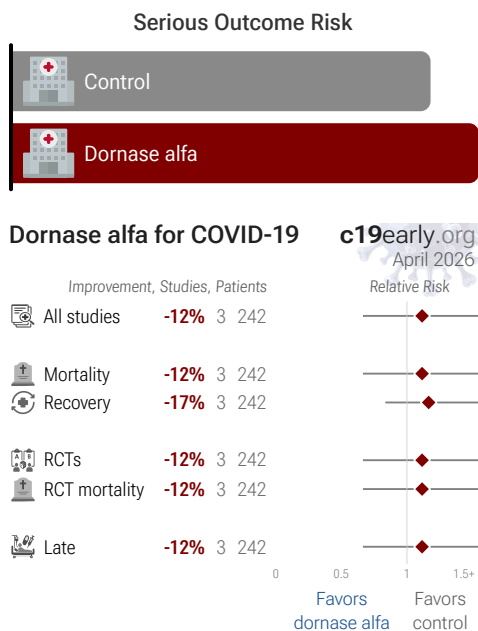
4 RCTs with 297 patients have not reported results (up to 5 years late).

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

DORNASE ALFA FOR COVID-19 — HIGHLIGHTS

Meta-analysis of studies to date shows no significant improvements with dornase alfa.

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.



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 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

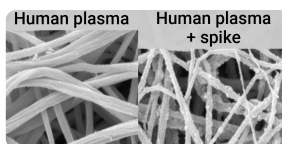


Fig. 1. SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from¹.

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 dornase alfa 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, and Randomized Controlled Trials (RCTs).

Treatment timing

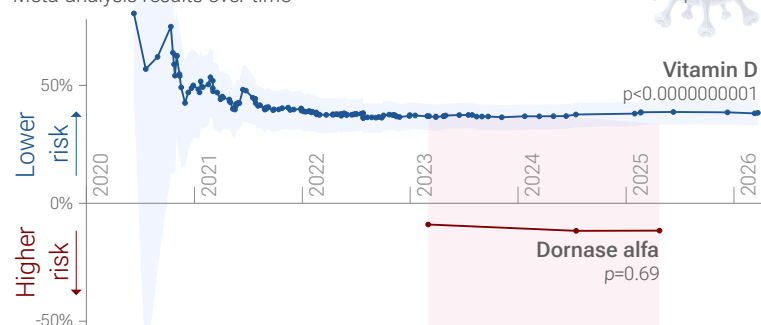
Fig. 2 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early treatment refers to treatment immediately or soon after symptoms appear, while late treatment refers to more delayed treatment.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

Results

Table 1 summarizes the results for all studies, for Randomized Controlled Trials, and for specific outcomes. Fig. 3 shows a timeline of the results in dornase alfa studies. Fig. 4, 5, and 6 show forest plots for random-effects meta-analysis of all studies with pooled effects, mortality results, and recovery.

Evolution of COVID-19 clinical evidence

Meta-analysis results over time



	Relative Risk	Studies	Patients
All studies	1.12 [0.66-1.87]	3	242
RCTs	1.12 [0.66-1.87]	3	242
Mortality	1.12 [0.66-1.87]	3	242
Recovery	1.17 [0.84-1.63]	3	242
RCT mortality	1.12 [0.66-1.87]	3	242

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

Timeline of COVID-19 dornase alfa studies (pooled effects)

c19early.org
April 2026

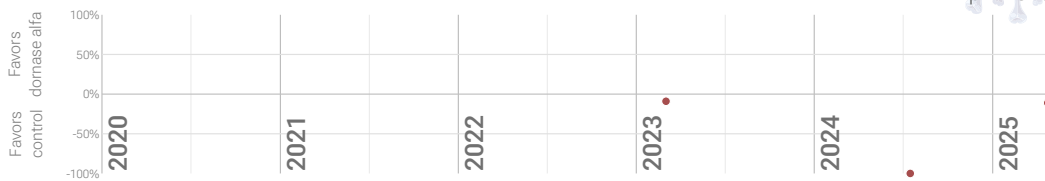


Fig. 3. Timeline of results in dornase alfa studies.

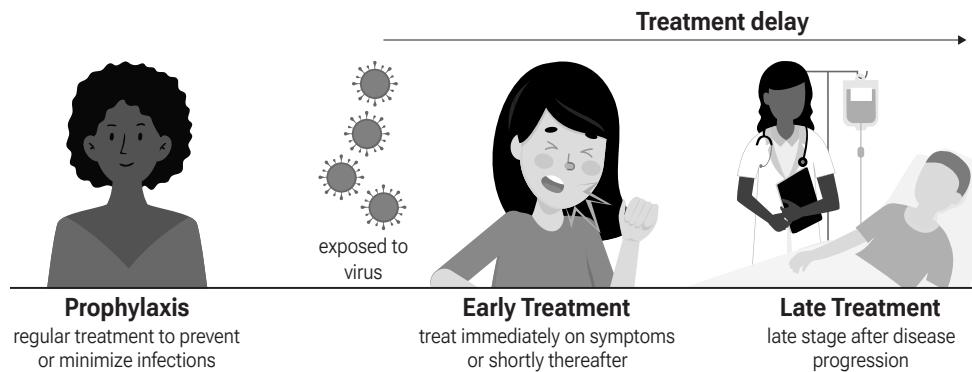


Fig. 2. Treatment stages.

3 dornase alfa COVID-19 studies (+4 unreported RCTs)

c19early.org
April 2026

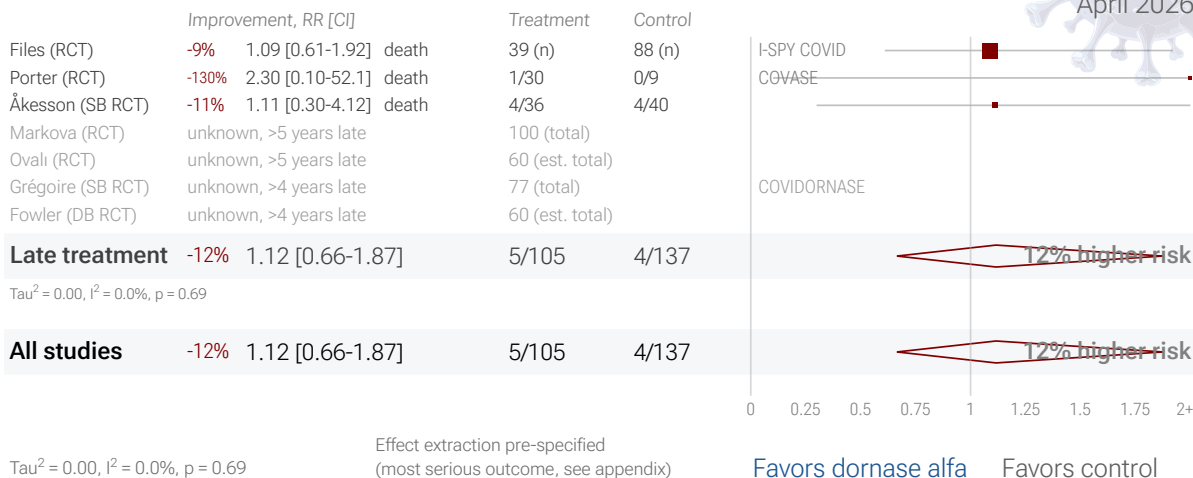


Fig. 4. Random-effects meta-analysis for all studies. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details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

3 dornase alfa COVID-19 mortality results

c19early.org
April 2026

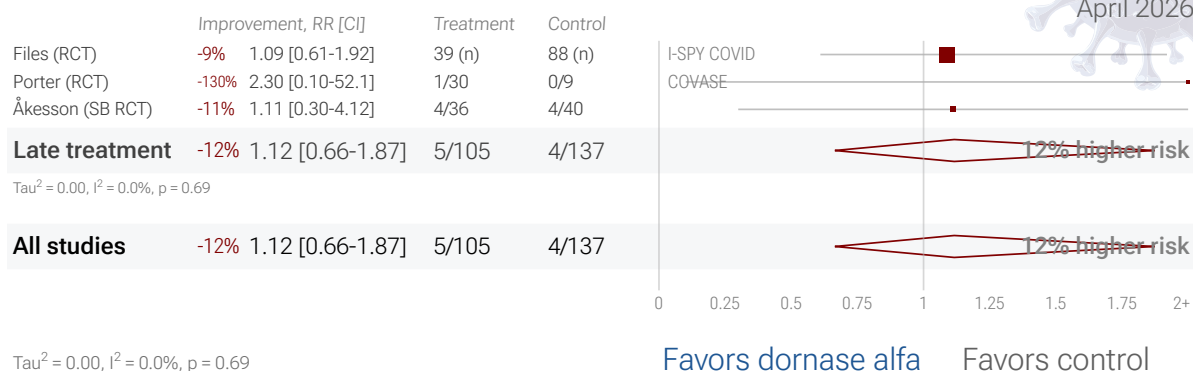


Fig. 5. Random-effects meta-analysis for mortality results.

3 dornase alfa COVID-19 recovery results

c19early.org
April 2026

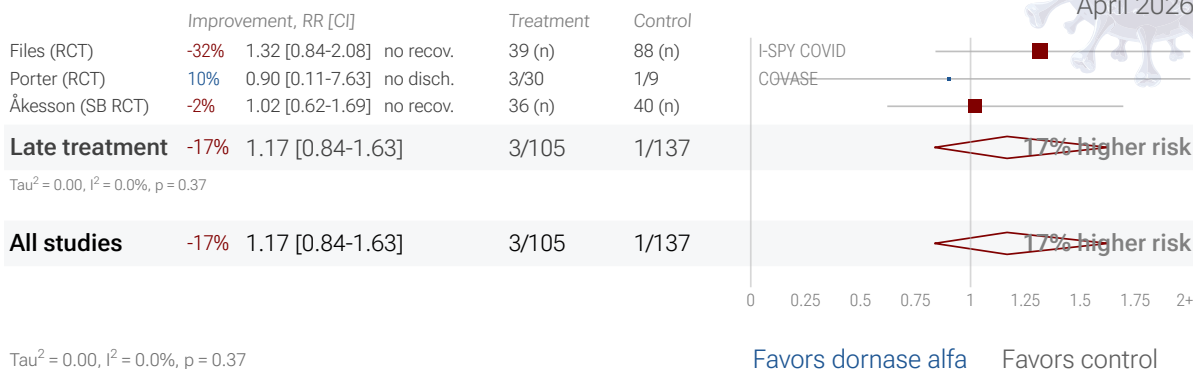


Fig. 6. Random-effects meta-analysis for recovery.

Randomized Controlled Trials (RCTs)

Currently all studies are RCTs.

Unreported RCTs

4 dornase alfa RCTs have not reported results³⁸⁻⁴¹. The trials report a total of 297 patients, with 2 trials having actual enrollment of 177, and the remainder estimated. The results are delayed from 4 years to over 5 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^{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. 7 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.

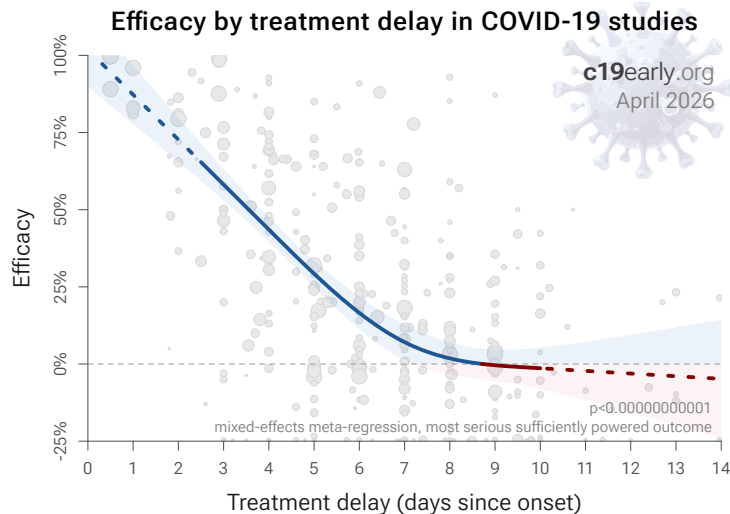


Fig. 7. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 216 treatments.

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 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.

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. 8 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Fig. 9 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. Fig. 10 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 $p = 0.0000000069$.

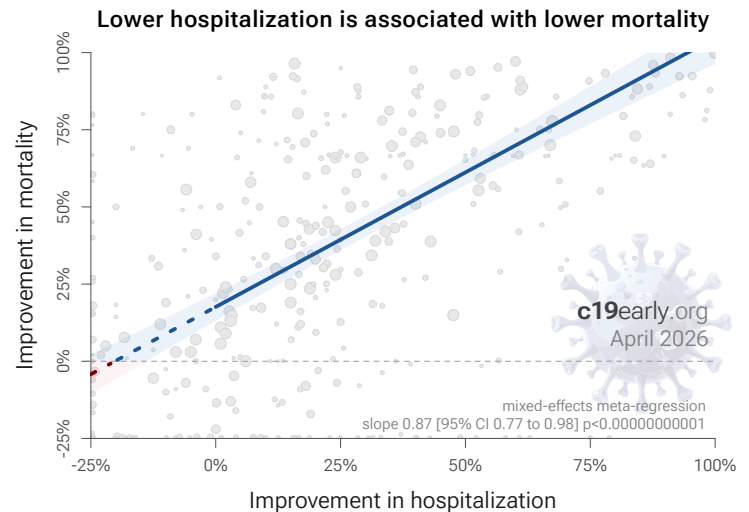


Fig. 8. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

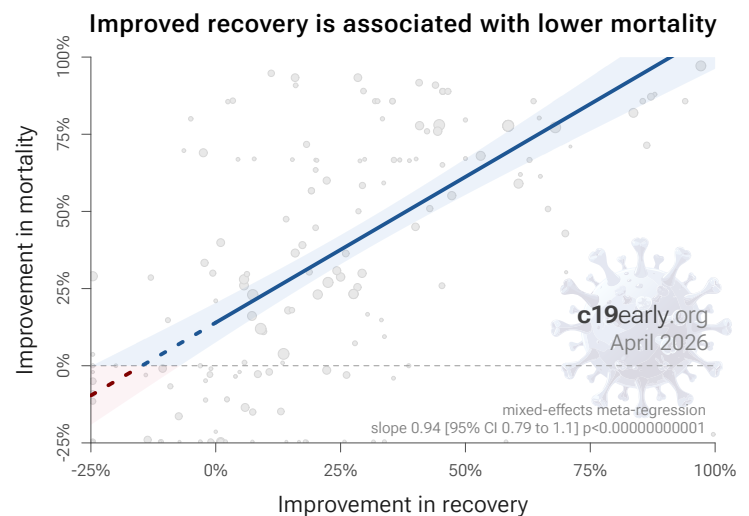


Fig. 9. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

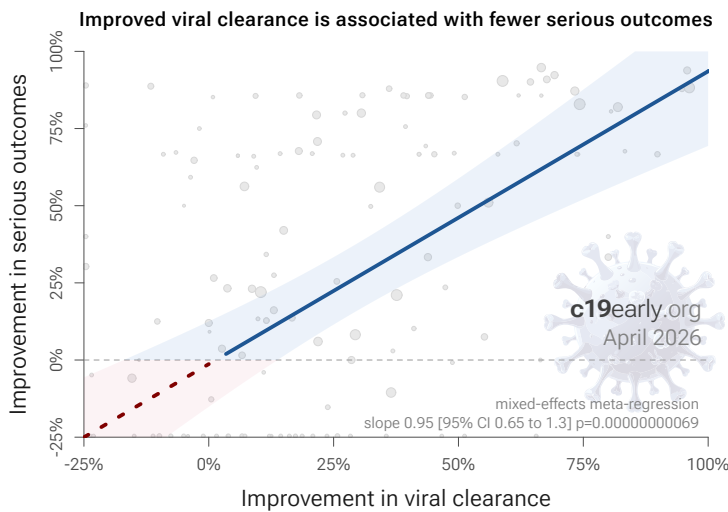


Fig. 8. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

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. 11 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

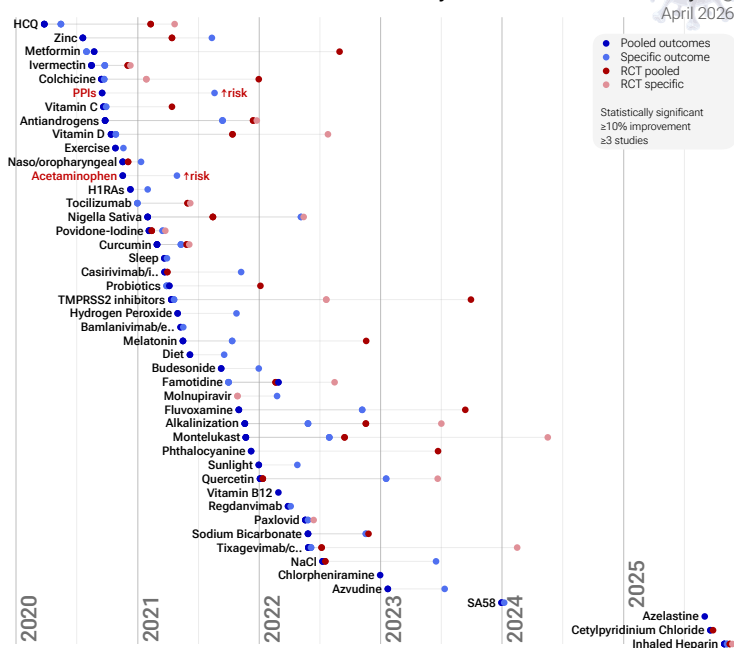


Fig. 11. The time when studies showed that treatments were effective, defined as statistically significant improvement of $\geq 10\%$ from ≥ 3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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 dornase alfa, 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.

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. 12 shows an overview of the results for dornase alfa in the context of multiple COVID-19 treatments, and Fig. 13 shows a plot of efficacy vs. cost for COVID-19 treatments.

Efficacy in COVID-19 studies (pooled effects)

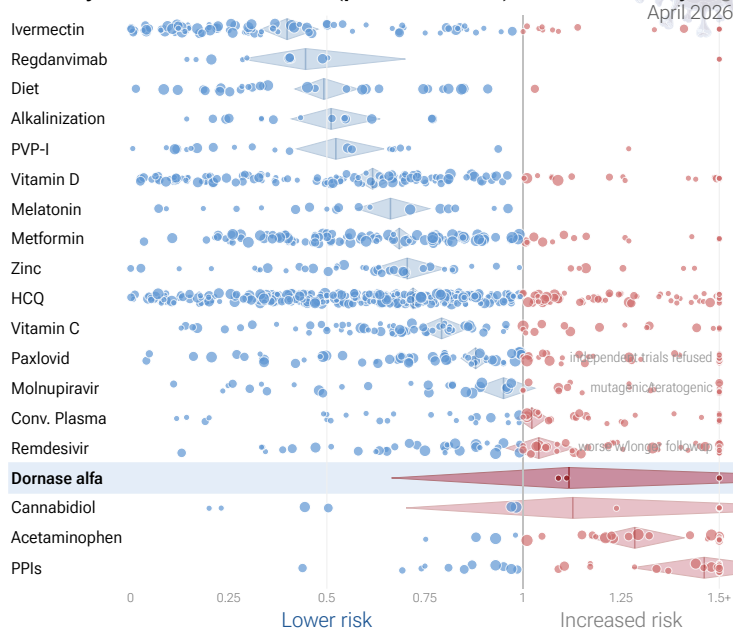


Fig. 12. Scatter plot showing results within the context of multiple COVID-19 treatments. Diamonds shows the results of random-effects meta-analysis. 0.5% of 11,000+ proposed treatments show efficacy⁷⁵.

Efficacy vs. cost for COVID-19 treatments

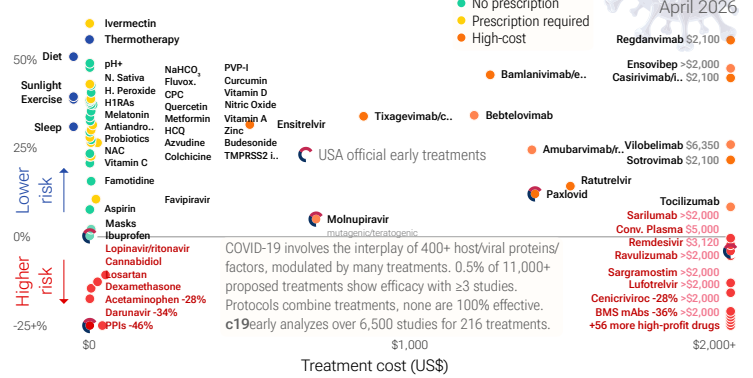


Fig. 13. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Meta-analysis using the most serious outcome reported shows 12% [-34-87%] higher risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 242 patients and only 4 control events for the most serious outcome in trials to date. Studies to date are from only 3 different groups.

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.

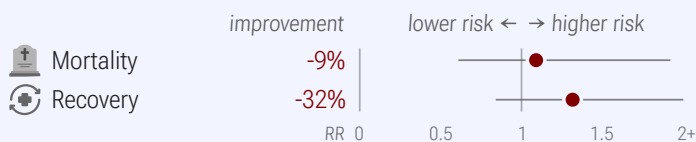
Dedication. This work is dedicated to those who risked their career to save lives under extreme censorship and persecution from authorities and media that have not even reviewed most of the science. In alphabetical order, those that paid the ultimate price: Dr. Thomas J. Borody, Dr. Jackie Stone, Dr. Vladimir (Zev) Zelenko; and those that continue to risk their careers to save lives: Dr. Mary Talley Bowden, Dr. Flavio Cadegegiani, 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.

Public domain. This is a public domain work distributed in accordance with the Creative Commons CC0 1.0 Universal license, which dedicates the work to the public domain by waiving all rights worldwide under copyright law. You can distribute, remix, adapt, and build upon this work in any medium or format, including for commercial purposes, without asking permission. Referenced material and third-party images retain any original copyrights or restrictions. See: <https://creativecommons.org/publicdomain/zero/1.0/>.

Study Notes

Files

Dornase alfa I-SPY COVID LATE TREATMENT RCT



Is **late** treatment with dornase alfa beneficial for COVID-19?

RCT 127 patients in the USA (July 2020 - June 2021)

Worse recovery with dornase alfa (not stat. sig., $p=0.24$)

Files et al., eClinicalMedicine, March 2023

c19early.org

RCT 127 severe COVID-19 patients showing no significant difference in outcomes with dornase alfa.

Fowler

Estimated 60 patient dornase alfa late treatment RCT with results not reported over 4 years after estimated completion.

Grégoire

77 patient dornase alfa late treatment RCT with results not reported over 4 years after completion.

Markova

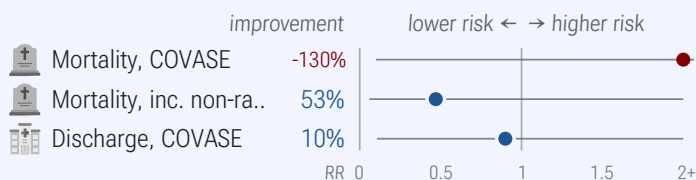
100 patient dornase alfa late treatment RCT with results not reported over 5 years after completion.

Ovali

Estimated 60 patient dornase alfa late treatment RCT with results not reported over 5 years after estimated completion.

Porter

Dornase alfa COVASE LATE TREATMENT RCT



Is **late** treatment with dornase alfa beneficial for COVID-19?

RCT 99 patients in the United Kingdom (June 2020 - October 2021)

Trial underpowered to detect differences

Porter et al., eLife, July 2024

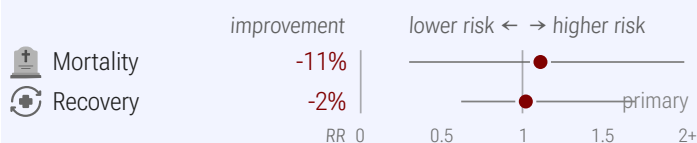
c19early.org

RCT 99 hospitalized COVID-19 patients showing significantly reduced C-reactive protein (CRP) levels and length of hospital stay with nebulized dornase alfa treatment in addition to standard of care (dexamethasone). Authors combine the randomized patients with retrospective patients using matching that does not match for COVID-19 severity. Dornase alfa was associated with a 33% re-

duction in CRP, a 63% higher chance of discharge at any timepoint up to 35 days, and increased lymphocyte counts. There was a trend towards reduced mortality which was not statistically significant.

Åkesson

Dornase alfa Åkesson et al. LATE TREATMENT RCT



Is **late** treatment with dornase alfa beneficial for COVID-19?

RCT 76 patients in Sweden (June 2020 - January 2022)

Trial underpowered for serious outcomes

Åkesson et al., Open Forum Infectious ..., Apr 2025

c19early.org

RCT 76 hospitalized COVID-19 patients showing no significant difference with inhaled dornase alfa (DNase I) for resolution of hypoxia or other clinical outcomes.

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 dornase alfa 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 dornase alfa 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 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 clear-

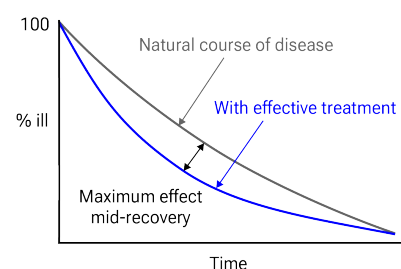


Fig. 14. Mid-recovery results can more accurately reflect efficacy when almost all patients recover. Mateja et al. confirm that intermediate viral load results more accurately reflect hospitalization/death.

ance 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 reduction⁷⁶. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO₂ is more important than cough.

Statistical methods

Forest plots are computed using PythonMeta⁷⁷ 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 I² 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 1⁸¹. 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 reliability⁸⁹. 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 issues⁹¹. *Axfors et al.* use RoB 2 to classify *Horby et al.* as low risk of bias, however this is the opposite of reality—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^{87,88} are far from the most informative. Both involve very late treat-

ment, 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/dnasemeta.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.

Files, 3/3/2023, Randomized Controlled Trial, USA, peer-reviewed, 91 authors, study period 30 July, 2020 - 11 June, 2021, average treatment delay 9.5 days, trial NCT04488081 (history) (I-SPY COVID).	risk of death, 9.0% higher, HR 1.09, p = 0.78, treatment 39, control 88, adjusted per study, day 60.
	risk of no recovery, 31.6% higher, HR 1.32, p = 0.24, treatment 39, control 88, adjusted per study, inverted to make HR<1 favor treatment, day 60.
Fowler, 12/31/2021, Double Blind Randomized Controlled	Estimated 60 patient RCT with results unknown and over 4 years late.

Trial, placebo-controlled, USA, trial NCT04402944 (history).	
Grégoire, 12/20/2021, Single Blind Randomized Controlled Trial, France, trial NCT04355364 (history) (COVIDORNASE).	77 patient RCT with results unknown and over 4 years late.
Markova, 7/20/2020, Randomized Controlled Trial, Russia, trial NCT04459325 (history).	100 patient RCT with results unknown and over 5 years late.
Ovali, 9/25/2020, Randomized Controlled Trial, Turkey, trial NCT04432987 (history).	Estimated 60 patient RCT with results unknown and over 5 years late.
Porter, 7/16/2024, Randomized Controlled Trial, United Kingdom, peer-reviewed, mean age 56.8, 25 authors, study period June 2020 - October 2021, trial NCT04359654 (history) (COVASE).	risk of death, 130.0% higher, RR 2.30, $p = 1.00$, treatment 1 of 30 (3.3%), control 0 of 9 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), COVASE randomized patients.
	risk of death, 53.0% lower, HR 0.47, $p = 0.49$, treatment 30, control 69, including non-randomized patients.
	risk of no hospital discharge, 10.0% lower, RR 0.90, $p = 1.00$, treatment 3 of 30 (10.0%), control 1 of 9 (11.1%), NNT 90, COVASE randomized patients.
Åkesson, 4/24/2025, Single Blind Randomized Controlled Trial, placebo-controlled, Sweden, peer-reviewed, mean age 60.5, 11 authors, study period 4 June, 2020 - 11 January, 2022, trial NCT04541979 (history).	risk of death, 11.1% higher, RR 1.11, $p = 1.00$, treatment 4 of 36 (11.1%), control 4 of 40 (10.0%).
	risk of no recovery, 2.0% higher, HR 1.02, $p = 0.94$, treatment 36, control 40, inverted to make HR<1 favor treatment, resolution of hypoxia, Kaplan-Meier, primary outcome.

Supplementary Data

Supplementary Data

Footnotes

- 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.
- 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^{83,84}. Research also suggests potential cardioprotective effects at lower doses, but cardiotoxicity with excessive dosage⁸⁵. *Bobrowski et al.* also indicate negative effects if HCQ and remdesivir are combined.
- 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.

References

- Ryu et al.*, *Fibrin drives thromboinflammation and neuropathology in COVID-19*, *Nature*, doi:10.1038/s41586-024-07873-4.
- Rong et al.*, *Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19*, *Cell Host & Microbe*, doi:10.1016/j.chom.2024.11.007.
- Yang et al.*, *SARS-CoV-2 infection causes dopaminergic neuron senescence*, *Cell Stem Cell*, doi:10.1016/j.stem.2023.12.012.
- Scardua-Silva et al.*, *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, *Scientific Reports*, doi:10.1038/s41598-024-52005-7.
- Hampshire et al.*, *Cognition and Memory after Covid-19 in a Large Community Sample*, *New England Journal of Medicine*, doi:10.1056/NEJMoa2311330.
- 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.
- Sodagar et al.*, *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, *Biomolecules*, doi:10.3390/biom12070971.
- Sagar et al.*, *COVID-19-associated cerebral microbleeds in the general population*, *Brain Communications*, doi:10.1093/braincomms/fcae127.
- Verma et al.*, *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, *bioRxiv*, doi:10.1101/2024.06.02.596989.
- Panagea et al.*, *Neurocognitive Impairment in Long COVID: A Systematic Review*, *Archives of Clinical Neuropsychology*, doi:10.1093/arclin/aca042.
- Ariza et al.*, *COVID-19: Unveiling the Neuropsychiatric Maze—From Acute to Long-Term Manifestations*, *Biomedicine*, doi:10.3390/biomedicine12061147.
- Vashisht et al.*, *Neurological Complications of COVID-19: Unraveling the Pathophysiological Underpinnings and Therapeutic Implications*, *Viruses*, doi:10.3390/v16081183.
- Ahmad et al.*, *Neurological Complications and Outcomes in Critically Ill Patients With COVID-19: Results From International Neurological Study Group From the COVID-19 Critical Care Consortium*, *The Neurohospitalist*, doi:10.1177/19418744241292487.
- Wang et al.*, *SARS-CoV-2 membrane protein induces neurodegeneration via affecting Golgi-mitochondria interaction*, *Translational Neurodegeneration*, doi:10.1186/s40035-024-00458-1.
- Freitas et al.*, *Central nervous system and systemic inflammatory networks associated with acute neurological outcomes in COVID-19*, *Scientific Reports*, doi:10.1038/s41598-025-08632-9.
- Lu et al.*, *Risk of neuropsychiatric and related conditions associated with SARS-CoV-2 infection: a difference-in-differences analysis*, *Nature Communications*, doi:10.1038/s41467-025-61961-1.
- Jachman-Kaputka et al.*, *Cross-Section of Neurological Manifestations Among SARS-CoV-2 Omicron Subvariants—Single-Center Study*, *Brain Sciences*, doi:10.3390/brainsci14111161.
- 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.

19. **Van Tin** et al., Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF- κ B Signaling, *Cells*, doi:10.3390/cells13161331.
20. **Borka Balas** et al., COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice, *Reviews in Cardiovascular Medicine*, doi:10.31083/j.rcm2405125.
21. **AlTaweel** et al., An In-Depth Insight into Clinical, Cellular and Molecular Factors in COVID-19-Associated Cardiovascular Ailments for Identifying Novel Disease Biomarkers, Drug Targets and Clinical Management Strategies, *Archives of Microbiology & Immunology*, doi:10.26502/ami.936500177.
22. **Saha** et al., COVID-19 beyond the lungs: Unraveling its vascular impact and cardiovascular complications—mechanisms and therapeutic implications, *Science Progress*, doi:10.1177/00368504251322069.
23. **Yin** et al., COVID-19: a vascular nightmare unfolding, *Frontiers in Immunology*, doi:10.3389/fimmu.2025.1593885.
24. **Bruno** et al., Accelerated vascular ageing after COVID-19 infection: the CARTESIAN study, *European Heart Journal*, doi:10.1093/eurheartj/ehaf430.
25. **Abiri** et al., The silent legacy of COVID-19: exploring genomic instability in long-term COVID-19 survivors, *BMC Infectious Diseases*, doi:10.1186/s12879-025-11419-y.
26. **Gioia** et al., SARS-CoV-2 infection induces DNA damage, through CHK1 degradation and impaired 53BP1 recruitment, and cellular senescence, *Nature Cell Biology*, doi:10.1038/s41556-023-01096-x.
27. **Doğan** et al., Clinical Investigation of Leukocyte DNA Damage in COVID-19 Patients, *Current Issues in Molecular Biology*, doi:10.3390/cimb45020062.
28. **Trender** et al., Changes in memory and cognition during the SARS-CoV-2 human challenge study, *eClinicalMedicine*, doi:10.1016/j.eclinm.2024.102842.
29. **Dugied** et al., Multimodal SARS-CoV-2 interactome sketches the virus-host spatial organization, *Communications Biology*, doi:10.1038/s42003-025-07933-z.
30. **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.
31. **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.
32. **Lv** et al., Host proviral and antiviral factors for SARS-CoV-2, *Virus Genes*, doi:10.1007/s11262-021-01869-2.
33. **Lui** et al., Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling, *Virology*, doi:10.1128/mbio.00392-24.
34. **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.
35. **Katiyar** et al., SARS-CoV-2 Assembly: Gaining Infectivity and Beyond, *Viruses*, doi:10.3390/v16111648.
36. **Wu** et al., Decoding the genome of SARS-CoV-2: a pathway to drug development through translation inhibition, *RNA Biology*, doi:10.1080/15476286.2024.2433830.
37. **c19early.org**, c19early.org/treatments.html.
38. **Fowler** et al., Pulmozyme to Improve COVID-19 ARDS Outcomes, NCT04402944, clinicaltrials.gov/study/NCT04402944.
39. **Grégoire** et al., Efficacy and Safety of Dornase Alfa Aerosol in ARDS Secondary to SARS-CoV-2 Coronavirus Respiratory Infection - COVID-19, NCT04355364, clinicaltrials.gov/study/NCT04355364.
40. **Ovali** et al., Determination of Dornase Alpha Effectiveness in COVID-19 Treatment, NCT04432987, clinicaltrials.gov/study/NCT04432987.
41. **Markova** et al., A Prospective Open-label Study of the Tigerase® Efficacy and Safety as Part of Complex Therapy in Patients With COVID-19, NCT04459325, clinicaltrials.gov/study/NCT04459325.
42. **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.
43. **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.
44. **Ikematsu** et al., Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts, *New England Journal of Medicine*, doi:10.1056/NEJMoa1915341.
45. **Hayden** et al., Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents, *New England Journal of Medicine*, doi:10.1056/NEJMoa1716197.
46. **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.
47. **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.
48. **Korves** et al., SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk, medRxiv, doi:10.1101/2024.03.08.24303818.
49. **Faria** et al., Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil, *Science*, doi:10.1126/science.abh2644.
50. **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.
51. **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.
52. **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.
53. **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.
54. **Peacock** et al., The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry, *bioRxiv*, doi:10.1101/2021.12.31.474653.
55. **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.
56. **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.
57. **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.
58. **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.
59. **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.
60. **Ostrov** et al., Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells, *Pathogens*, doi:10.3390/pathogens10111514.
61. **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.

62. **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.
63. **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.
64. **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.
65. **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.
66. **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.
67. **Xing** et al., *Published anti-SARS-CoV-2 in vitro hits share common mechanisms of action that synergize with antivirals*, Briefings in Bioinformatics, doi:10.1093/bib/bbab249.
68. **Chen** et al., *Synergistic Inhibition of SARS-CoV-2 Replication Using Disulfiram/Eb-selen and Remdesivir*, ACS Pharmacology & Translational Science, doi:10.1021/acsptsci.1c00022.
69. **Hempel** et al., *Synergistic inhibition of SARS-CoV-2 cell entry by otamixaban and covalent protease inhibitors: pre-clinical assessment of pharmacological and molecular properties*, Chemical Science, doi:10.1039/D1SC01494C.
70. **Schultz** et al., *Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2*, Nature, doi:10.1038/s41586-022-04482-x.
71. **Ohashi** et al., *Potential anti-COVID-19 agents, cepharanthine and nelfinavir, and their usage for combination treatment*, iScience, doi:10.1016/j.isci.2021.102367.
72. **Al Krad** et al., *The protease inhibitor Nirmatrelvir synergizes with inhibitors of GRP78 to suppress SARS-CoV-2 replication*, bioRxiv, doi:10.1101/2025.03.09.642200.
73. **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.
74. **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.
75. **c19early.org (B)**, c19early.org/timeline.html.
76. **Mateja** et al., *The choice of viral load endpoint in early phase trials of COVID-19 treatments aiming to reduce 28-day hospitalization and/or death*, The Journal of Infectious Diseases, doi:10.1093/infdis/jiaf282.
77. **Deng**, H., PyMeta, Python module for meta-analysis, www.pymeta.com/.
78. **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.
79. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.
80. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.
81. **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.
82. **Altman (C)** et al., *Interaction revisited: the difference between two estimates*, BMJ, doi:10.1136/bmj.326.7382.219.
83. **Michelucci** et al., *SARS-CoV-2 ORF3a accessory protein is a water-permeable channel that induces lysosome swelling*, Communications Biology, doi:10.1038/s42003-024-07442-5.
84. **Ghosh** et al., *β-Coronaviruses Use Lysosomes for Egress Instead of the Biosynthetic Secretory Pathway*, Cell, doi:10.1016/j.cell.2020.10.039.
85. **Kamga Kapchoup** et al., *In vitro effect of hydroxychloroquine on pluripotent stem cells and their cardiomyocytes derivatives*, Frontiers in Pharmacology, doi:10.3389/fphar.2023.1128382.
86. **Bobrowski** et al., *Synergistic and Antagonistic Drug Combinations against SARS-CoV-2*, Molecular Therapy, doi:10.1016/j.ymthe.2020.12.016.
87. **Peters** et al., *Outcomes of Persons With COVID-19 in Hospitals With and Without Standard Treatment With (Hydroxy)chloroquine*, Clinical Microbiology and Infection, doi:10.1016/j.cmi.2020.10.004.
88. **Mahévas** et al., *Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data*, BMJ 2020, doi:10.1136/bmj.m1844.
89. **Minozzi** et al., *The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application*, Journal of Clinical Epidemiology, doi:10.1016/j.jclinepi.2020.06.015.
90. **Popp** et al., *Ivermectin for preventing and treating COVID-19*, Cochrane Database of Systematic Reviews, doi:10.1002/14651858.CD015017.pub3.
91. **Reis** et al., *Effect of Early Treatment with Ivermectin among Patients with Covid-19*, New England Journal of Medicine, doi:10.1056/NEJMoa2115869.
92. **Axfors** et al., *Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials*, Nature, doi:10.1038/s41467-021-22446-z.
93. **Horby** et al., *Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial*, NEJM, doi:10.1056/NEJMoa2022926.
94. **Hempenius** et al., *Bias in observational studies on the effectiveness of in hospital use of hydroxychloroquine in COVID-19*, Pharmacoepidemiology and Drug Safety, doi:10.1002/pds.5632.
95. **Files** et al., *Report of the first seven agents in the I-SPY COVID trial: a phase 2, open label, adaptive platform randomised controlled trial*, eClinicalMedicine, doi:10.1016/j.eclinm.2023.101889.
96. **Porter** et al., *Anti-inflammatory therapy with nebulized dornase alfa for severe COVID-19 pneumonia: a randomized unblinded trial*, eLife, doi:10.7554/eLife.87030.4.
97. **Åkesson** et al., *Aerosolized dornase alfa (DNase I) for the treatment of severe respiratory failure in COVID-19: a randomized controlled trial*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofaf246.