Niclosamide for COVID-19: real-time meta analysis of 6 studies

@CovidAnalysis, July 2025, Version 6
https://c19early.org/ncmeta.html

Abstract

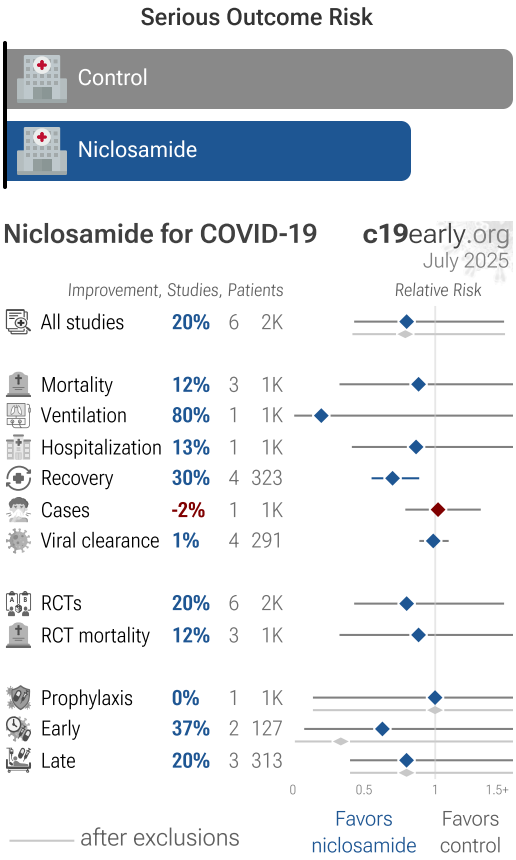
Significantly lower risk is seen for recovery. 2 studies from 2 independent teams in 2 countries show significant benefit.

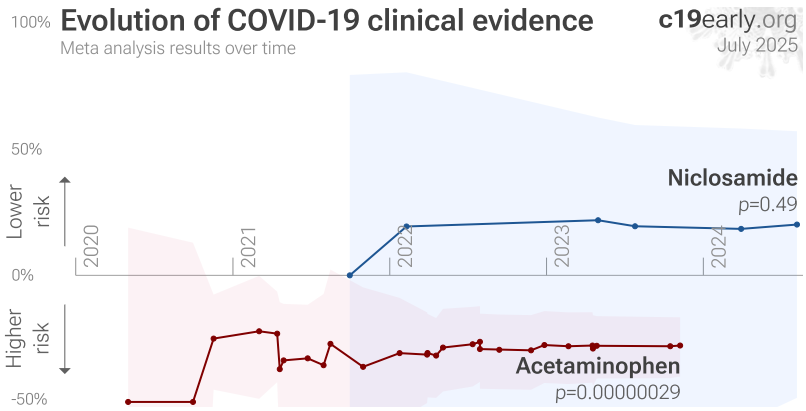
Meta analysis using the most serious outcome reported shows 20% [-48-57%] lower risk, without reaching statistical significance. Results are similar for higher quality studies and worse for peer-reviewed studies. Results are consistent with early treatment being more effective than late treatment. Currently all studies are RCTs.

Currently there is limited data, with only 20 control events for the most serious outcome in trials to date.

1 RCT with 200 patients has not reported results (4 years late) [1].

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. All data and sources to reproduce this analysis are in the appendix.

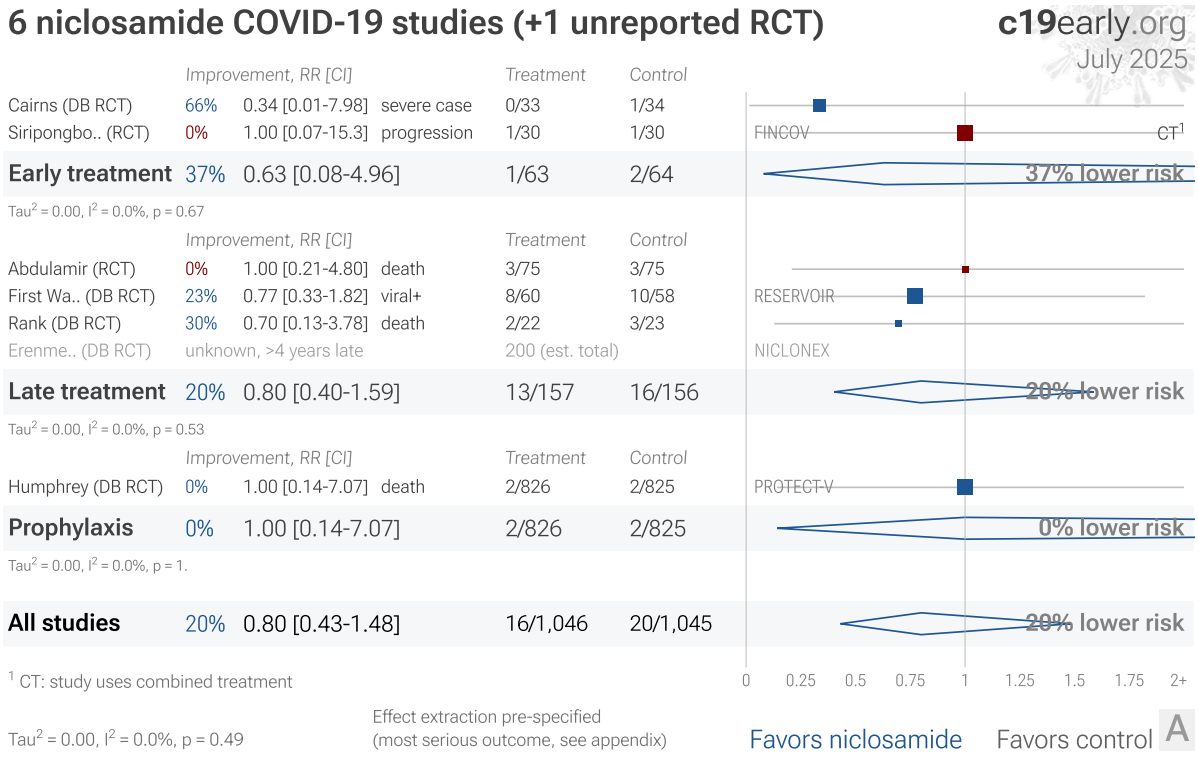




NICLOSAMIDE FOR COVID-19 — HIGHLIGHTS

Niclosamide reduces risk with very high confidence for recovery.

Real-time updates and corrections with a consistent protocol for 172 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.



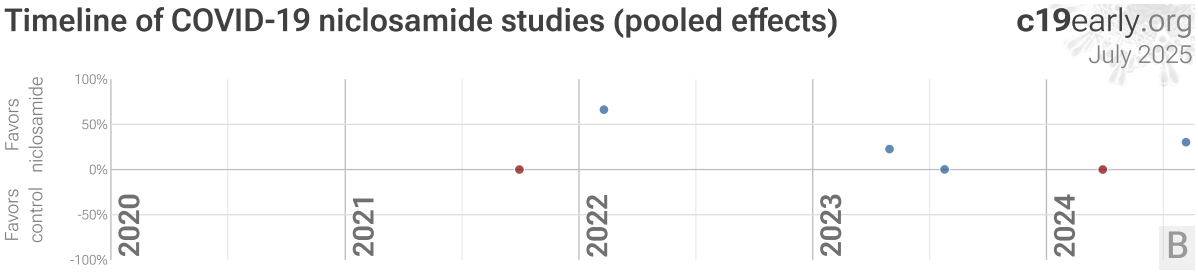


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the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

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury[3-15] and cognitive deficits[6,11], cardiovascular complications[16-20], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[21]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

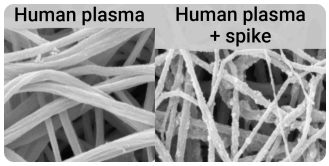


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[2].**

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,22-29], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[30], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research

In Silico studies predict inhibition of SARS-CoV-2 with niclosamide or metabolites via binding to the spike [B,31], M^{pro} [C,31], RNA-dependent RNA polymerase [D,31], PLpro [E,31], nucleocapsid [F,31], and helicase [G,31] proteins. Niclosamide inhibits endolysosomal acidification and suppresses TLR3-mediated pro-inflammatory signaling in human small airway epithelial cells stimulated with TLR3 agonists mimicking viral RNA [32], modulates host lipid metabolism and reduces infectious SARS-CoV-2 virion production in Vero E6 cells [33], reduces CD147 protein levels and inhibits SARS-CoV-2-induced upregulation of CD147 in A549-ACE2 cells, including the highly glycosylated form of CD147 which has been implicated in COVID-19 disease progression and post-COVID-19 cardiac complications [34], blocked the formation of syncytia mediated by SARS-CoV-2 spike protein pseudovirus-producing cells [35], may reduce inflammation, NLRP3 formation, and caspase-1 activity [36], may inhibit viral uncoating, replication, and assembly via disruption of pH gradients and reduced ATP production in host cells [37], may counter immune evasion by reversing E-, ORF7a-, and ORF8-mediated down-regulation of MHC-I, preserving $CD8^+$ T-cell recognition [38], and shows strong synergy when combined with ivermectin [39].

Analysis

We analyze all significant controlled studies of niclosamide for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, peer-reviewed studies, Randomized Controlled Trials (RCTs), and higher quality studies.

Treatment timing

Figure 3 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

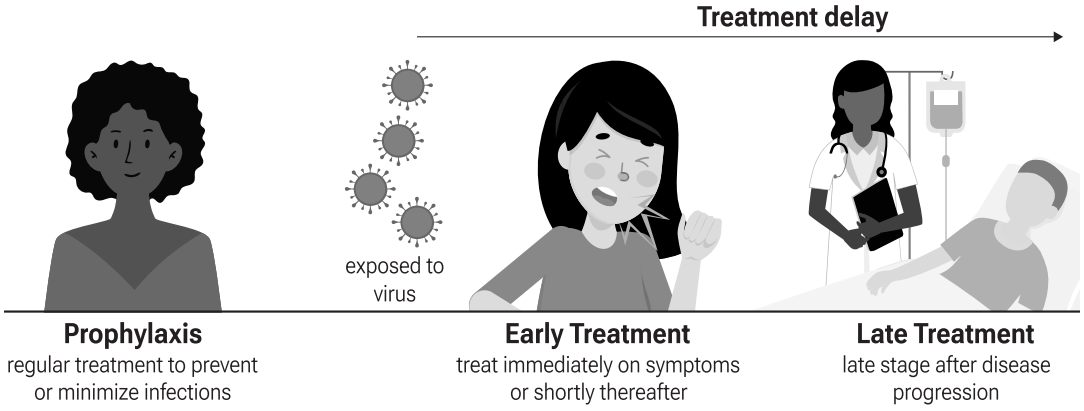


Figure 3. Treatment stages.

Preclinical Research

In Silico studies predict inhibition of SARS-CoV-2 with niclosamide or metabolites via binding to the spike [B,31], M^{pro} [C,31], RNA-dependent RNA polymerase [D,31], PLpro [E,31], nucleocapsid [F,31], and helicase [G,31] proteins. Niclosamide inhibits endolysosomal acidification and suppresses TLR3-mediated pro-inflammatory signaling in human small airway epithelial cells stimulated with TLR3 agonists mimicking viral RNA [32], modulates host lipid metabolism and reduces infectious SARS-CoV-2 virion production in Vero E6 cells [33], reduces CD147 protein levels and inhibits SARS-CoV-2-induced upregulation of CD147 in A549-ACE2 cells, including the highly glycosylated form of CD147 which has been implicated in COVID-19 disease progression and post-COVID-19 cardiac complications [34], blocked the formation of syncytia mediated by SARS-CoV-2 spike protein pseudovirus-producing cells [35], may reduce inflammation, NLRP3 formation, and caspase-1 activity [36], may inhibit viral uncoating, replication, and assembly via disruption of pH

gradients and reduced ATP production in host cells[37], may counter immune evasion by reversing E-, ORF7a-, and ORF8-mediated down-regulation of MHC-I, preserving $CD8^+$ T-cell recognition[38], and shows strong synergy when combined with ivermectin[39].

An *In Silico* study supports the efficacy of niclosamide[31].

8 *In Vitro* studies support the efficacy of niclosamide[32-37,39,40].

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, and 13 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

	Relative Risk	Studies	Patients
All studies	0.80 [0.43-1.48]	6	2,091
After exclusions	0.79 [0.42-1.49]	5	2,031
Peer-reviewed	0.89 [0.31-2.54]	4	1,928
RCTs	0.80 [0.43-1.48]	6	2,091
Mortality	0.88 [0.33-2.38]	3	1,846
Recovery	0.70 [0.55-0.89] **	4	323
Viral	0.99 [0.89-1.09]	4	291
RCT mortality	0.88 [0.33-2.38]	3	1,846

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

	Early treatment	Late treatment	Prophylaxis
All studies	0.63 [0.08-4.96]	0.80 [0.40-1.59]	1.00 [0.14-7.07]
After exclusions	0.34 [0.01-7.98]	0.80 [0.40-1.59]	1.00 [0.14-7.07]
Peer-reviewed	0.63 [0.08-4.96]	1.00 [0.21-4.80]	1.00 [0.14-7.07]
RCTs	0.63 [0.08-4.96]	0.80 [0.40-1.59]	1.00 [0.14-7.07]
Mortality		0.85 [0.27-2.67]	1.00 [0.14-7.07]
Recovery	0.78 [0.57-1.07]	0.61 [0.43-0.87] **	
Viral	0.83 [0.52-1.32]	1.00 [0.89-1.11]	
RCT mortality		0.85 [0.27-2.67]	1.00 [0.14-7.07]

***Table 2.* Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. ** $p<0.01$.

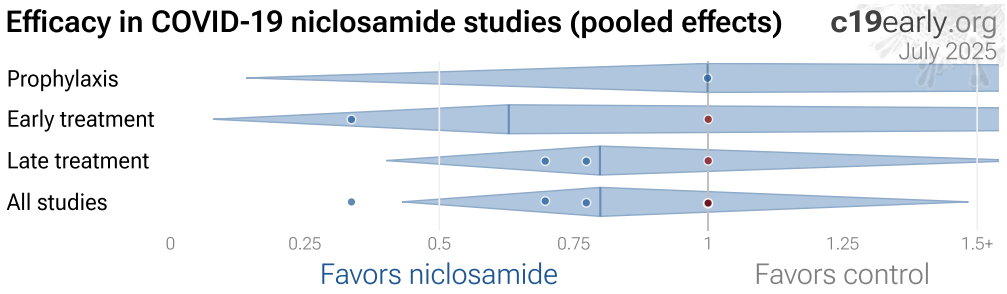


***Figure 4.* Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

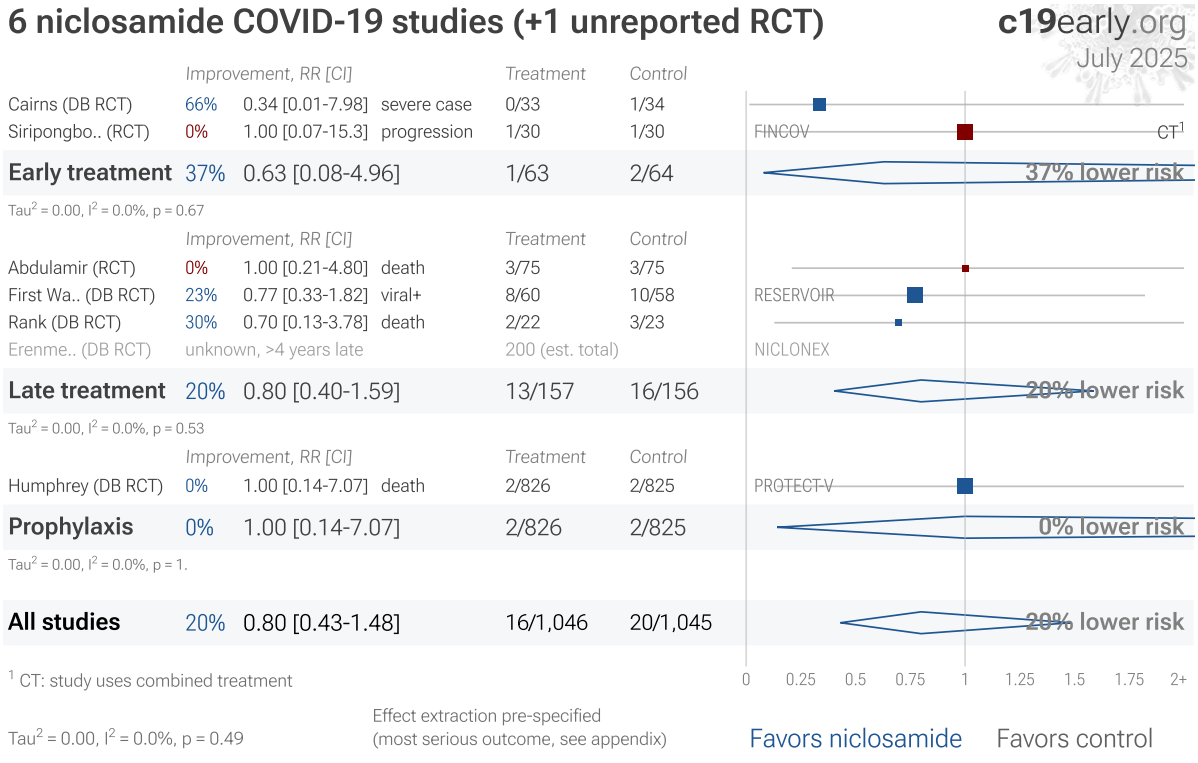


***Figure 5.* Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

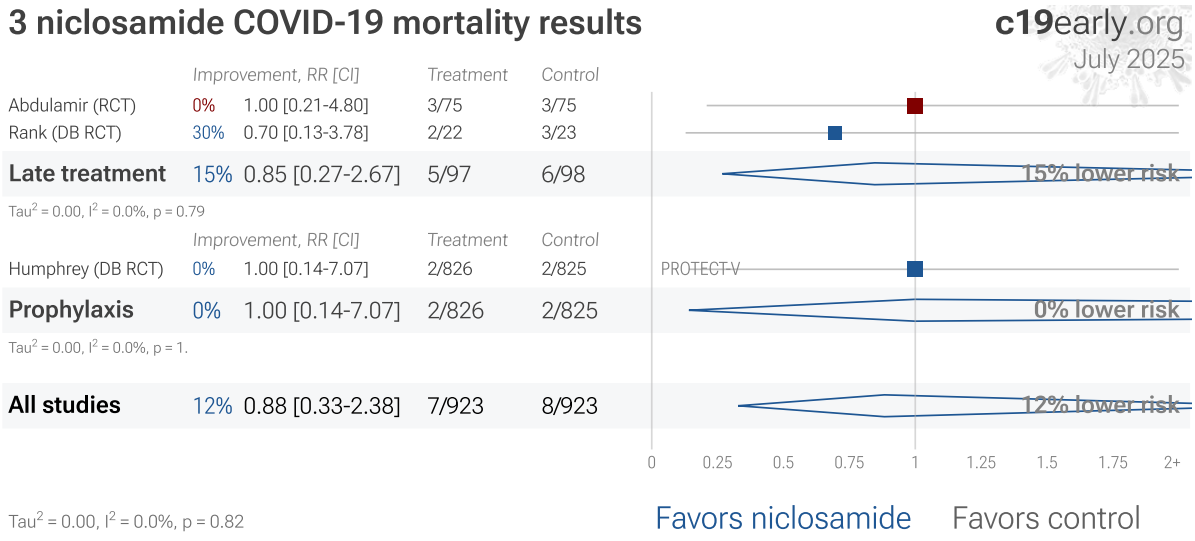


Figure 6. Random effects meta-analysis for mortality results.

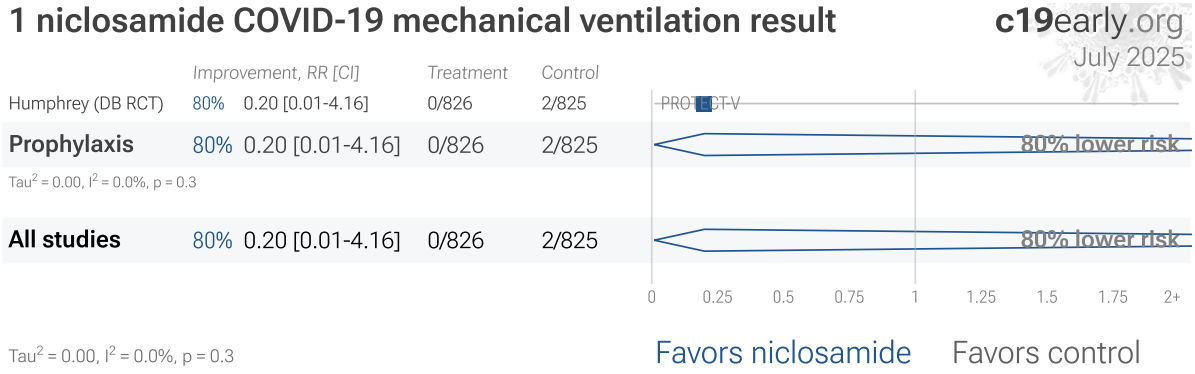


Figure 7. Random effects meta-analysis for ventilation.

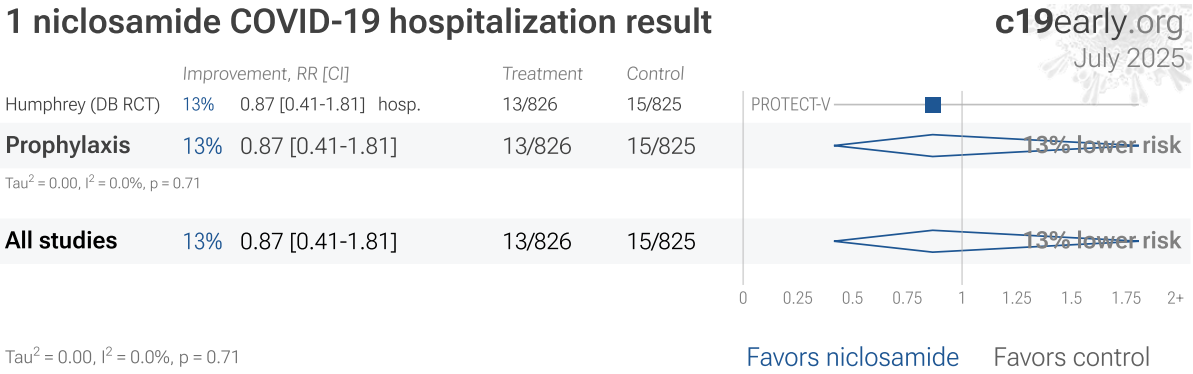


Figure 8. Random effects meta-analysis for hospitalization.

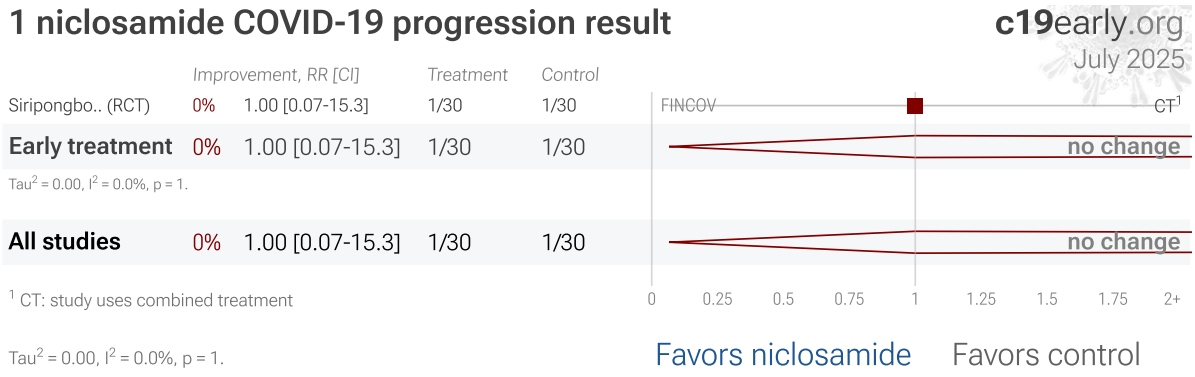


Figure 9. Random effects meta-analysis for progression.

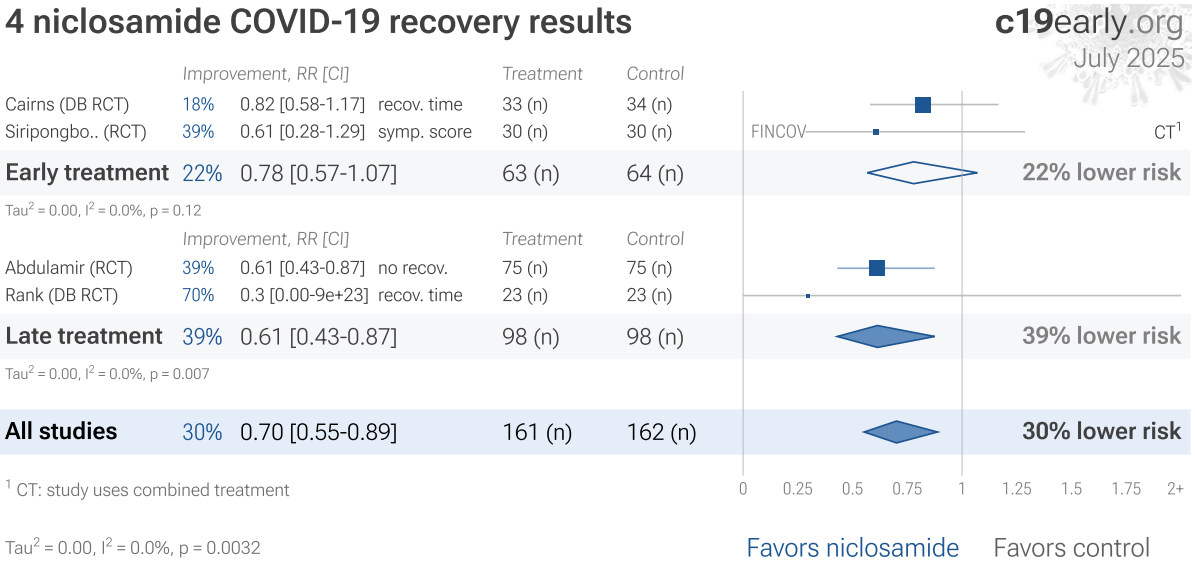


Figure 10. Random effects meta-analysis for recovery.

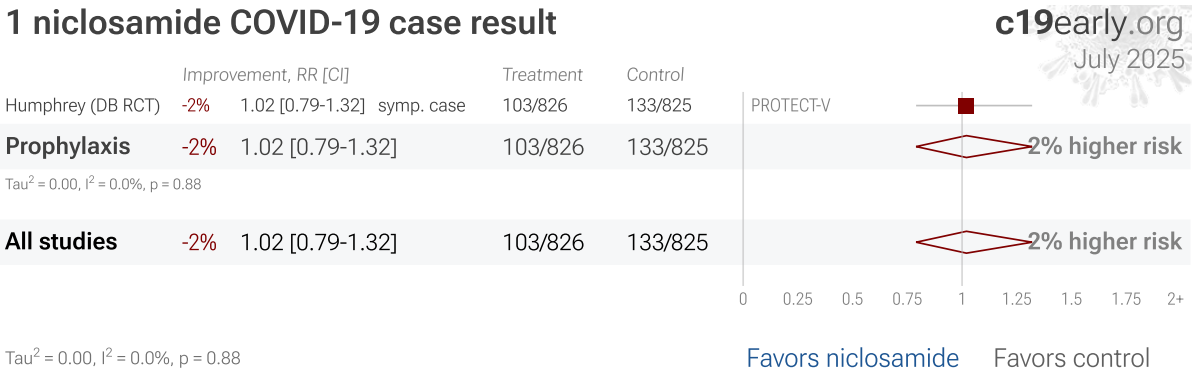


Figure 11. Random effects meta-analysis for cases.

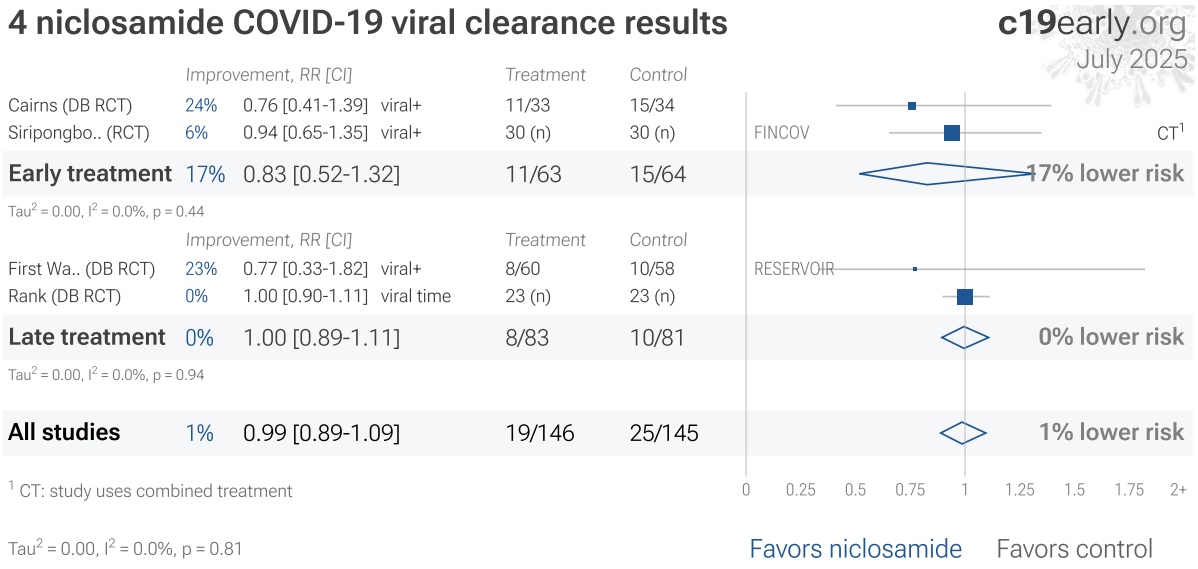


Figure 12. Random effects meta-analysis for viral clearance.

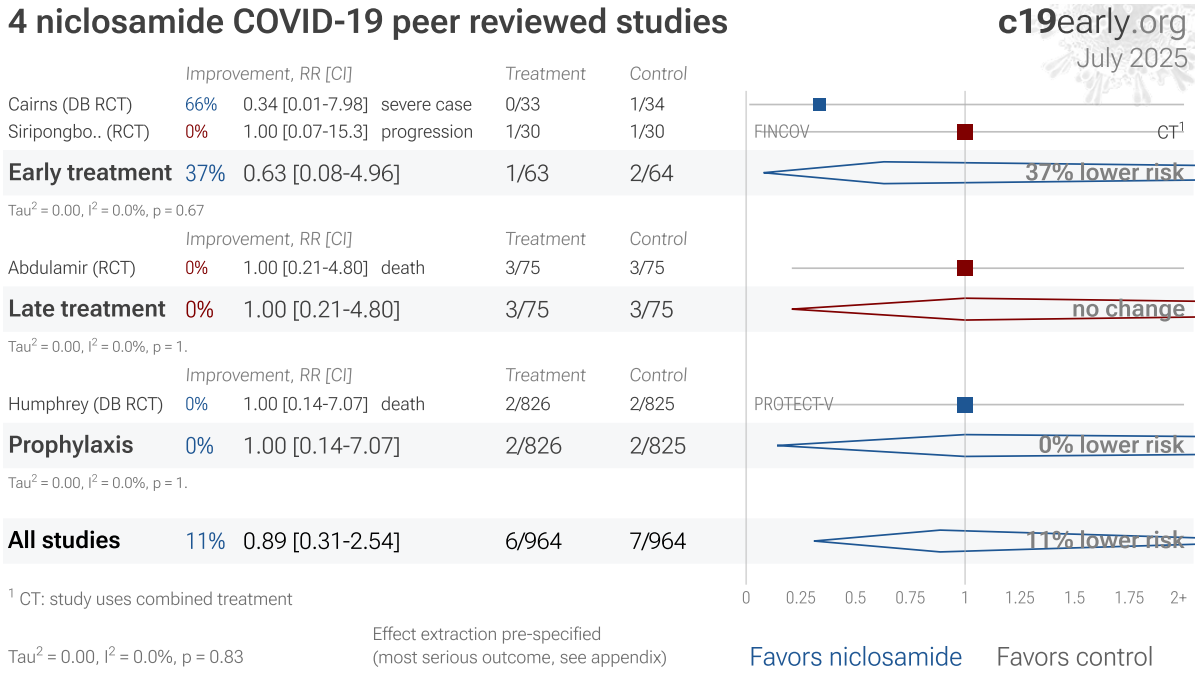


Figure 13. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Currently all studies are RCTs.

Unreported RCTs

1 niclosamide RCT has not reported results [1]. The trial reports report an estimated total of 200 patients. The result is delayed over 4 years.

Exclusions

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

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

Siripongboonsitti, data consistency issues, very low risk patients/variants with almost no progression, all patients received known effective antiviral, baseline differences.

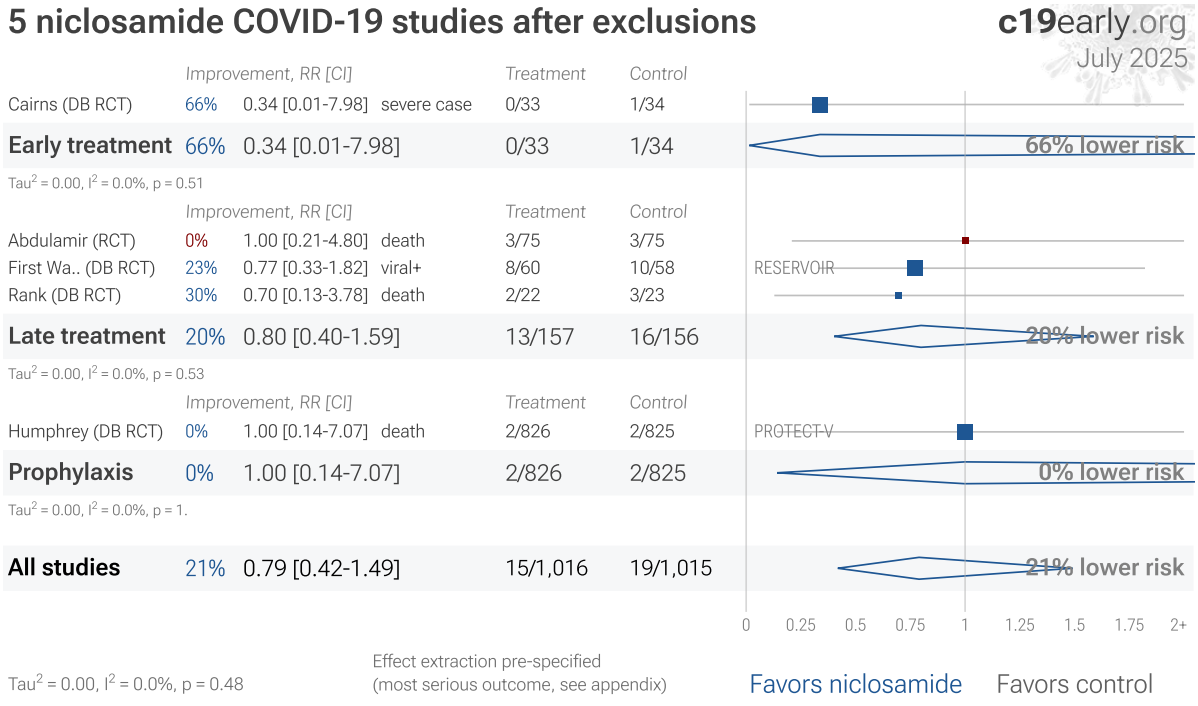


Figure 14. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome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

Heterogeneity

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

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours[44,45]. 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[46]
<24 hours	-33 hours symptoms[47]
24-48 hours	-13 hours symptoms[47]
Inpatients	-2.5 hours to improvement[48]

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

Figure 15 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

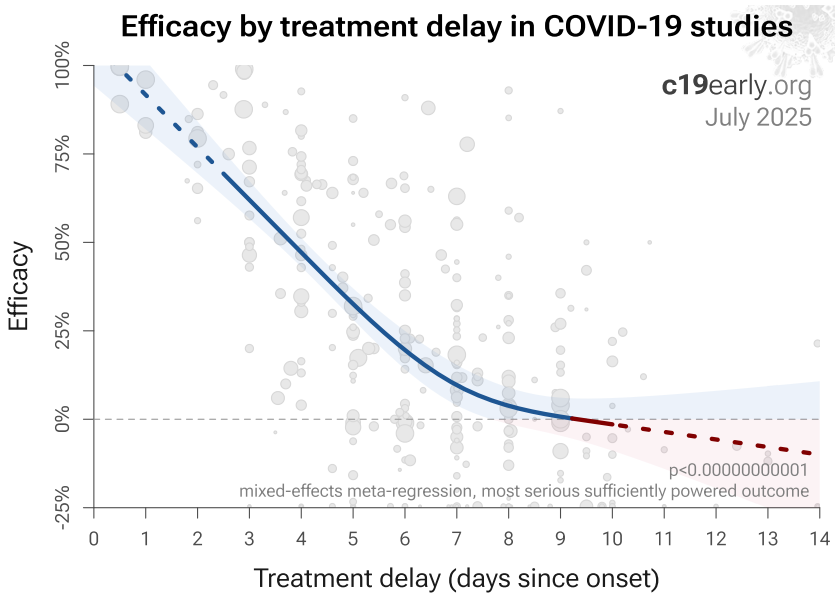


Figure 15. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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 variants[50], for example the Gamma variant shows significantly different characteristics[51-54]. 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[55,56].

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 synergistic[39,59-74], 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 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 16 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 17 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 18 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.000000082$ to $p = 0.0000000033$.

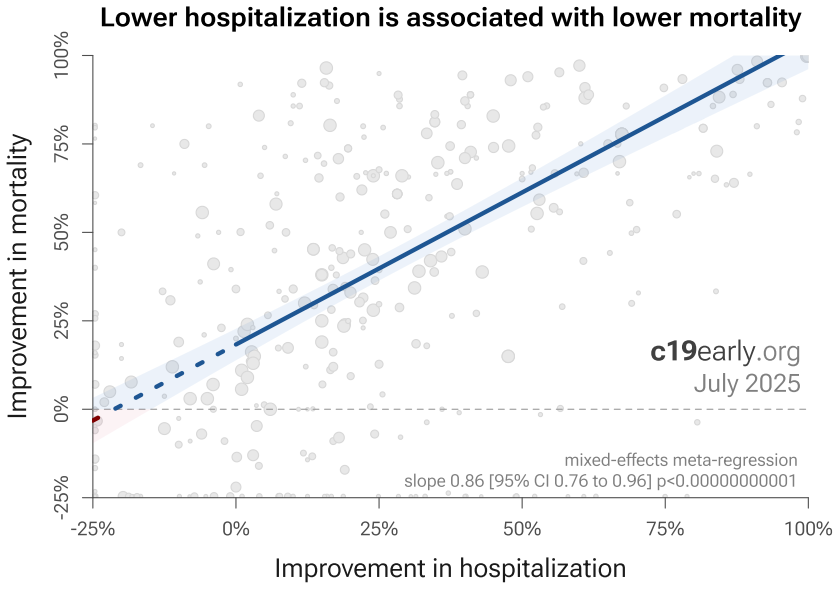


Figure 16. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

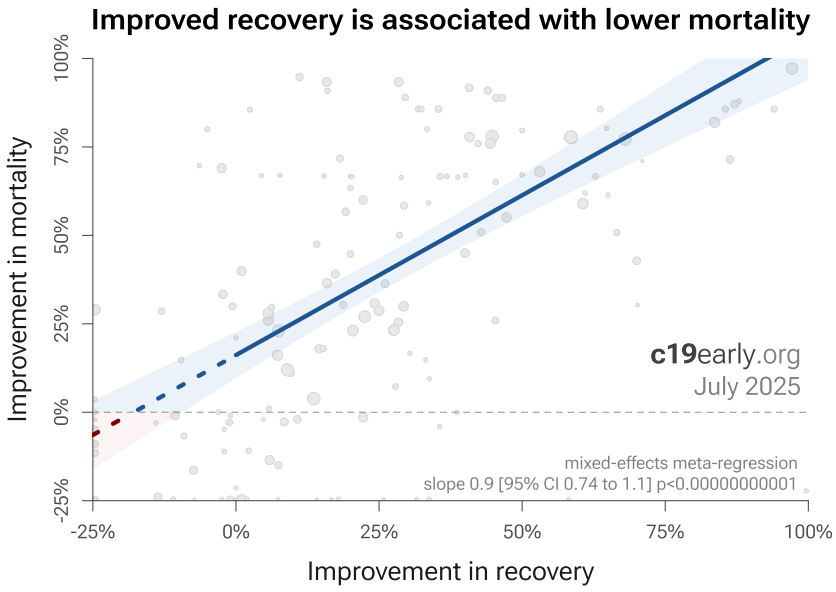


Figure 17. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

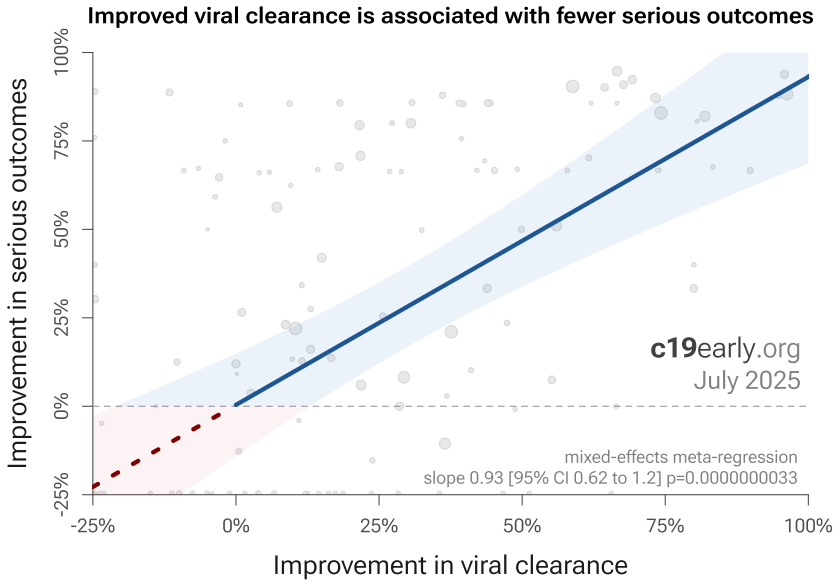


Figure 16. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

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

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 19 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

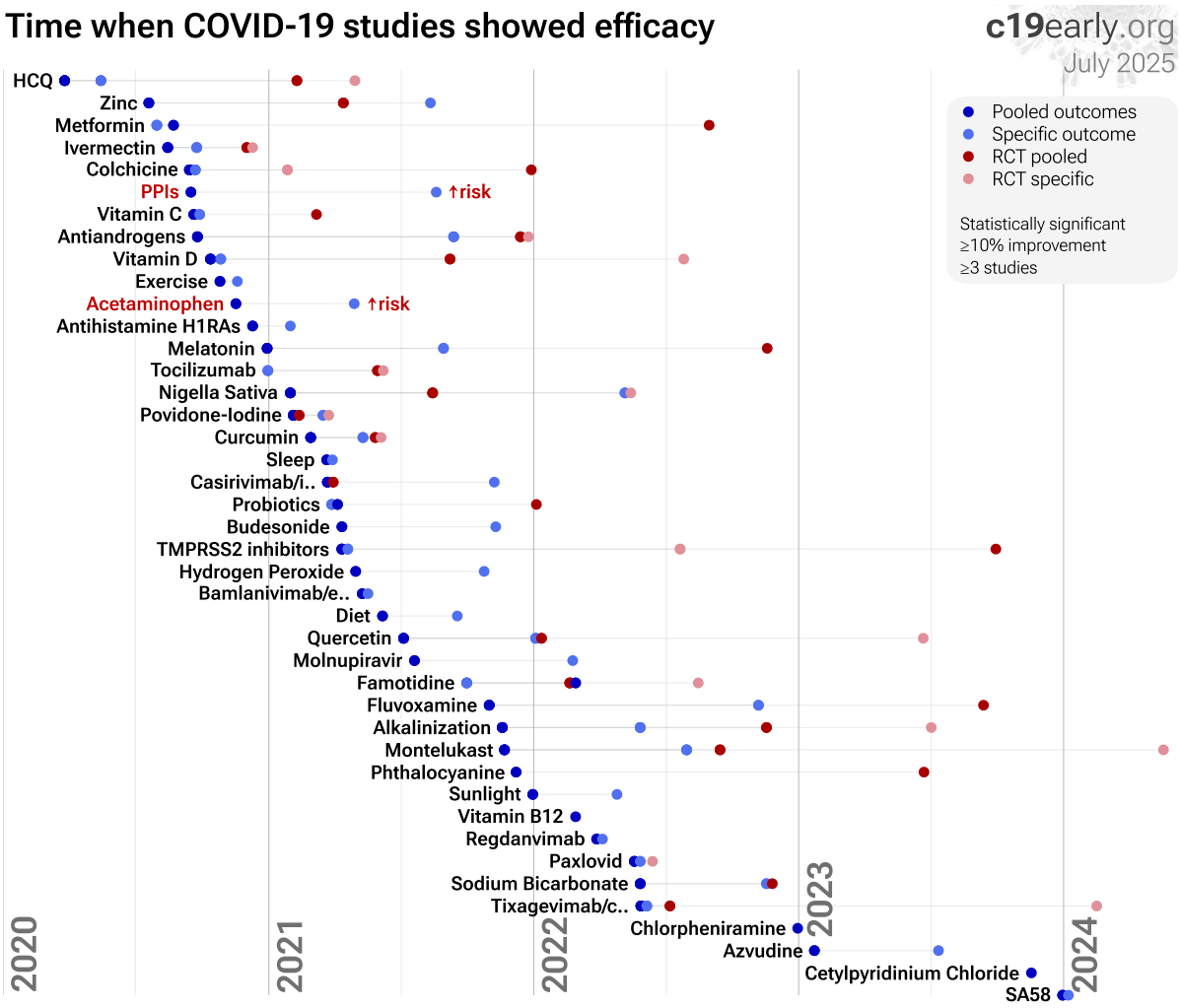


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting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

Limitations

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

Summary

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

Discussion

Publication bias

Publishing is often biased towards positive results. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and

CTRI/2021/08/0354242). For niclosamide, there is currently not enough data to evaluate publication bias with high confidence.

Funnel plot analysis

Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 20 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ [76-83]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

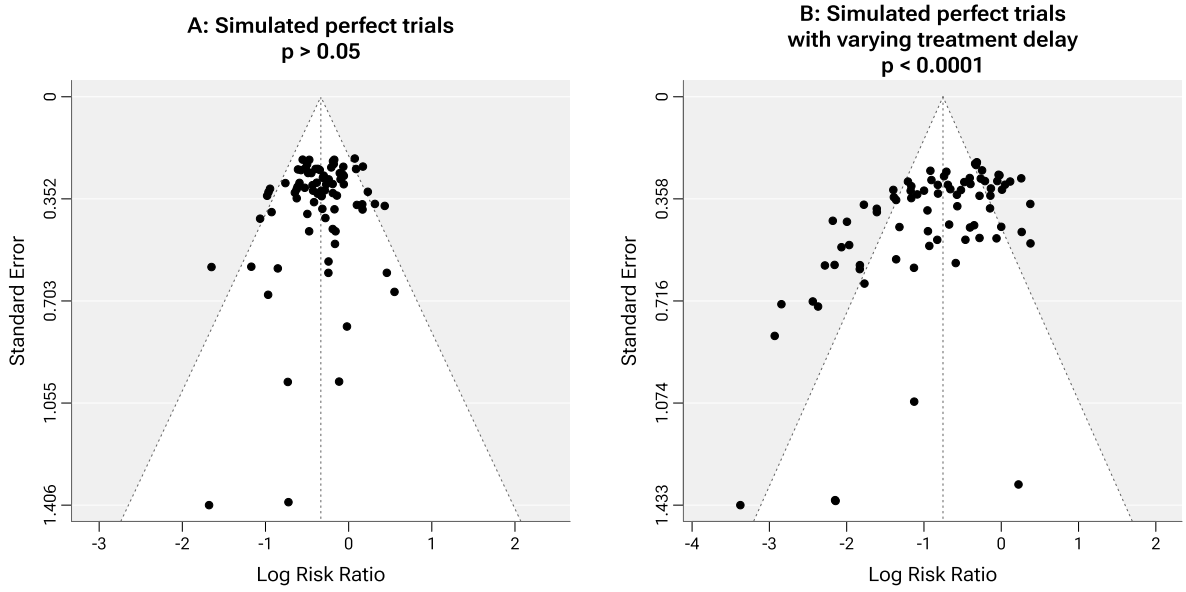


Figure 20. **Example funnel plot analysis for simulated perfect trials.**

Limitations

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone[39,59-74]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes

1 of 6 studies combine treatments. The results of niclosamide alone may differ. 1 of 6 RCTs use combined treatment.

Reviews

Many reviews cover niclosamide for COVID-19, presenting additional background on mechanisms and related results, including[38,84-90].

Other studies

Additional preclinical or review papers suggesting potential benefits of niclosamide for COVID-19 include[96-128]. 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 100+ host and viral proteins and other factors[22-29], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk[30], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 21 shows an overview of the results for niclosamide in the context of multiple COVID-19 treatments, and Figure 22 shows a plot of efficacy vs. cost for COVID-19 treatments.

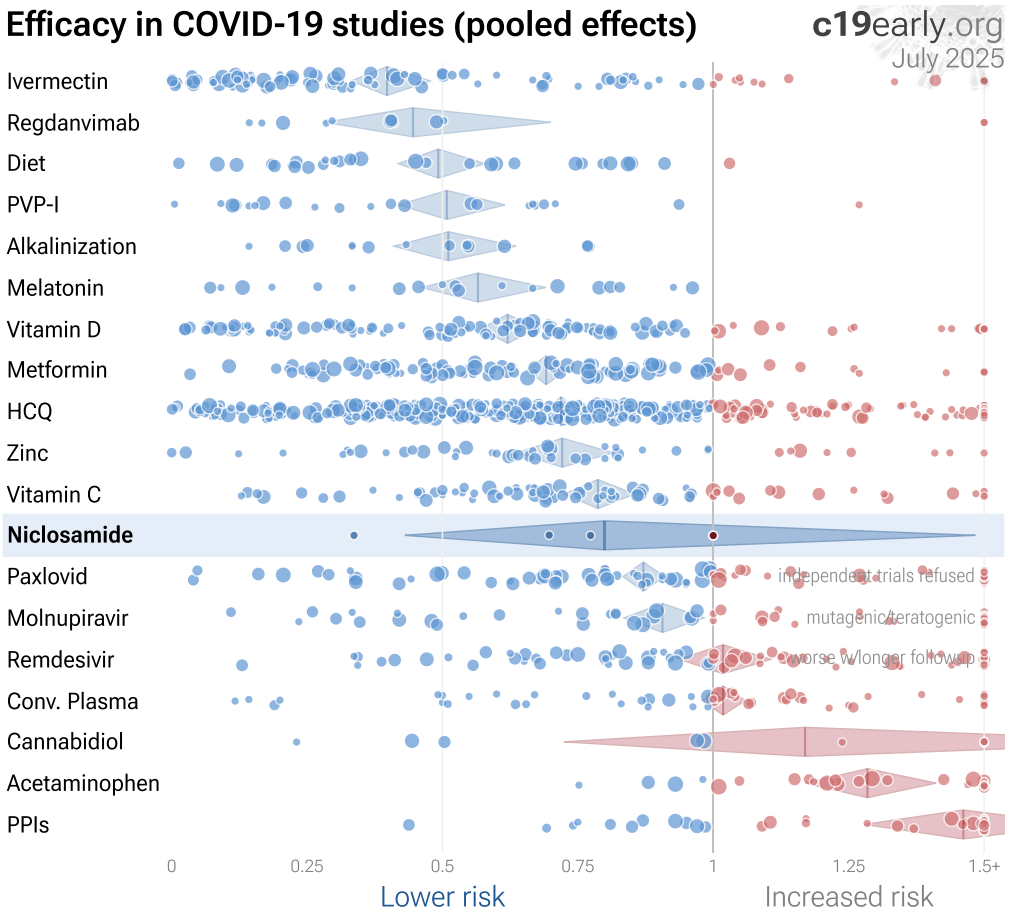


Figure 21. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [129].

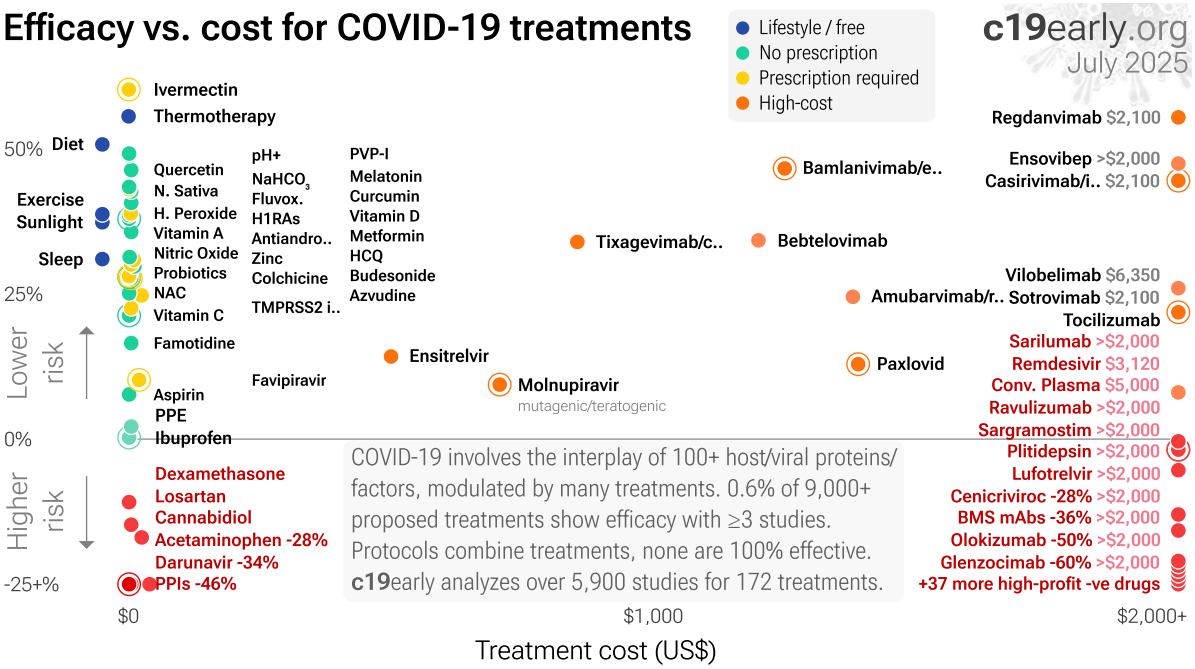


Figure 22. **Efficacy vs. cost for COVID-19 treatments.**

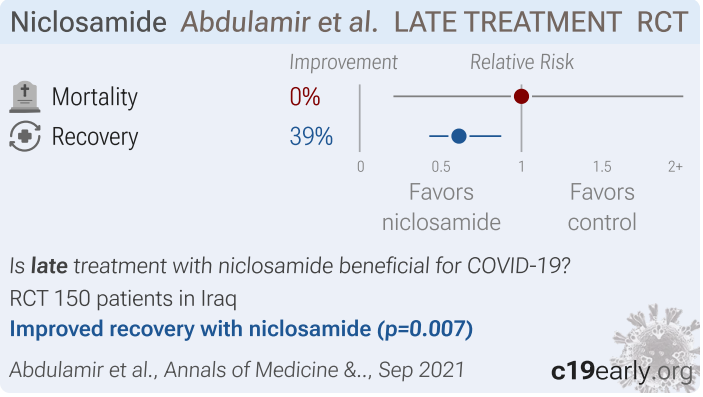
Conclusion

Significantly lower risk is seen for recovery. 2 studies from 2 independent teams in 2 countries show significant benefit. Meta analysis using the most serious outcome reported shows 20% [-48-57%] lower risk, without reaching statistical significance. Results are similar for higher quality studies and worse for peer-reviewed studies. Results are consistent with early treatment being more effective than late treatment. Currently all studies are RCTs.

Currently there is limited data, with only 20 control events for the most serious outcome in trials to date.

Study Notes

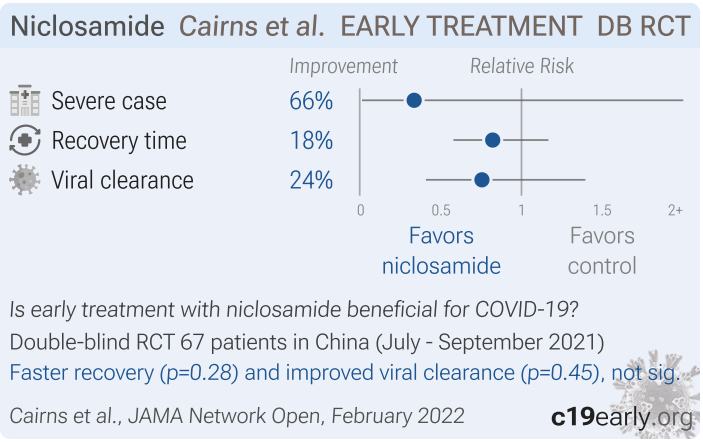
Abdulamir



RCT with 75 COVID-19 patients showing significantly faster recovery but no change in mortality with niclosamide.

The treatment group had more patients aged 60+ and more patients treated over a week after symptom onset.

Cairns

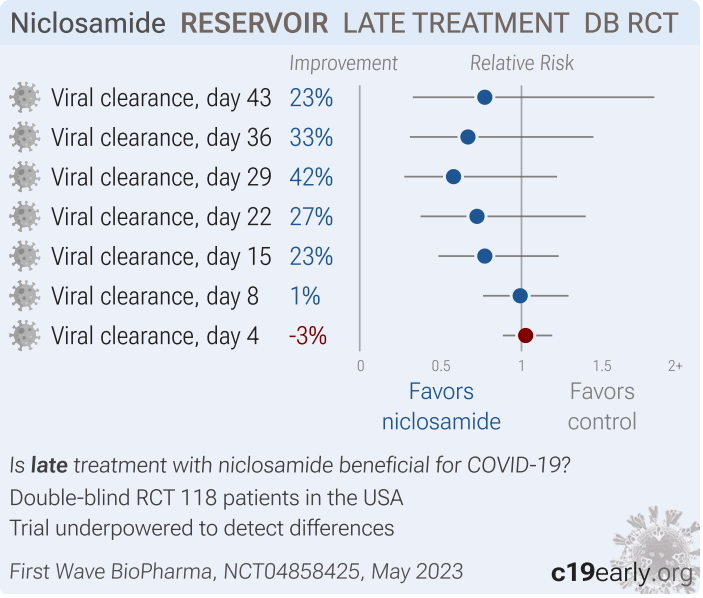


RCT with 73 mild to moderate outpatients, showing faster recovery and improved viral clearance with niclosamide, without statistical significance. Greater improvements in recovery were seen for high-risk patients, again without statistical significance. The study was underpowered due to decreased enrollment related to falling COVID-19 cases.

Erenmemisoglu

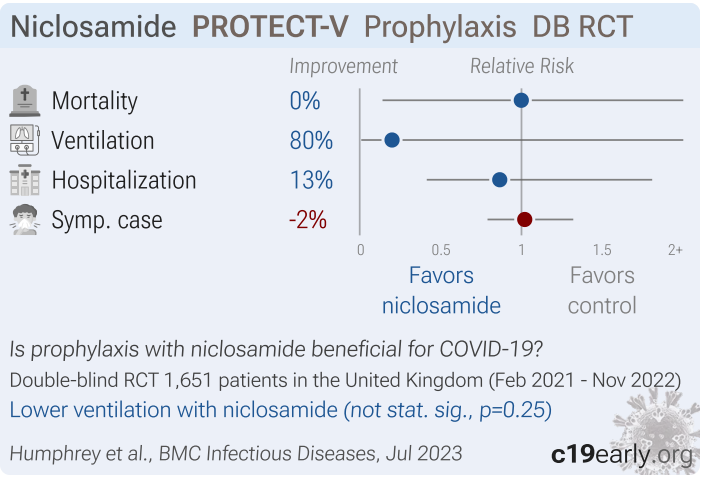
Estimated 200 patient niclosamide late treatment RCT with results not reported over 4 years after estimated completion.

First Wave BioPharma



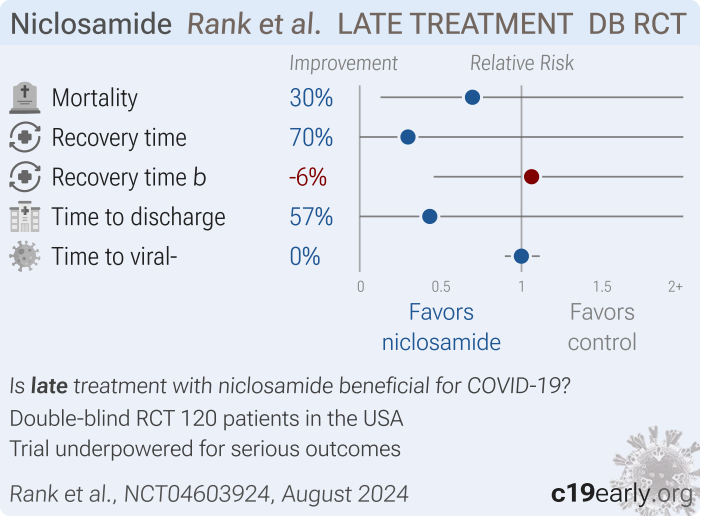
RCT 118 hospitalized patients with gastrointestinal infection showing no significant difference in viral clearance with niclosamide. Viral clearance results are available on clinicaltrials.gov but clinical results are missing.

Humphrey



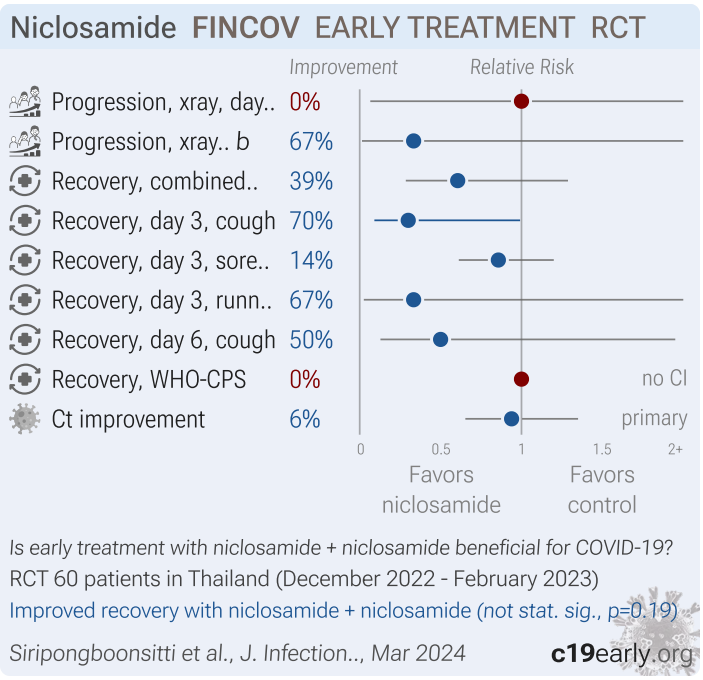
RCT 1,651 patients with kidney disease showing no significant difference in symptomatic COVID-19, hospitalization, or mortality with intranasal niclosamide compared to placebo. The UNI911 nasal spray had very poor adherence and a higher withdrawal rate (40% vs. 23.8% for placebo), partially due to local nasal and upper airway irritation.

Rank



RCT 46 moderate to severe hospitalized COVID-19 patients showing shorter time to discharge and WHO clinical scale improvement with niclosamide, but no significant difference for resolution of all symptoms and viral clearance.

Siripongboonsitti



RCT 60 low-risk outpatients, median age 31, with mild to moderate COVID-19 showing no significant differences with combined favipiravir/ivermectin/niclosamide treatment compared to favipiravir alone. There was limited room for improvement with almost no progression and no hospitalization, ICU admission, supplemental oxygen, or mortality.

The combined group showed significantly improved visual analog scale (VAS) scores for cough, runny nose, and diarrhea from day 3.

Authors note that "the WHO-CPS were significantly decreased among FPV/IVM/NCL vs FPV alone on day 10", however the degree of improvement cannot be determined based on the values reported.

Authors state that "All data generated or analyzed during this study are included in this published article", which is incorrect - only summary statistics are published. The trial registration states that data will not be made available.

This raises concerns, especially given many inconsistencies in the published data:

- E gene and ORF1 a/b gene day 1 Ct values are different between Table S1 and Table S3.
- Figure S1 shows 25% >= 38.5, however no number of 30 patients is 25%, and this does not match Table 2 (at most 23.3% >= 38.5).
- The first three calculations in section 3.3 all show p = 0.515, an unusual match for different calculations.
- "the FPV/IVM/NCL group had 0.62 cycles per day fewer than did the FPV group" does not match the data.
- Table 1 shows 30% loss of taste in the control group, however Table S2 shows a Q3 VAS score of 0, which is inconsistent.
- The abstract reference to significant differences for sore throat does not match the results in Table S6.

Not releasing data is a change from earlier COVID-19 trials by the same main author: TCTR20210615002 and TCTR20210609001 both indicate that individual patient level data would be available.

The trial was registered retrospectively. Discussion of prior research is very biased, however this may be required for publication. There were more patients with fever, anosmia, and loss of taste at baseline in the combined group. The adverse events reported show none of the expected side effects of ivermectin at the dose used.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are niclosamide 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 niclosamide for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. 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. This is a living analysis and is updated regularly.

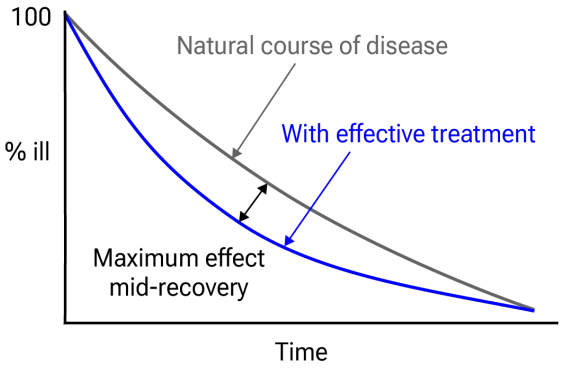


Figure 23. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 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 reduction [130]. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang 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 1 [134]. 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 (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

Forest plots are computed using PythonMeta [135] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective [44,45].

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

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

Early treatment

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

Cairns, 2/9/2022, Double Blind Randomized Controlled Trial, placebo-controlled, China, peer-reviewed, 9 authors, study period July 2021 - September 2021, trial NCT04399356 (history).	risk of severe case, 66.3% lower, RR 0.34, *p* = 1.00, treatment 0 of 33 (0.0%), control 1 of 34 (2.9%), NNT 34, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	recovery time, 17.8% lower, relative time 0.82, *p* = 0.28, treatment mean 12.01 (±9.35) n=33, control mean 14.61 (±9.98) n=34.
	risk of no viral clearance, 24.4% lower, RR 0.76, *p* = 0.45, treatment 11 of 33 (33.3%), control 15 of 34 (44.1%), NNT 9.3.

Siripongboonsitti, 3/29/2024, Randomized Controlled Trial, Thailand, peer-reviewed, 5 authors, study period 7 December, 2022 - 3 February, 2023, this trial uses multiple treatments in the treatment arm (combined with niclosamide) - results of individual treatments may vary, trial TCTR20230403007 (FINCOV), excluded in exclusion analyses: data consistency issues, very low risk patients/variants with almost no progression, all patients received known effective antiviral, baseline differences.	risk of progression, no change, RR 1.00, $p = 1.00$, treatment 1 of 30 (3.3%), control 1 of 30 (3.3%), chest xray progression, day 6.
	risk of progression, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 30 (0.0%), control 1 of 30 (3.3%), NNT 30, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), chest xray progression, day 3.
	risk of no recovery, 39.4% lower, RR 0.61, $p = 0.19$, treatment 30, control 30, combined symptoms.
	risk of no recovery, 70.0% lower, RR 0.30, $p = 0.048$, treatment 30, control 30, mid-recovery, day 3, cough.
	risk of no recovery, 14.3% lower, RR 0.86, $p = 0.38$, treatment 30, control 30, mid-recovery, day 3, sore throat.
	risk of no recovery, 66.7% lower, RR 0.33, $p = 0.41$, treatment 30, control 30, inverted to make RR<1 favor treatment, mid-recovery, day 3, runny nose.
	risk of no recovery, 50.0% lower, RR 0.50, $p = 0.32$, treatment 30, control 30, inverted to make RR<1 favor treatment, day 6, cough.
	relative Ct improvement, 6.1% better, RR 0.94, $p = 0.75$, treatment median 9.15 IQR 9.7 n=30, control median 8.59 IQR 8.24 n=30, E gene, mid-recovery, day 5, primary outcome.

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.

Abdulamir, 9/30/2021, Randomized Controlled Trial, Iraq, peer-reviewed, 7 authors, trial NCT04753619 (history).	risk of death, no change, RR 1.00, $p = 1.00$, treatment 3 of 75 (4.0%), control 3 of 75 (4.0%).
	risk of no recovery, 38.7% lower, HR 0.61, $p = 0.007$, treatment 75, control 75, adjusted per study, inverted to make HR<1 favor treatment, multivariable, Cox proportional hazards.
Erenmemisoglu, 2/14/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Turkey, trial NCT04558021 (history) (NICLONEX).	Estimated 200 patient RCT with results unknown and over 4 years late.
First Wave BioPharma, 5/1/2023, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 1 author, trial NCT04858425 (history) (RESERVOIR).	risk of no viral clearance, 22.7% lower, RR 0.77, $p = 0.61$, treatment 8 of 60 (13.3%), control 10 of 58 (17.2%), NNT 26, day 43.
	risk of no viral clearance, 33.1% lower, RR 0.67, $p = 0.35$, treatment 9 of 60 (15.0%), control 13 of 58 (22.4%), NNT 13, day 36.
	risk of no viral clearance, 42.0% lower, RR 0.58, $p = 0.17$, treatment 9 of 60 (15.0%), control 15 of 58 (25.9%), NNT 9.2, day 29.
	risk of no viral clearance, 27.5% lower, RR 0.73, $p = 0.39$, treatment 12 of 60 (20.0%), control 16 of 58 (27.6%), NNT 13, day 22.

	risk of no viral clearance, 22.7% lower, RR 0.77, p = 0.34, treatment 20 of 60 (33.3%), control 25 of 58 (43.1%), NNT 10, day 15.
	risk of no viral clearance, 0.8% lower, RR 0.99, p = 1.00, treatment 39 of 60 (65.0%), control 38 of 58 (65.5%), NNT 193, day 8.
	risk of no viral clearance, 2.6% higher, RR 1.03, p = 0.80, treatment 52 of 60 (86.7%), control 49 of 58 (84.5%), day 4.
Rank, 8/6/2024, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 1 author, trial NCT04603924 (history).	risk of death, 30.3% lower, RR 0.70, p = 1.00, treatment 2 of 22 (9.1%), control 3 of 23 (13.0%), NNT 25.
	recovery time, 70.2% lower, relative time 0.30, p = 0.97, treatment mean 4.15 (±4.87) n=23, control mean 13.91 (±1220) n=23, time to 2 point improvement.
	recovery time, 6.2% higher, relative time 1.06, p = 0.90, treatment mean 17.0 (±33.0) n=23, control mean 16.0 (±15.9) n=23, time to resolution of symptoms.
	time to discharge, 56.7% lower, relative time 0.43, p = 0.98, treatment mean 6.03 (±14.5) n=23, control mean 13.92 (±1220) n=23.
	time to viral-, 0.1% lower, relative time 1.00, p = 1.00, treatment mean 13.09 (±29.6) n=23, control mean 13.1 (±14.8) n=23.

Prophylaxis

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

Humphrey, 7/26/2023, Double Blind Randomized Controlled Trial, placebo-controlled, United Kingdom, peer-reviewed, median age 55.9, 21 authors, study period 19 February, 2021 - 28 November, 2022, trial NCT04870333 (history) (PROTECT-V).	risk of death, 0.1% lower, RR 1.00, p = 1.00, treatment 2 of 826 (0.2%), control 2 of 825 (0.2%), NNT 340725.
	risk of mechanical ventilation, 80.0% lower, RR 0.20, p = 0.25, treatment 0 of 826 (0.0%), control 2 of 825 (0.2%), NNT 412, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 13.4% lower, RR 0.87, p = 0.71, treatment 13 of 826 (1.6%), control 15 of 825 (1.8%), NNT 409.
	risk of symptomatic case, 2.0% higher, HR 1.02, p = 0.89, treatment 103 of 826 (12.5%), control 133 of 825 (16.1%), adjusted per study, multivariable, Cox proportional hazards.

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. The trimeric spike (S) protein is a glycoprotein that mediates viral entry by binding to the host ACE2 receptor, is critical for SARS-CoV-2's ability to infect host cells, and is a target of neutralizing antibodies. Inhibition of the spike protein prevents viral attachment, halting infection at the earliest stage.

c. The main protease or M^{pro}, also known as $3CL^{pro}$ or nsp5, is a cysteine protease that cleaves viral polyproteins into functional units needed for replication. Inhibiting M^{pro} disrupts the SARS-CoV-2 lifecycle within the host cell, preventing the creation of new copies.

d. RNA-dependent RNA polymerase (RdRp), also called nsp12, is the core enzyme of the viral replicase-transcriptase complex that copies the positive-sense viral RNA genome into negative-sense templates for progeny RNA synthesis. Inhibiting RdRp blocks viral genome replication and transcription.

e. The papain-like protease (PLpro) has multiple functions including cleaving viral polyproteins and suppressing the host immune response by deubiquitination and deISGylation of host proteins. Inhibiting PLpro may block viral replication and help restore normal immune responses.

f. The nucleocapsid (N) protein binds and encapsulates the viral genome by coating the viral RNA. N enables formation and release of infectious virions and plays additional roles in viral replication and pathogenesis. N is also an immunodominant antigen used in diagnostic assays.

g. The helicase, or nsp13, protein unwinds the double-stranded viral RNA, a crucial step in replication and transcription. Inhibition may prevent viral genome replication and the creation of new virus components.

References

1. ***Erenmemisoglu*** et al., *A Phase III, Randomized, Placebo-controlled, Clinical Trial to Evaluate the Efficacy and Safety of Co-administered Niclosamide in Patients Treated With an Established Regimen for Novel Coronavirus Infectious Disease (COVID-19)*, NCT04558021, clinicaltrials.gov/study/NCT04558021.

2. ***Ryu*** et al., *Fibrin drives thromboinflammation and neuropathology in COVID-19*, Nature, doi:10.1038/s41586-024-07873-4.

3. ***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.

4. ***Yang*** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.

5. ***Scardua-Silva*** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.

6. ***Hampshire*** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.

7. ***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.

8. ***Sodagar*** et al., *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, Biomolecules, doi:10.3390/biom12070971.

9. ***Sagar*** et al., *COVID-19-associated cerebral microbleeds in the general population*, Brain Communications, doi:10.1093/braincomms/fcae127.

10. ***Verma*** et al., *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, bioRxiv, doi:10.1101/2024.06.02.596989.

11. ***Panagea*** et al., *Neurocognitive Impairment in Long COVID: A Systematic Review*, Archives of Clinical Neuropsychology, doi:10.1093/arclin/acae042.

12. ***Ariza*** et al., *COVID-19: Unveiling the Neuropsychiatric Maze—From Acute to Long-Term Manifestations*, Biomedicines, doi:10.3390/biomedicines12061147.

13. ***Vashisht*** et al., *Neurological Complications of COVID-19: Unraveling the Pathophysiological Underpinnings and Therapeutic Implications*, Viruses, doi:10.3390/v16081183.

14. ***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.

15. ***Wang*** et al., *SARS-CoV-2 membrane protein induces neurodegeneration via affecting Golgi-mitochondria interaction*, Translational Neurodegeneration, doi:10.1186/s40035-024-00458-1.

16. ***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.

17. **Van Tin** et al., *Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF-κB Signaling*, Cells, doi:10.3390/cells13161331.

18. **Borka Balas** et al., *COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice*, Reviews in Cardiovascular Medicine, doi:10.31083/j.rcm2405125.

19. **AlTaweel** et al., *An In-Depth Insight into Clinical, Cellular and Molecular Factors in COVID19-Associated Cardiovascular Ailments for Identifying Novel Disease Biomarkers, Drug Targets and Clinical Management Strategies*, Archives of Microbiology & Immunology, doi:10.26502/ami.936500177.

20. **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.

21. **Trender** et al., *Changes in memory and cognition during the SARS-CoV-2 human challenge study*, eClinicalMedicine, doi:10.1016/j.eclinm.2024.102842.

22. **Dugied** et al., *Multimodal SARS-CoV-2 interactome sketches the virus-host spatial organization*, Communications Biology, doi:10.1038/s42003-025-07933-z.

23. **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.

24. **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.

25. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.

26. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.

27. **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.

28. **Katiyar** et al., *SARS-CoV-2 Assembly: Gaining Infectivity and Beyond*, Viruses, doi:10.3390/v16111648.

29. **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.

30. **c19early.org**, c19early.org/treatments.html.

31. **Haque** et al., *Exploring potential therapeutic candidates against COVID-19: a molecular docking study*, Discover Molecules, doi:10.1007/s44345-024-00005-5.

32. **Pejler** et al., *Blockade of endolysosomal acidification suppresses TLR3-mediated pro-inflammatory signaling in airway epithelial cells*, Journal of Allergy and Clinical Immunology, doi:10.1016/j.jaci.2024.05.031.

33. **Garrett** et al., *Niclosamide as a chemical probe for analyzing SARS-CoV-2 modulation of host cell lipid metabolism*, Frontiers in Microbiology, doi:10.3389/fmicb.2023.1251065.

34. **Yang (B)** et al., *Repurposing Niclosamide as a Novel Anti-SARS-CoV-2 Drug by Restricting Entry Protein CD147*, Biomedicines, doi:10.3390/biomedicines11072019.

35. **Sheng** et al., *A pseudovirus-based method to dynamically mimic SARS-CoV-2-associated cell-to-cell fusion and transmission*, Acta Biochimica et Biophysica Sinica, doi:10.3724/abbs.2023129.

36. **Munson** et al., *Niclosamide and ivermectin modulate caspase-1 activity and proinflammatory cytokine secretion in a monocytic cell line*, British Society For Nanomedicine Early Career Researcher Summer Meeting, 2021, web.archive.org/web/20230401070026/https://michealmunson.github.io/COVID.pdf.

37. **Needham**, D., *The pH Dependence of Niclosamide Solubility, Dissolution, and Morphology: Motivation for Potentially Universal Mucin-Penetrating Nasal and Throat Sprays for COVID19, its Variants and other Viral Infections*, Pharmaceutical Research, doi:10.1007/s11095-021-03112-x.

38. **Mothae** et al., *SARS-CoV-2 host-pathogen interactome: insights into more players during pathogenesis*, Virology, doi:10.1016/j.virol.2025.110607.

39. **Jitobaom** 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.

40. **Walia** et al., *SARS-CoV-2 virulence factor ORF3a blocks lysosome function by modulating TBC1D5-dependent Rab7 GTPase cycle*, Nature Communications, doi:10.1038/s41467-024-46417-2.

41. **Zeraatkar** et al., *Consistency of covid-19 trial preprints with published reports and impact for decision making: retrospective review*, BMJ Medicine, doi:10.1136/bmjmed-2022-0003091.

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

43. **Siripongboonsitti** et al., *A Randomized Trial to Assess the Acceleration of Viral Clearance by the Combination Favipiravir/Ivermectin/Niclosamide in Mild-to-Moderate COVID-19 Adult Patients (FINCOV)*, Journal of Infection and Public Health, doi:10.1016/j.jiph.2024.03.030.

44. **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.

45. **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.

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

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

48. **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.

49. **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.

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

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

52. **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.

53. **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.

54. **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.

55. **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.

56. **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.

57. **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.

58. **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.

59. **Jitobaom (B)** 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.

60. **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.

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

62. **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.

63. **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.

64. **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.

65. **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.

66. **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.

67. **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.

68. **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.

69. **Chen** et al., *Synergistic Inhibition of SARS-CoV-2 Replication Using Disulfiram/Ebselen and Remdesivir*, ACS Pharmacology & Translational Science, doi:10.1021/acsptsci.1c00022.

70. **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.

71. **Schultz** et al., *Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2*, Nature, doi:10.1038/s41586-022-04482-x.

72. **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.

73. **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.

74. **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.

75. **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.

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

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

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

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

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

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

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

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

84. **Saha (B)** et al., *Inhaled Dry Powder of Antiviral Agents: A Promising Approach to Treating Respiratory Viral Pathogens*, Viruses, doi:10.3390/v17020252.

85. **Ali** et al., *SARS-CoV-2 Syncytium under the Radar: Molecular Insights of the Spike-Induced Syncytia and Potential Strategies to Limit SARS-CoV-2 Replication*, Journal of Clinical Medicine, doi:10.3390/jcm12186079.

86. **Vibhute** et al., *Niclosamide: a potential treatment option for COVID-19*, International Journal of Applied Pharmaceutics, doi:10.22159/ijap.2023v15i1.45850.

87. **Abed** et al., *Evaluation the plausibility of repurpose of levamisole and niclosamide in treatment of covid-19*, Journal of Pharmaceutical Technolgy, doi:10.37662/jpt.2022.999481.

88. **Cesar-Silva** et al., *The Endolysosomal System: The Acid Test for SARS-CoV-2*, International Journal of Molecular Sciences, doi:10.3390/ijms23094576.

89. **Singh (B)** et al., *Niclosamide—A promising treatment for COVID-19*, British Journal of Pharmacology, doi:10.1111/bph.15843.

90. **Al-kuraishy** et al., *Niclosamide for Covid-19: bridging the gap*, Molecular Biology Reports, doi:10.1007/s11033-021-06770-7.

91. **Cairns** et al., *Efficacy of Niclosamide vs Placebo in SARS-CoV-2 Respiratory Viral Clearance, Viral Shedding, and Duration of Symptoms Among Patients With Mild to Moderate COVID-19*, JAMA Network Open, doi:10.1001/jamanetworkopen.2021.44942.

92. **Rank** et al., *A Phase 2/3 Randomized and Placebo-Controlled Study of ANA001 in Moderate and Severe COVID-19 Patients*, NCT04603924, clinicaltrials.gov/study/NCT04603924.

93. **First Wave BioPharma**, *A 2-Part, 2-Arm, Phase 2, Randomized, Double-Blind, Placebo-Controlled Study on the Safety and Efficacy of Niclosamide in Patients With COVID-19 With Gastrointestinal Infection*, NCT04858425, clinicaltrials.gov/study/NCT04858425.

94. **Abdulamir** et al., *A randomised controlled trial of effectiveness and safety of Niclosamide as add on therapy to the standard of care measures in COVID-19 management*, Annals of Medicine & Surgery, doi:10.1016/j.amsu.2021.102779.

95. **Humphrey** et al., *Prophylaxis for renal patients at risk of COVID-19 infection: results from the intranasal niclosamide randomised, double blinded, placebo controlled arm of the PROTECT-V platform trial*, BMC Infectious Diseases, doi:10.1186/s12879-025-10584-4.

96. **Jagtap** et al., *Exploring Niclosamide as a Multi-target Drug Against SARS-CoV-2: Molecular Dynamics Simulation Studies on Host and Viral Proteins*, Molecular Biotechnology, doi:10.1007/s12033-024-01296-2.

97. **Liu** et al., *Discovery and structural optimization of 3-O-β-Chacotriosyl betulonic acid saponins as potent fusion inhibitors of Omicron virus infections*, Bioorganic Chemistry, doi:10.1016/j.bioorg.2022.106316.

98. **Kumar (B)** et al., *Advancements in the development of antivirals against SARS-Coronavirus*, Frontiers in Cellular and Infection Microbiology, doi:10.3389/fcimb.2025.1520811.

99. **Rath** et al., *A Glimpse for the subsistence from pandemic SARS-CoV-2 infection*, Bioorganic Chemistry, doi:10.1016/j.bioorg.2024.107977.

100. **Saini** et al., *The Potential of Drug Repurposing as a Rapid Response Strategy in COVID-19 Therapeutics*, Journal of Advances in Medical and Pharmaceutical Sciences, doi:10.9734/jamps/2024/v26i12728.

101. **Barghash** et al., *Navigating the COVID-19 Therapeutic Landscape: Unveiling Novel Perspectives on FDA-Approved Medications, Vaccination Targets, and Emerging Novel Strategies*, MDPI AG, doi:10.20944/preprints202409.2409.v1.

102. **Ebrahimi** et al., *Systems biology approaches to identify driver genes and drug combinations for treating COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52484-8.

103. **Zhong** et al., *Bioinformatics and system biology approach to identify potential common pathogenesis for COVID-19 infection and sarcopenia*, Frontiers in Medicine, doi:10.3389/fmed.2024.1378846.

104. **Choi** et al., *Review of COVID-19 Therapeutics by Mechanism: From Discovery to Approval*, Journal of Korean Medical Science, doi:10.3346/jkms.2024.39.e134.

105. **Sharun** et al., *A comprehensive review on pharmacologic agents, immunotherapies and supportive therapeutics for COVID-19*, Narra J, doi:10.52225/narra.v2i3.92.

106. **Jeon** et al., *Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs*, bioRxiv, doi:10.1101/2020.03.20.999730.

107. **Gassen** et al., *Analysis of SARS-CoV-2-controlled autophagy reveals spermidine, MK-2206, and niclosamide as putative antiviral therapeutics*, bioRxiv, doi:10.1101/2020.04.15.997254.

108. **Mirabelli** et al., *Morphological Cell Profiling of SARS-CoV-2 Infection Identifies Drug Repurposing Candidates for COVID-19*, bioRxiv, doi:10.1101/2020.05.27.117184.

109. **Patten** et al., *Identification of druggable host targets needed for SARS-CoV-2 infection by combined pharmacological evaluation and cellular network directed prioritization both in vitro and in vivo*, bioRxiv, doi:10.1101/2021.04.20.440626.

110. **Braga** et al., *Drugs that inhibit TMEM16 proteins block SARS-CoV-2 spike-induced syncytia*, Nature, doi:10.1038/s41586-021-03491-6.

111. **Marwick** et al., *Application of a High-Content Screening Assay Utilizing Primary Human Lung Fibroblasts to Identify Antifibrotic Drugs for Rapid Repurposing in COVID-19 Patients*, SLAS Discovery, doi:10.1177/24725552211019405.

112. **Bess** et al., *Identification of oral therapeutics using an AI platform against the virus responsible for COVID-19, SARS-CoV-2*, Frontiers in Pharmacology, doi:10.3389/fphar.2023.1297924.

113. **Cesar-Silva (B)** et al., *Lipid compartments and lipid metabolism as therapeutic targets against coronavirus*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1268854.

114. **Mushebenge** et al., *Assessing the Potential Contribution of In Silico Studies in Discovering Drug Candidates That Interact with Various SARS-CoV-2 Receptors*, International Journal of Molecular Sciences, doi:10.3390/ijms242115518.

115. **Jeon (B)** et al., *Identification of Antiviral Drug Candidates against SARS-CoV-2 from FDA-Approved Drugs*, Antimicrobial Agents and Chemotherapy, doi:10.1128/AAC.00819-20.

116. **Mirabelli (B)** et al., *Morphological cell profiling of SARS-CoV-2 infection identifies drug repurposing candidates for COVID-19*, Proceedings of the National Academy of Sciences, doi:10.1073/pnas.2105815118.

117. **Mushebenge (B)** et al., *Assessing the Potential Contribution of in Silico Studies in Discovering Drug Candidates that Interact with Various SARS-CoV-2 Receptors*, MDPI AG, doi:10.20944/preprints202308.0434.v1.

118. **Low** et al., *COVID-19 Therapeutic Potential of Natural Products*, International Journal of Molecular Sciences, doi:10.3390/ijms24119589.

119. **Wang (B)** et al., *Inflammasomes: a rising star on the horizon of COVID-19 pathophysiology*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1185233.

120. **Oliver** et al., *Different drug approaches to COVID-19 treatment worldwide: an update of new drugs and drugs repositioning to fight against the novel coronavirus*, Therapeutic Advances in Vaccines and Immunotherapy, doi:10.1177/25151355221144845.

121. **Wang (C)** et al., *Repurposing Drugs for the Treatment of COVID-19 and Its Cardiovascular Manifestations*, Circulation Research, doi:10.1161/circresaha.122.321879.

122. **Mostafa** et al., *FDA-Approved Drugs with Potent In Vitro Antiviral Activity against Severe Acute Respiratory Syndrome Coronavirus 2*, Pharmaceuticals, doi:10.3390/ph13120443.

123. **Zeng** et al., *Repurpose Open Data to Discover Therapeutics for COVID-19 Using Deep Learning*, Journal of Proteome Research, doi:10.1021/acs.jproteome.0c00316.

124. **Wang (D)** et al., *Screening Potential Drugs for COVID-19 Based on Bound Nuclear Norm Regularization*, Frontiers in Genetics, doi:10.3389/fgene.2021.749256.

125. **Arshad** et al., *Prioritization of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics*, Clinical Pharmacology & Therapeutics, doi:10.1002/cpt.1909.

126. **Sperry** et al., *Target-agnostic drug prediction integrated with medical record analysis uncovers differential associations of statins with increased survival in COVID-19 patients*, PLOS Computational Biology, doi:10.1371/journal.pcbi.1011050.

127. **Gassen (B)** et al., *SARS-CoV-2-mediated dysregulation of metabolism and autophagy uncovers host-targeting antivirals*, Nature Communications, doi:10.1038/s41467-021-24007-w.

128. **Basu** et al., *Therapeutics for COVID-19 and post COVID-19 complications: An update*, Current Research in Pharmacology and Drug Discovery, doi:10.1016/j.crphar.2022.100086.

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

130. **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.

131. **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.

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

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

134. **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.

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