Thermotherapy reduces COVID-19 risk: real-time meta analysis of 4 studies

@CovidAnalysis, July 2025, Version 2
https://c19early.org/ttmeta.html

Abstract

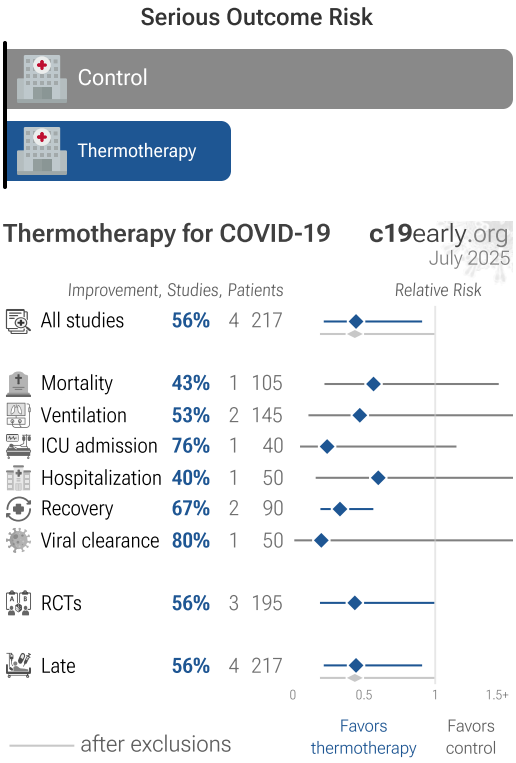
Thermotherapy, or heat therapy includes hydrothermotherapy, hydrotherapy, and diathermy, methods for increasing internal body temperature which may have benefits similar to natural fever, while providing potential advantages regarding localization, precision, and lower metabolic cost.

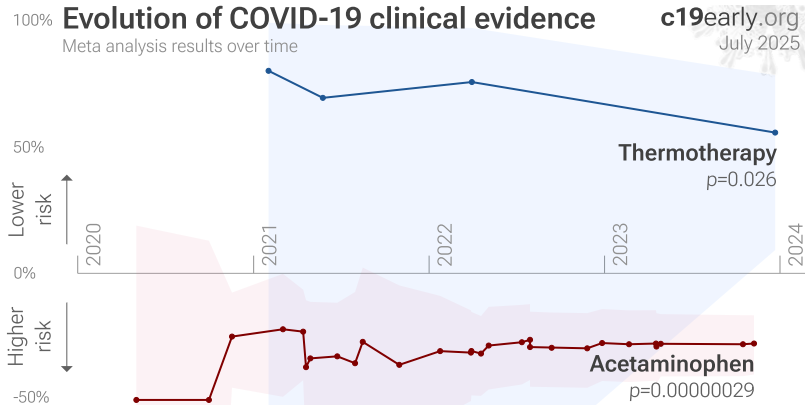
Significantly lower risk is seen for recovery. 3 studies from 3 independent teams in 2 countries show significant benefit.

Meta analysis using the most serious outcome reported shows 56% [9-78%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies.

Currently there is limited data, with only 217 patients and only 20 control events for the most serious outcome in trials to date.

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Thermotherapy currently has no early treatment studies. Thermotherapy methods may have additional mechanisms of action beyond increased internal body temperatures. Studies of ventilated patients are excluded [1]. All data and sources to reproduce this analysis are in the appendix.



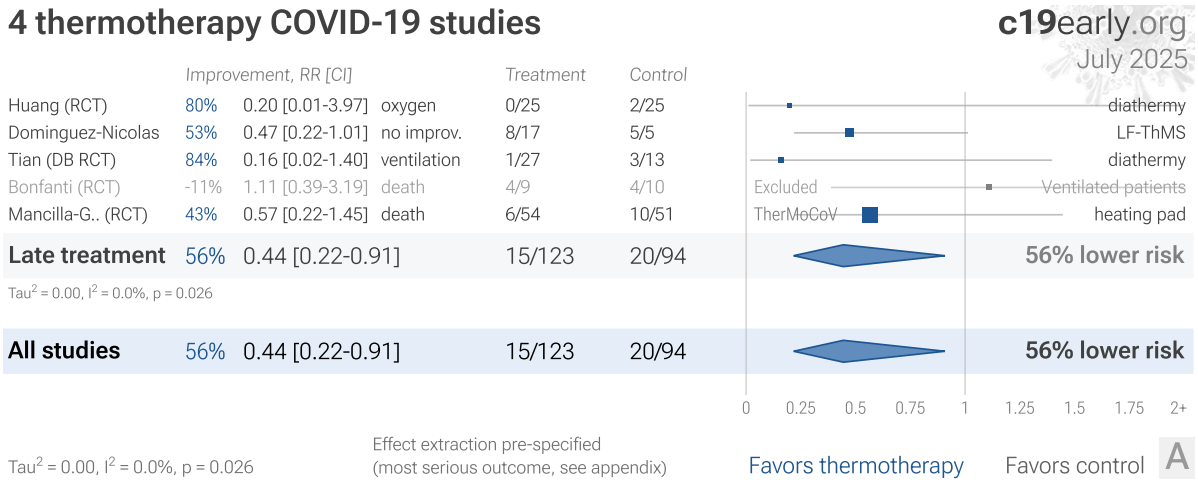


THERMOTHERAPY FOR COVID-19 — HIGHLIGHTS

Thermotherapy reduces risk with high confidence for pooled analysis, low confidence for ICU admission and recovery, and very low confidence for mortality.

53rd treatment shown effective in December 2023, now with $p = 0.026$ from 4 studies.

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.



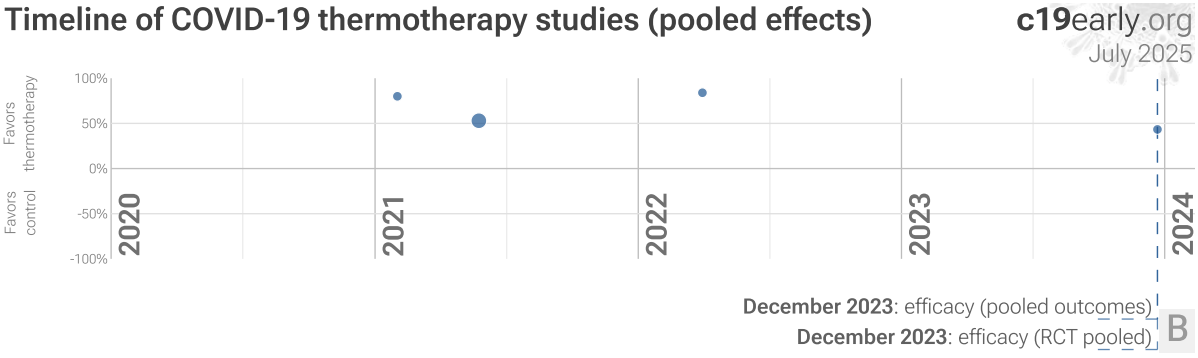


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in thermotherapy studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes and pooled outcomes in RCTs.

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.

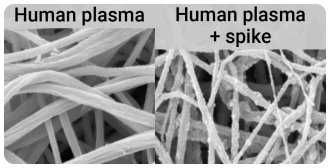


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[2].**

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.

Thermotherapy

Thermotherapy, or heat therapy includes hydrothermotherapy, hydrotherapy, and diathermy, methods for increasing internal body temperature which may have benefits similar to natural fever, while providing potential advantages regarding localization, precision, and lower metabolic cost. Thermotherapy is known to modulate the immune system [31] and to minimize SARS-CoV-2 replication [32].

Other infections

Studies have shown efficacy with thermotherapy for pneumonia [33], the common cold [34], SARS-CoV-1 [35], and influenza [36].

Analysis

We analyze all significant controlled studies of thermotherapy for COVID-19, excluding studies with mechanically ventilated patients. 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, 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. For thermotherapy, we do not consider prophylaxis. Currently all thermotherapy studies use late treatment.

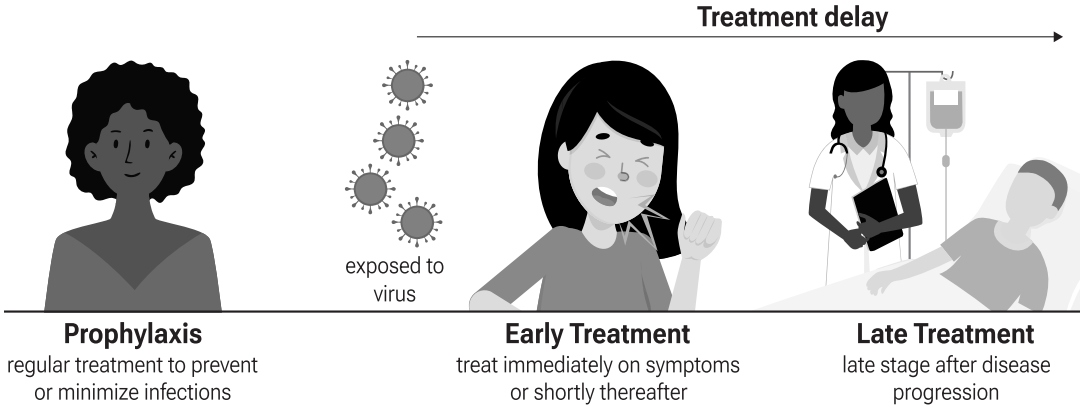


Figure 3. Treatment stages.

Preclinical Research

An *In Silico* study supports the efficacy of thermotherapy [37].

An *In Vitro* study supports the efficacy of thermotherapy [32].

An *In Vivo* animal study supports the efficacy of thermotherapy [38].

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.

Beneficial Effects of Fever

Fever is an important component of the acute response to coronavirus infection[39]. The evolutionary conservation of fever for over 600 million years supports a survival benefit[40]. Viral particle sensing occurs via pattern recognition receptors, such as toll-like receptors, triggering release of endogenous pyrogens such as interleukin-1. These cytokines induce thermoregulatory centers in the hypothalamus to elevate core temperature setpoints above normal homeostasis. The resulting fever enhances multiple aspects of the innate and adaptive immune systems[40], and creates a suboptimal internal environment that impairs SARS-CoV-2 enzyme function and replication. *In Vitro* studies demonstrate reduced viral output at sustained febrile temperatures of 38-39°C compared to basal 37°C conditions. Fever also correlates clinically with heightened interferon-γ, interleukin-6, lymphocyte activation, and antibody production critical for viral clearance.

Los et al. showed that higher temperature enhanced the expression of antiviral genes and reduced SARS-CoV-2 replication in Calu-3 and Caco-2 cells. An in vivo hamster model showed that higher body temperature at the time of infection correlated with lower viral loads.

Zhou et al. showed that SARS-CoV-2 patients with higher fever had lower viral load. Molecular dynamics simulations, surface plasmon resonance experiments, and pseudovirus cell entry assays showed decreased SARS-CoV-2 binding affinity to the human ACE2 receptor at higher temperature (40°C vs. 37°C).

Downing et al. induced hyperthermia (fever-like temperatures) in human volunteers by immersing them in warm water baths. They found that lymphocytes isolated from individuals with core body temperatures elevated to 39°C produced up to 10 times more interferon-γ, as shown in Figure 4. They also found an increase in suppressor/cytotoxic T cells and natural killer cells. The threshold of 39°C suggests relevance to fever, and the results suggest fever may play a role in boosting antiviral and immunoregulatory activities.

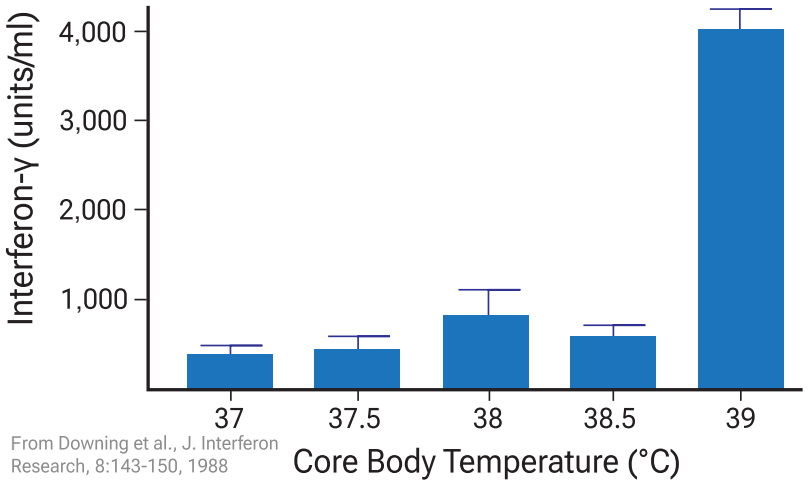


Figure 4. **A 10 fold increase in interferon-γ production was seen when core body temperature reached 39°C, from** *Downing et al.*

Herder et al. perform *in vitro* analysis with a 3D respiratory epithelial model using cells from human donors. Authors showed that elevated temperature (39-40°C) restricts SARS-CoV-2 infection and replication independently of interferon-mediated antiviral defenses. Authors found SARS-CoV-2 can still enter respiratory cells at 40°C but viral transcription and replication are inhibited, limiting the production of infectious virus. This temperature-dependent restriction correlates with altered host gene expression related to antiviral immunity and epigenetic regulation. The results suggest that febrile temperature ranges may confer protection to respiratory tissues by restricting SARS-CoV-2 propagation.

Dominguez-Nicolas et al. induced localized hyperthermia using LF-ThMS applied to the dorsal thorax (up to 44°C externally), resulting in significantly increased peripheral oxygen saturation (SpO_2) levels in COVID-19 patients, as shown in Figure 5.

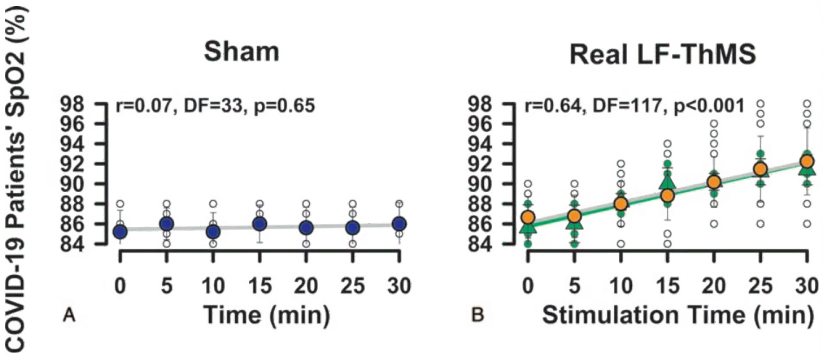


Figure 5. Rapidly increasing SpO_2 in COVID-19 patients with localized thoracic hyperthermia, from *Dominguez-Nicolas et al.*

Ramirez et al. compared COVID-19 mortality in Finland and Estonia, where sauna use is part of the culture and is typically practiced at least once a week, with the rest of Europe. Authors found significantly lower mortality with sauna culture, and suggest this may be due to the beneficial effects of hydrothermotherapy.

Ruble et al. compared army hospital vs. sanitarium treatment for the 1918 Spanish influenza, showing lower progression to pneumonia and lower mortality with sanitarium treatment, which involves hydrothermotherapy, sunlight, and fresh air.

Stewart reports on the use of diathermy in the treatment of pneumonia in 1926, with case reports from several physicians covering over 300 patients. Author reports that diathermy had consistent positive effects without significant adverse events, resulted in about half the mortality of the control group, significantly alleviated symptoms such as dyspnea, pain, and cardiac strain, and improved sleep and reduced respiratory rates.

Recent atom-level work strengthens the mechanistic case for fever-mediated viral attenuation. *Xie et al.* performed 200-ns equilibration followed by replicate 100-ns all-atom MD simulations of the spike RBD–ACE2 peptidase complex across physiologic-to-febrile temperatures. At 315 K the interface lost ~1 hydrogen bond, solvent exposure grew by ~4 Å², dissociation probability tripled, and MM-PBSA binding free energy became ≈59 kcal mol-¹ less favorable, driven by heat-induced straightening of the ACE2 α1-helix and withdrawal of the β3β4 hairpin that jointly destabilise the two anchor regions. Mild-cool conditions (305 K) had the opposite effect, α1-helix curvature tightened the interface, dissociation dropped eight-fold, and binding free energy became ~21 kcal mol-¹ more favorable. These thermodynamic shifts directly support febrile-range hyperthermia as a barrier to initial viral attachment.

In summary, fever is a key component of the response to infection. Fever enhances immune cell performance, induces cellular stress on pathogens, and may act synergistically with other stressors like iron deprivation. While results show beneficial effects of fever, it is not universally beneficial. Extreme or prolonged cases may be harmful. Fever may be more detrimental for individuals with lower tolerance for the increased metabolic demands.

Thermotherapy or heat therapy, which uses various methods for increasing internal body temperature, may have benefits similar to natural fever. Thermotherapy has potential advantages due to localization of treatment, precise temperature control, and lower metabolic cost; and potential risks due to improper application, excessive heat, contraindications, and not fully replicating the complex physiological effects of fever.

Results

Table 1 summarizes the results for all studies, for Randomized Controlled Trials, after exclusions, and for specific outcomes. Figure 6, 7, 8, 9, 10, 11, 12, and 13 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, and viral clearance.

	Relative Risk	Studies	Patients
All studies	0.44 [0.22-0.91] *	4	217
After exclusions	0.44 [0.19-0.99] *	3	195
RCTs	0.44 [0.19-0.99] *	3	195
Ventilation	0.47 [0.11-2.02]	2	145
Recovery	0.33 [0.19-0.57] ****	2	90

Table 1. **Random effects meta-analysis for all studies, for Randomized Controlled Trials, after exclusions, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ **** $p<0.0001$.

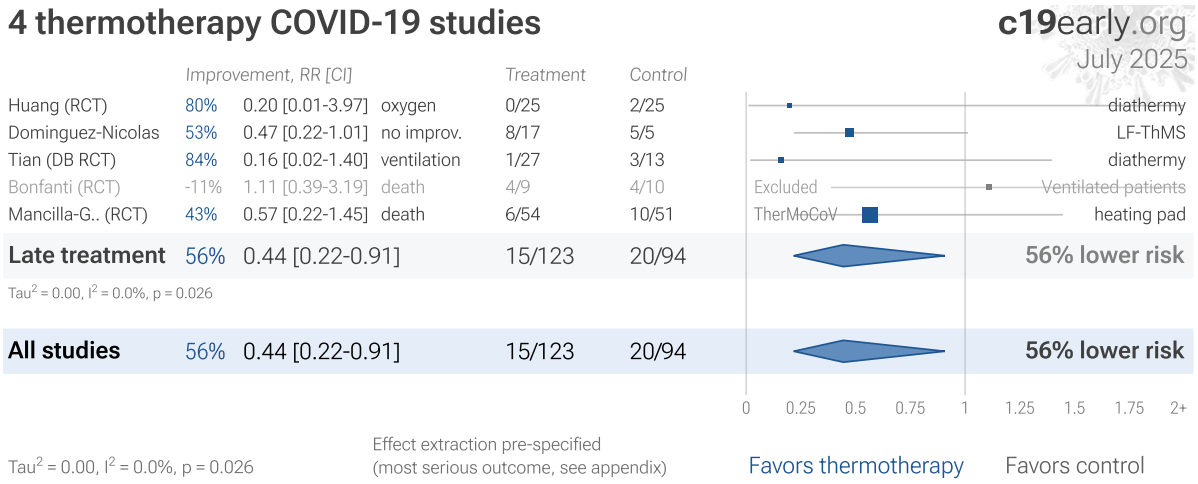


Figure 6. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

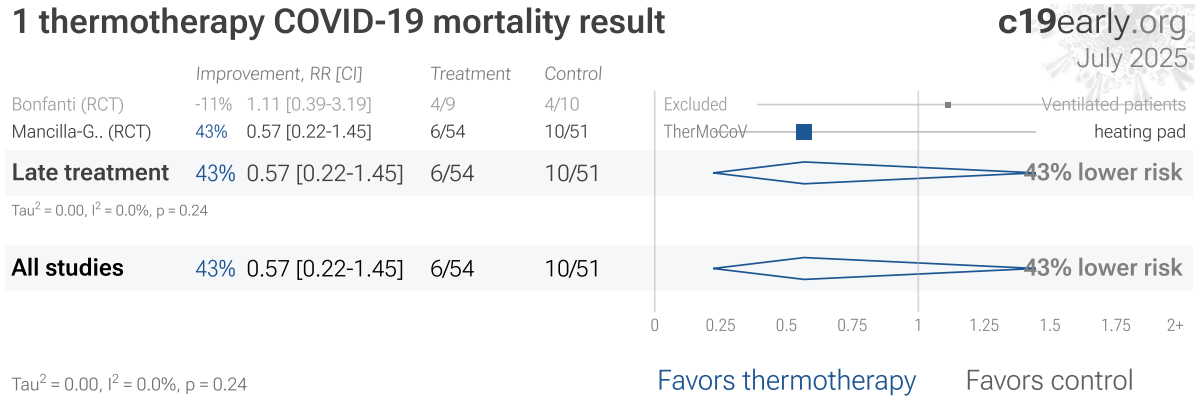


Figure 7. **Random effects meta-analysis for mortality results.**

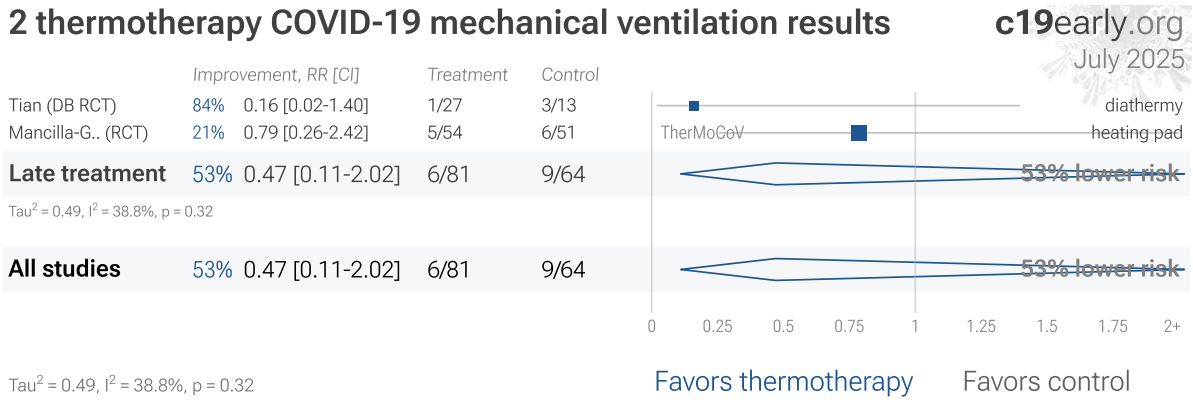


Figure 8. Random effects meta-analysis for ventilation.

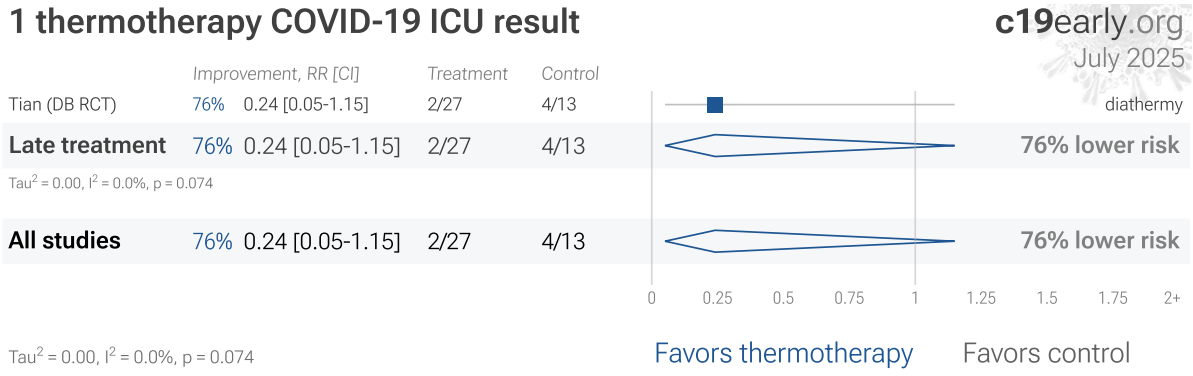


Figure 9. Random effects meta-analysis for ICU admission.

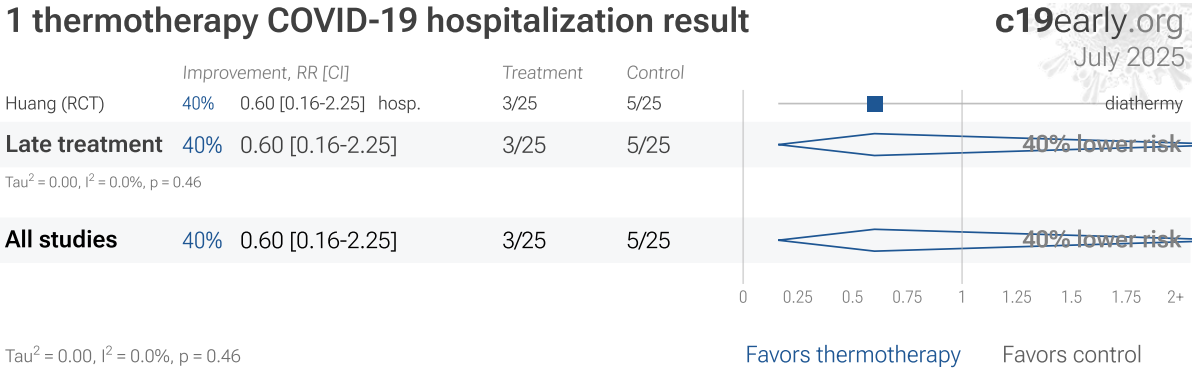


Figure 10. Random effects meta-analysis for hospitalization.

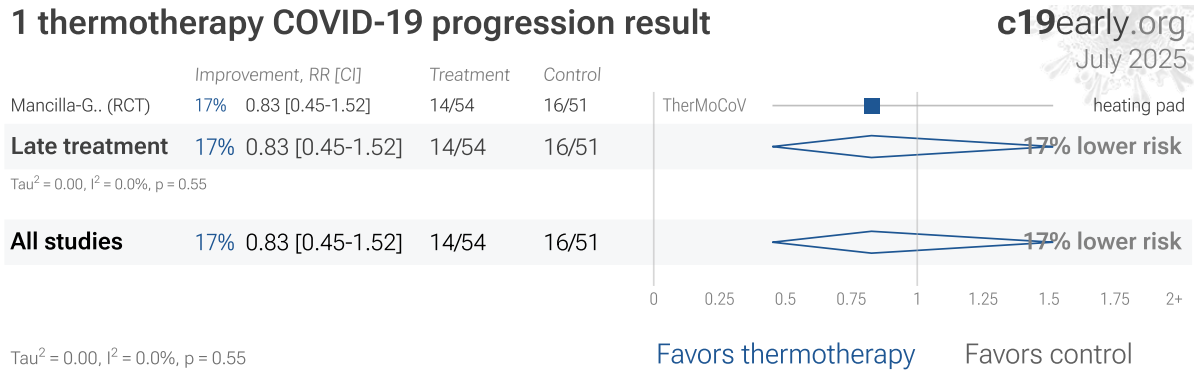


Figure 11. Random effects meta-analysis for progression.

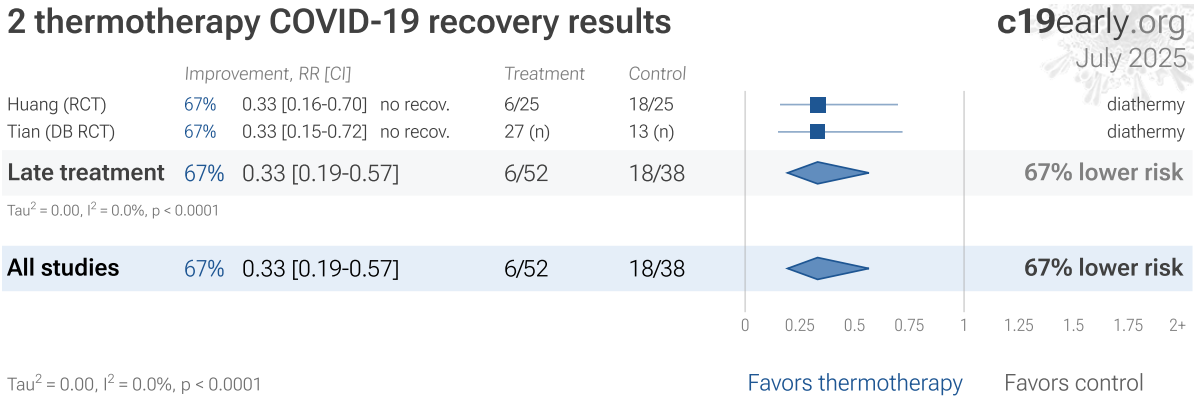


Figure 12. Random effects meta-analysis for recovery.

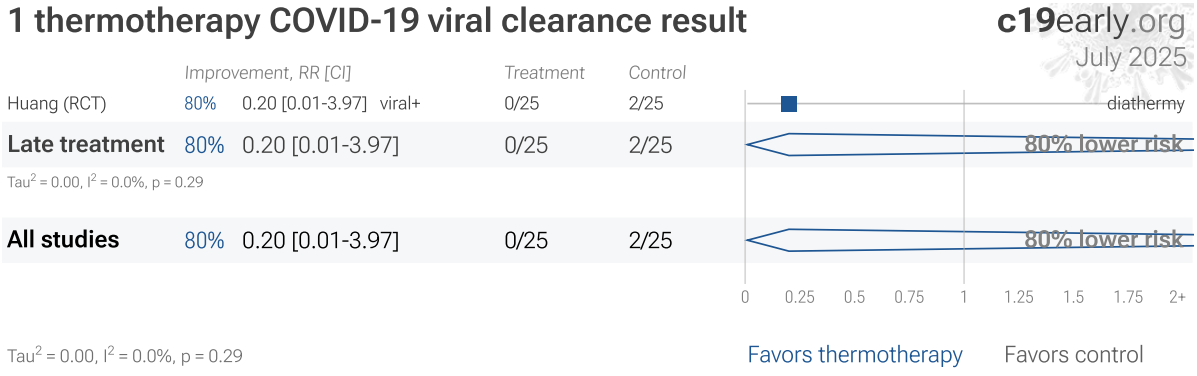


Figure 13. Random effects meta-analysis for viral clearance.

Randomized Controlled Trials (RCTs)

Figure 14 shows a comparison of results for RCTs and observational studies. Random effects meta analysis of RCTs shows 56% improvement, compared to 53% for other studies. Figure 15 and 16 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 1.

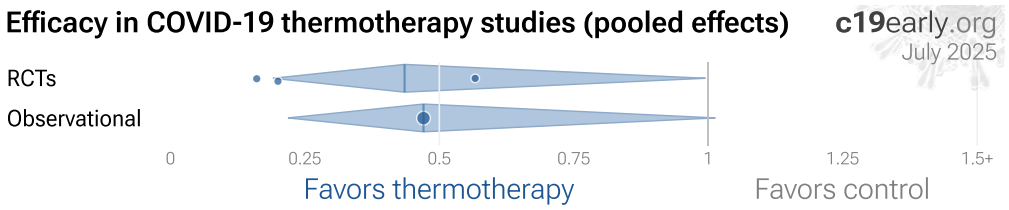


Figure 14. **Results for RCTs and observational studies.**

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases[46], and analysis of double-blind RCTs has identified extreme levels of bias[47]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs

RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment

High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 172 treatments we have analyzed, 67% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

Observational studies have been shown to be reliable

Evidence shows that observational studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* analyzed reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. We performed a similar analysis across the 172 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.98 [0.92-1.05][52]. Similar results are found for all low-cost treatments, RR 1.00 [0.91-1.09]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the supplementary data. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh

the benefits, for example excessive dosages, excessive treatment delays, or remote survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see[54,55].

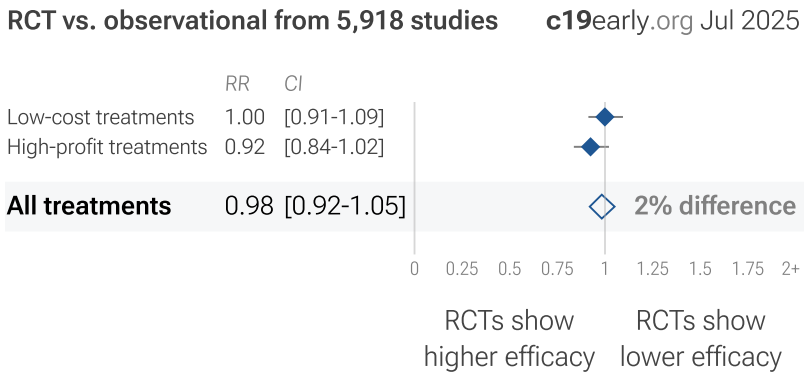


Figure 17. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[49].**

Using all studies identifies efficacy 8+ months faster (9+ months for low-cost treatments)

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. Of these, 58% have been confirmed in RCTs, with a mean delay of 7.7 months (64% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

Summary

We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

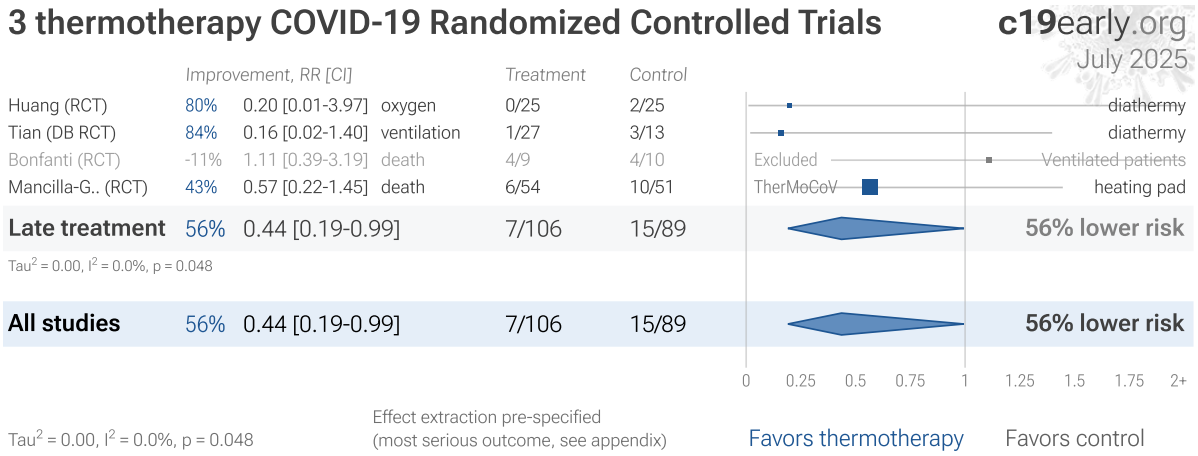


Figure 15. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious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

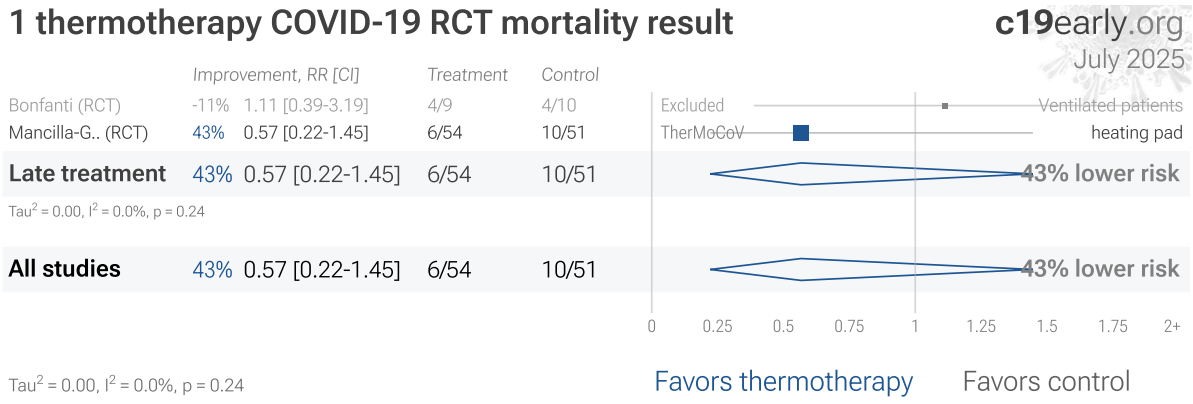


Figure 16. Random effects meta-analysis for RCT mortality results.

Exclusions

We exclude studies with mechanically ventilated patients because thermotherapy is typically recommended earlier in infection where the mechanisms of action are expected to be more relevant.

To avoid bias in the selection of studies, we analyze all other 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 18 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Dominguez-Nicolas, the study design does not provide a clear relative risk.

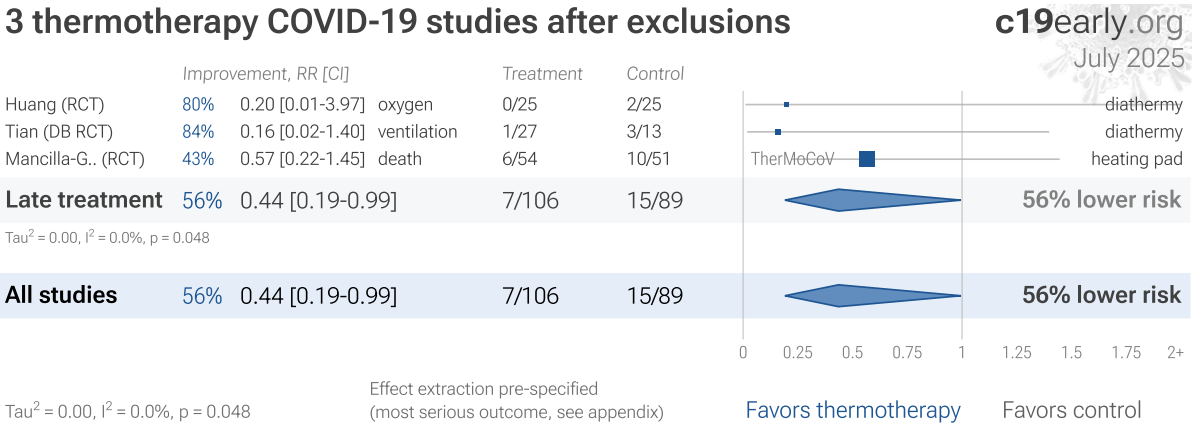


Figure 18. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome 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[56,57]. 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[58]
<24 hours	-33 hours symptoms[59]
24-48 hours	-13 hours symptoms[59]
Inpatients	-2.5 hours to improvement[60]

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

Figure 19 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.

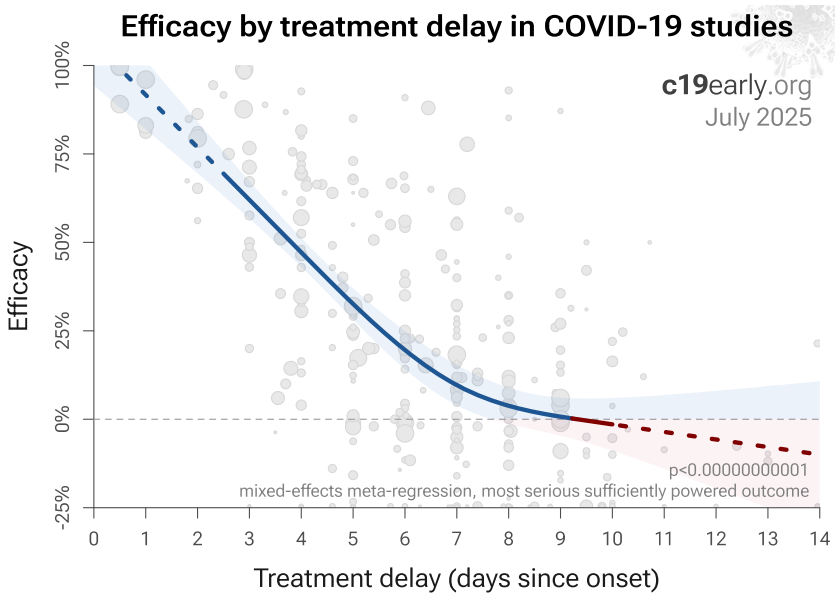


Figure 19. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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 [62], for example the Gamma variant shows significantly different characteristics [63-66]. 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 [67,68].

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 [71-87], 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 20 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 21 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 22 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 $p = 0.0000000033$.

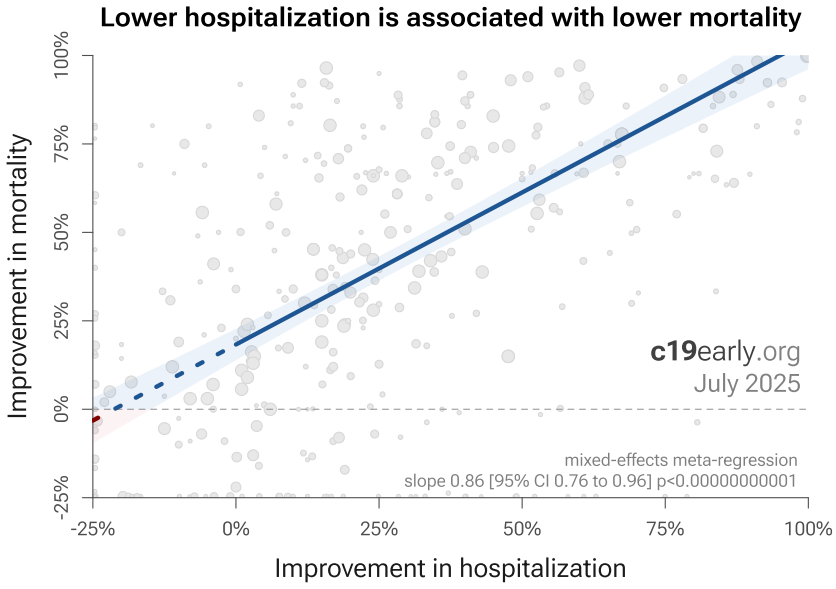


Figure 20. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

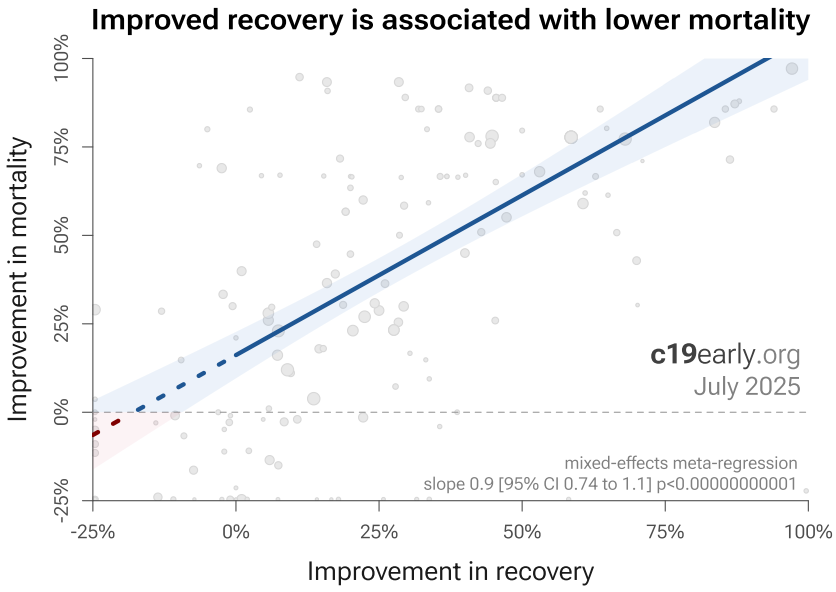


Figure 21. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

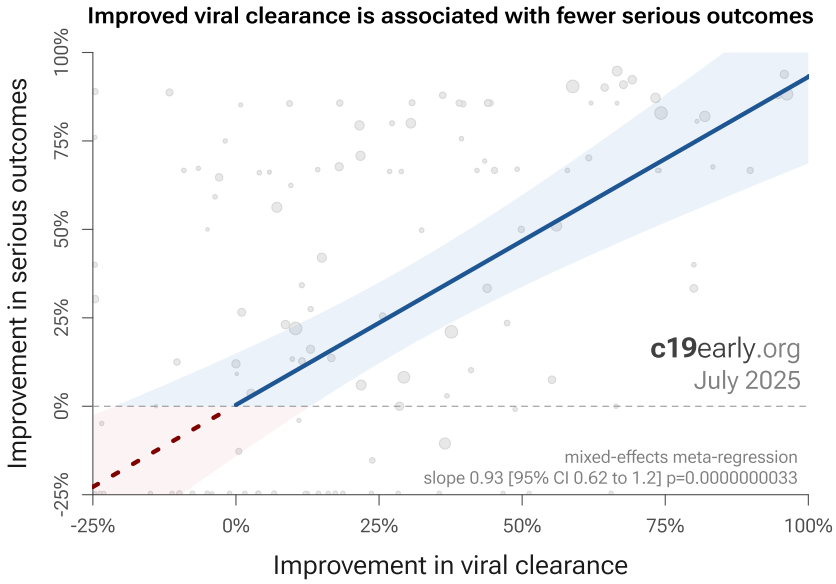


Figure 20. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

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 23 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

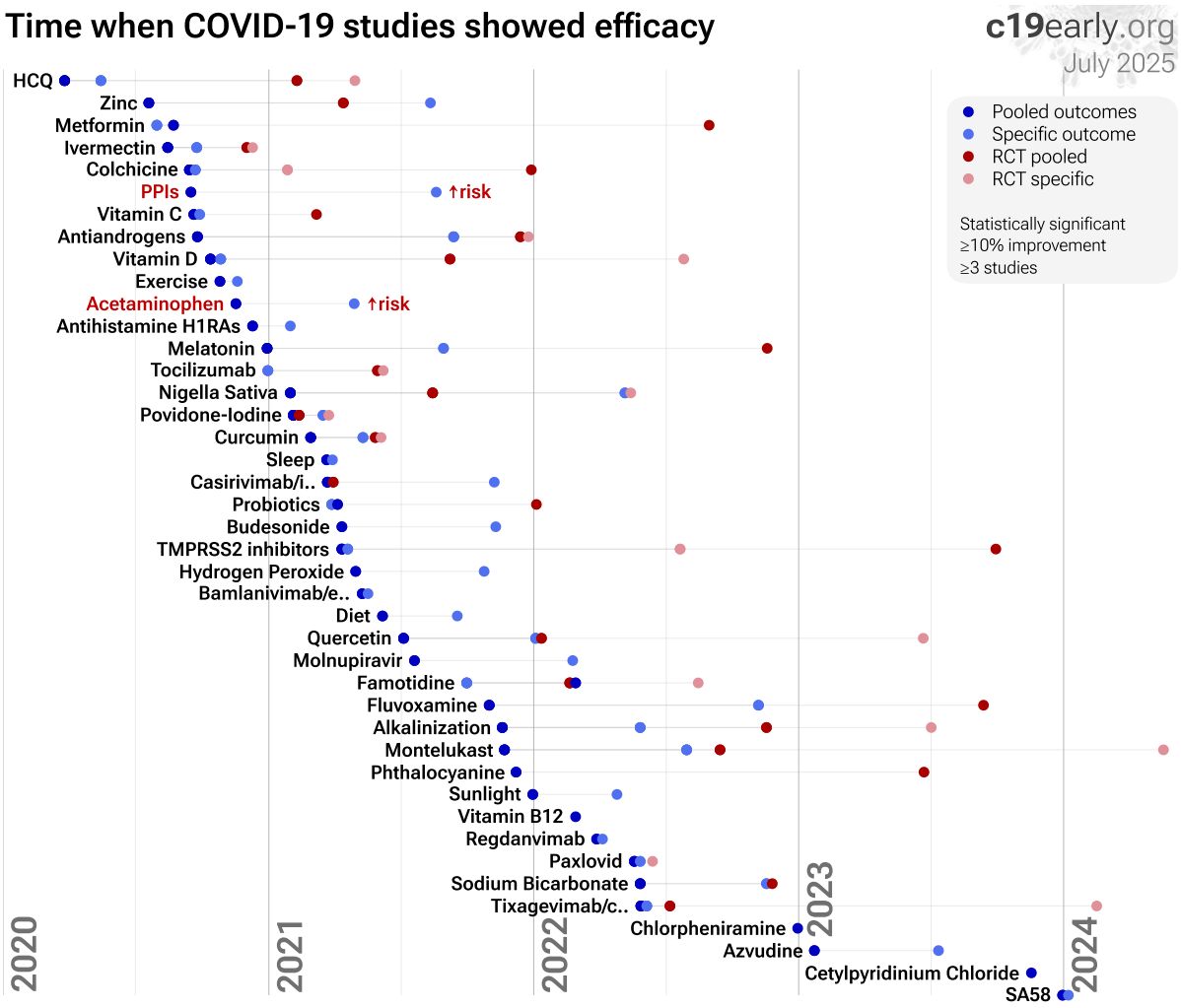


Figure 23. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

Thermotherapy

Thermotherapy, or heat therapy includes hydrothermotherapy, hydrotherapy, and diathermy, methods for increasing internal body temperature which may have benefits similar to natural fever. Thermotherapy has potential advantages over natural fever: treatment can be localized to specific tissues or regions, the temperature can be precisely controlled, and it may greatly reduce the metabolic cost and potential for tissue damage compared with more

systemic fever. However, thermotherapy may not fully replicate the complex physiological effects of fever, and may also carry risks - improper application or excessive heat may lead to burns, dehydration, or heat-induced injuries. Thermotherapy may be contraindicated with certain medical conditions, for example when increased blood flow poses a risk.

Results for other infections

Studies have also shown efficacy with thermotherapy for pneumonia[33], the common cold[34], SARS-CoV-1[35], and influenza[36].

Publication bias

Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results[89-92]. For thermotherapy, 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 alone[71-87]. 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

Currently all studies are peer-reviewed. Thermotherapy methods may have additional mechanisms of action beyond increased internal body temperatures. Studies of ventilated patients are excluded[1]. *Dominguez-Nicolas et al.* is included in the main analysis, however the weight is limited. While providing significant evidence of benefit, the study does not provide a clear relative risk.

Reviews

Many reviews cover thermotherapy for COVID-19, presenting additional background on mechanisms and related results, including[40,44,93-97].

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. Thermotherapy is known to modulate the immune system[31] and to minimize SARS-CoV-2 replication[32]. Figure 24 shows an overview of the results for thermotherapy in the context of multiple COVID-19 treatments, and Figure 25 shows a plot of efficacy vs. cost for COVID-19 treatments.

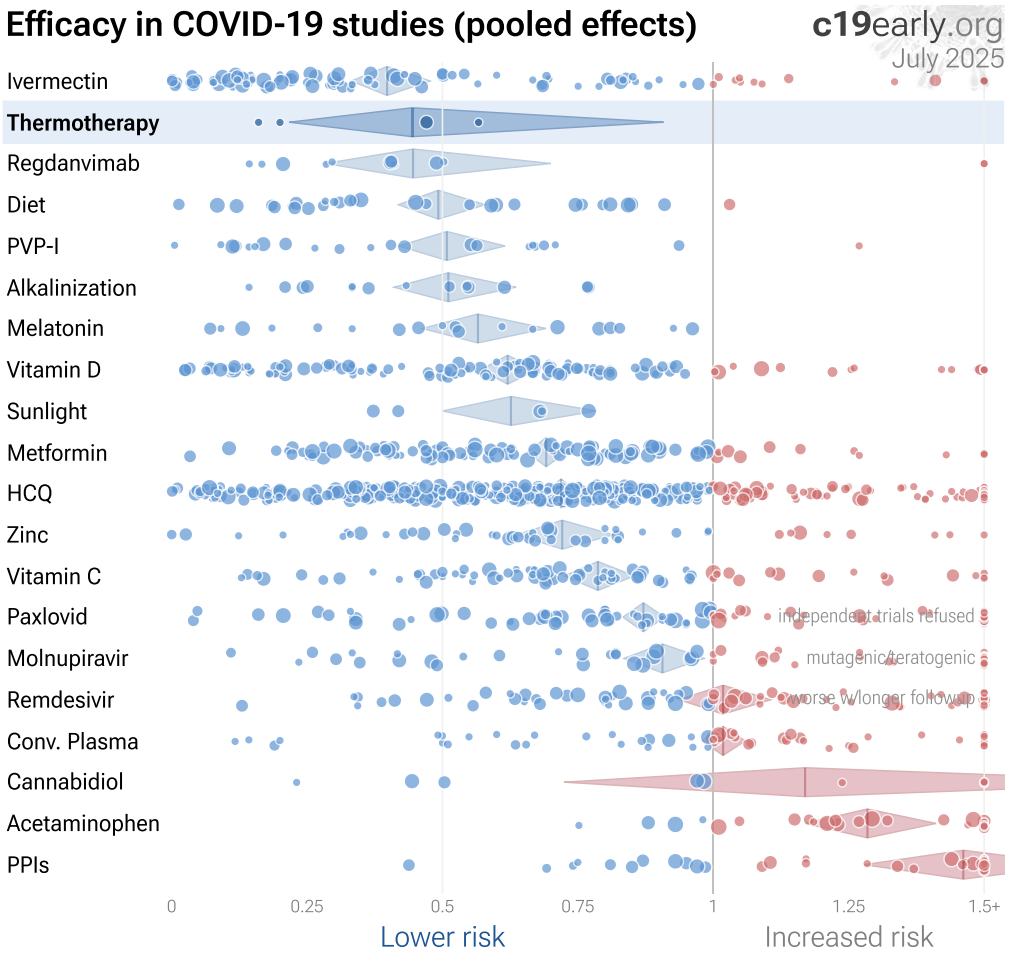


***Figure 24.* Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy[98].

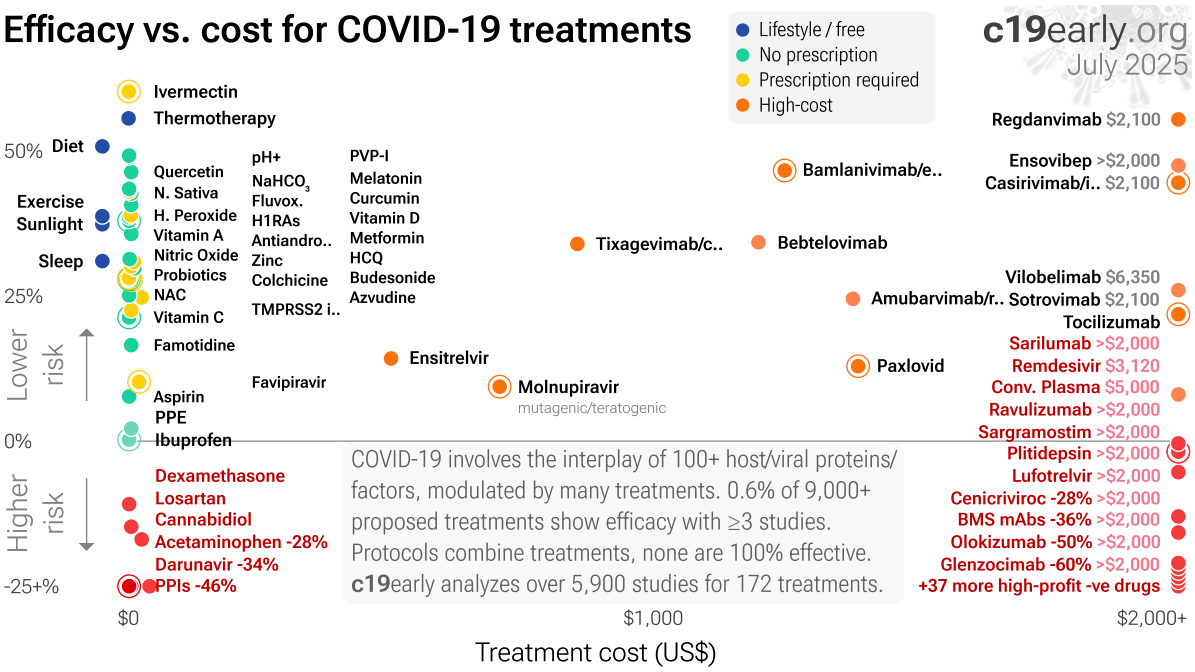


Figure 25. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Thermotherapy, or heat therapy includes hydrothermotherapy, hydrotherapy, and diathermy, methods for increasing internal body temperature which may have benefits similar to natural fever, while providing potential advantages regarding localization, precision, and lower metabolic cost. Thermotherapy is known to modulate the immune system[31] and to minimize SARS-CoV-2 replication[32].

Studies to date show that thermotherapy is an effective treatment for COVID-19. Significantly lower risk is seen for recovery. 3 studies from 3 independent teams in 2 countries show significant benefit. Meta analysis using the most serious outcome reported shows 56% [9-78%] lower risk. Results are similar for Randomized Controlled Trials and higher quality studies.

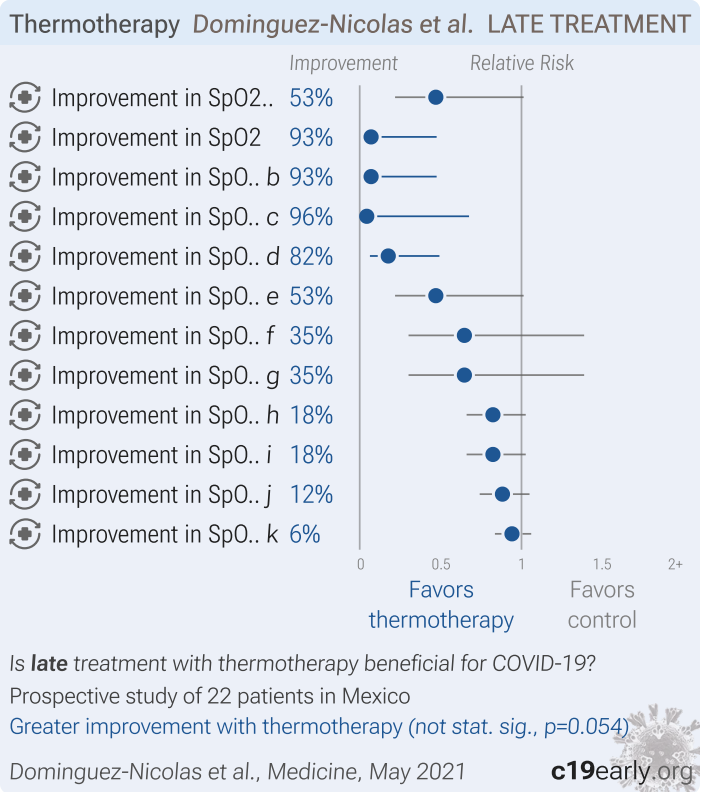
Currently there is limited data, with only 217 patients and only 20 control events for the most serious outcome in trials to date.

Studies have also shown efficacy with thermotherapy for pneumonia[33], the common cold[34], SARS-CoV-1[35], and influenza[36].

Thermotherapy methods may have additional mechanisms of action beyond increased internal body temperatures. Studies of ventilated patients are excluded[1]. *Dominguez-Nicolas et al.* is included in the main analysis, however the weight is limited. While providing significant evidence of benefit, the study does not provide a clear relative risk.

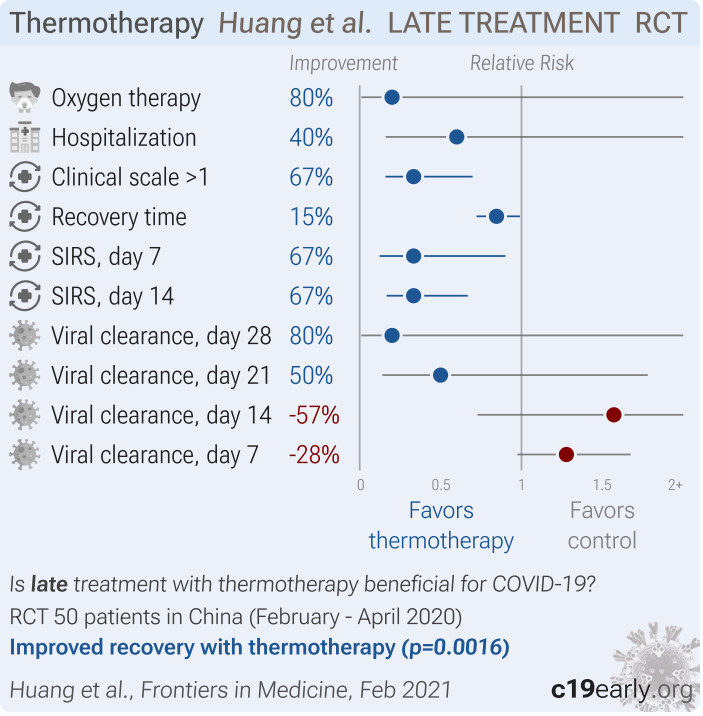
Study Notes

Dominguez-Nicolas



Single-blind, sham-controlled, crossover study of 17 COVID-19 outpatients showing significantly increased peripheral oxygen saturation (SpO2) levels correlated with hyperthermia (up to 44°C) produced by 30 minutes of low-field thoracic magnetic stimulation (LF-ThMS) applied to the dorsal thorax. The safety and lack of adverse events supports future research into mechanisms and potential therapeutic use of localized heat therapy for improving respiratory function in COVID-19 patients.

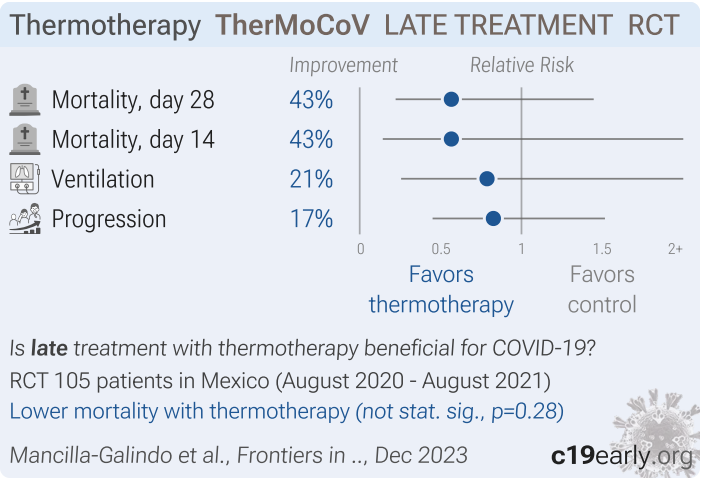
Huang



RCT 50 hospitalized COVID-19 pneumonia patients showing faster recovery with ultra-short wave diathermy (USWD). The USWD group received standard treatment plus USWD applied to the chest for 10 minutes twice daily for 12 days. The USWD group had significantly faster clinical recovery by 6.7 days, lower systemic inflammation, and better outcomes on the 7-point clinical status scale on days 21 and 28 compared to the control group receiving only standard treatment. There was no significant difference in SARS-CoV-2 viral clearance. Pulmonary fibrosis observed prior to treatment was recovered in most patients in both groups, alleviating concerns over potential harms of USWD.

Baseline severe cases were more common in the treatment group, 52 vs. 28%.

Mancilla-Galindo



RCT 105 hospitalized patients with mild-to-moderate COVID-19, evaluating the efficacy and safety of local thermotherapy (heating pads applied to the chest for 90 minutes twice daily for 5 days) to prevent disease progression, compared to standard care alone. The thermotherapy was well-tolerated with no significant adverse events.

Reduction in NEWS-2 score was significantly faster with treatment. There was lower progression and mortality with

treatment, without statistical significance. The study was underpowered due to early termination.

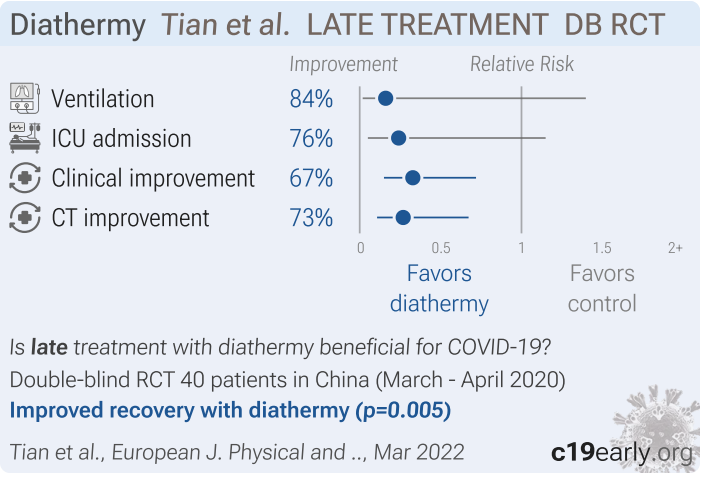
The temperature used may be too low. Lung temperature is expected to be lower than the external skin surface temperature measured on the thorax, due to heat diffusion and dissipation that occurs in transferring thermal energy across the tissue layers of skin, adipose, muscle, connective tissue and bone between the heating pad and the lung.

The treatment group had greater severity at baseline, NEWS-2 7 vs. 5, and PH-COVID-19 high-risk 7.5% vs. 0%.

Mortality numbers do not match - Figure 3 shows 10 control deaths at 28 days, while Table 3 shows 8. Percentages reported in Table 3 do not match the counts.

ICU numbers do not match the other data, for example in the control group 6 patients required invasive mechanical ventilation and 10 patients died, but only 3 patients were admitted to the ICU.

Tian



RCT 42 moderate COVID-19 inpatients showing significantly faster clinical and CT scan improvement with short-wave diathermy (SWD) treatment added to standard care, compared to placebo SWD plus standard care. 92.6% of the SWD group had clinical improvement at 14 days, compared to 69.2% in the control group. The SWD group also had significantly faster CT scan improvement. There was no significant difference in adverse events between groups, with only minor side effects like headache and dizziness reported.

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 thermotherapy 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 thermotherapy 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.

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 [99]. 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 (B) 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 [103]. 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).

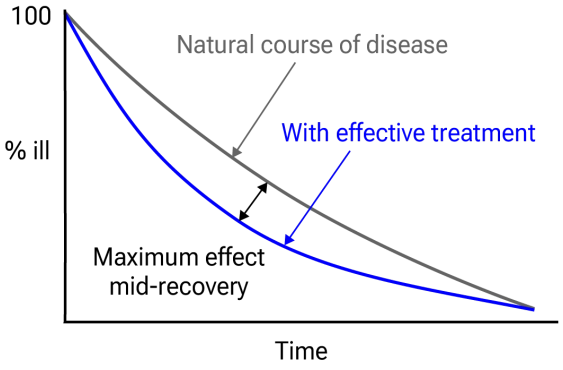


Figure 26. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

Forest plots are computed using PythonMeta [104] 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 [56,57].

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/ttmeta.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.

Bonfanti, 11/30/2023, Randomized Controlled Trial, USA, peer-reviewed, mean age 60.5, 8 authors, study period September 2020 - February 2022, average treatment delay 9.4 days, trial NCT04494867 (history), excluded: very late treatment, mechanically ventilated patients, baseline SOFA and PaO2/FiO2 show higher severity in the treatment group; very late stage, ventilated patients.	**risk of death, 11.1% higher, RR 1.11, $p = 1.00$**, treatment 4 of 9 (44.4%), control 4 of 10 (40.0%).
	risk of death, 25.9% lower, RR 0.74, $p = 1.00$, treatment 2 of 9 (22.2%), control 3 of 10 (30.0%), NNT 13, day 30.
Dominguez-Nicolas, 5/25/2021, prospective, Mexico, peer-reviewed, 2 authors, LF-ThMS, trial NCT04895267 (history), excluded in exclusion analyses: the study design does not provide a clear relative risk.	**improvement in SpO_2 <5, 52.9% lower, RR 0.47, $p = 0.05$**, treatment 8 of 17 (47.1%), control 5 of 5 (100.0%), NNT 1.9.
	no improvement in SpO_2, 93.0% lower, RR 0.07, $p = 0.006$, treatment 0 of 17 (0.0%), control 3 of 5 (60.0%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	improvement in SpO_2 <2, 93.0% lower, RR 0.07, $p = 0.006$, treatment 0 of 17 (0.0%), control 3 of 5 (60.0%), NNT 1.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	improvement in SpO_2 <3, 95.7% lower, RR 0.04, $p < 0.001$, treatment 0 of 17 (0.0%), control 5 of 5 (100.0%), NNT 1.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	improvement in SpO_2 <4, 82.4% lower, RR 0.18, $p = 0.002$, treatment 3 of 17 (17.6%), control 5 of 5 (100.0%), NNT 1.2.
	improvement in SpO_2 <5, 52.9% lower, RR 0.47, $p = 0.05$, treatment 8 of 17 (47.1%), control 5 of 5 (100.0%), NNT 1.9.
	improvement in SpO_2 <6, 35.3% lower, RR 0.65, $p = 0.27$, treatment 11 of 17 (64.7%), control 5 of 5 (100.0%), NNT 2.8.
	improvement in SpO_2 <7, 35.3% lower, RR 0.65, $p = 0.27$, treatment 11 of 17 (64.7%), control 5 of 5 (100.0%), NNT 2.8.
	improvement in SpO_2 <8, 17.6% lower, RR 0.82, $p = 1.00$, treatment 14 of 17 (82.4%), control 5 of 5 (100.0%), NNT 5.7.
	improvement in SpO_2 <9, 17.6% lower, RR 0.82, $p = 1.00$, treatment 14 of 17 (82.4%), control 5 of 5 (100.0%), NNT 5.7.
	improvement in SpO_2 <10, 11.8% lower, RR 0.88, $p = 1.00$, treatment 15 of 17 (88.2%), control 5 of 5 (100.0%), NNT 8.5.
	improvement in SpO_2 <11, 5.9% lower, RR 0.94, $p = 1.00$, treatment 16 of 17 (94.1%), control 5 of 5 (100.0%), NNT 17.
Huang, 2/1/2021, Randomized Controlled Trial, China, peer-reviewed, 8 authors, study period 18 February, 2020 - 20 April, 2020, diathermy, trial ChiCTR2000029972.	**risk of oxygen therapy, 80.0% lower, RR 0.20, $p = 0.49$**, treatment 0 of 25 (0.0%), control 2 of 25 (8.0%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of hospitalization, 40.0% lower, RR 0.60, $p = 0.70$, treatment 3 of 25 (12.0%), control 5 of 25 (20.0%), NNT 12, day 28.
	clinical scale >1, 66.7% lower, RR 0.33, $p = 0.002$, treatment 6 of 25 (24.0%), control 18 of 25 (72.0%), NNT 2.1, day 28.

	recovery time, 15.4% lower, relative time 0.85, *p* = 0.04, treatment 25, control 25.
	SIRS, 66.7% lower, RR 0.33, *p* = 0.03, treatment 25, control 25, inverted to make RR<1 favor treatment, day 7.
	SIRS, 66.7% lower, RR 0.33, *p* = 0.002, treatment 25, control 25, inverted to make RR<1 favor treatment, day 14.
	risk of no viral clearance, 80.0% lower, RR 0.20, *p* = 0.49, treatment 0 of 25 (0.0%), control 2 of 25 (8.0%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of no viral clearance, 50.0% lower, RR 0.50, *p* = 0.46, treatment 3 of 25 (12.0%), control 6 of 25 (24.0%), NNT 8.3, day 21.
	risk of no viral clearance, 57.1% higher, RR 1.57, *p* = 0.38, treatment 11 of 25 (44.0%), control 7 of 25 (28.0%), day 14.
	risk of no viral clearance, 27.8% higher, RR 1.28, *p* = 0.14, treatment 23 of 25 (92.0%), control 18 of 25 (72.0%), day 7.
Mancilla-Galindo (B), 12/22/2023, Randomized Controlled Trial, Mexico, peer-reviewed, median age 53.0, 15 authors, study period 27 August, 2020 - 23 August, 2021, heating pad, trial NCT04363541 (history) (TherMoCoV).	**risk of death, 43.3% lower, RR 0.57, *p* = 0.28**, treatment 6 of 54 (11.1%), control 10 of 51 (19.6%), NNT 12, day 28.
	risk of death, 43.3% lower, RR 0.57, *p* = 0.48, treatment 3 of 54 (5.6%), control 5 of 51 (9.8%), NNT 24, day 14.
	risk of mechanical ventilation, 21.3% lower, RR 0.79, *p* = 0.76, treatment 5 of 54 (9.3%), control 6 of 51 (11.8%), NNT 40.
	risk of progression, 17.4% lower, RR 0.83, *p* = 0.67, treatment 14 of 54 (25.9%), control 16 of 51 (31.4%), NNT 18.
Tian, 3/31/2022, Double Blind Randomized Controlled Trial, placebo-controlled, China, peer-reviewed, 12 authors, study period 1 March, 2020 - 5 April, 2020, diathermy.	**risk of mechanical ventilation, 84.0% lower, RR 0.16, *p* = 0.09**, treatment 1 of 27 (3.7%), control 3 of 13 (23.1%), NNT 5.2.
	risk of ICU admission, 75.9% lower, RR 0.24, *p* = 0.07, treatment 2 of 27 (7.4%), control 4 of 13 (30.8%), NNT 4.3.
	clinical improvement, 67.2% lower, HR 0.33, *p* = 0.005, treatment 27, control 13, inverted to make HR<1 favor treatment, Cox proportional hazards.
	CT improvement, 73.1% lower, HR 0.27, *p* = 0.005, treatment 27, control 13, inverted to make HR<1 favor treatment, 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.

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