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

@CovidAnalysis, July 2025, Version 3
https://c19early.org/inmeta.html

Abstract

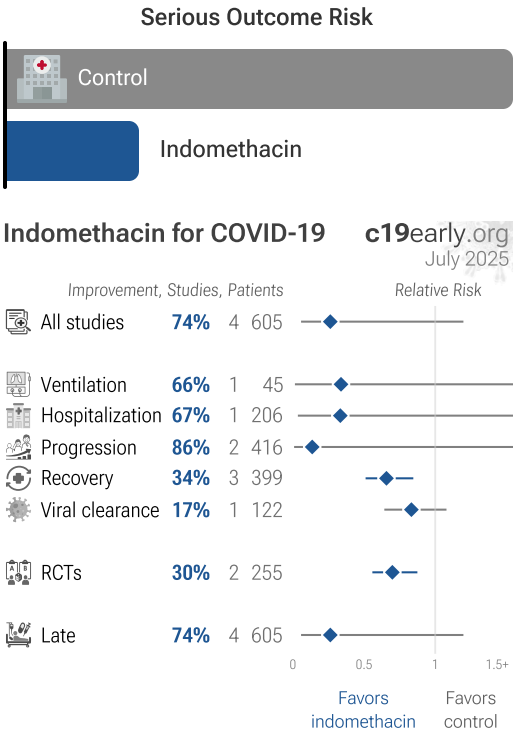
Significantly lower risk is seen for recovery. 2 studies (both from the same team/sponsor) show significant benefit.

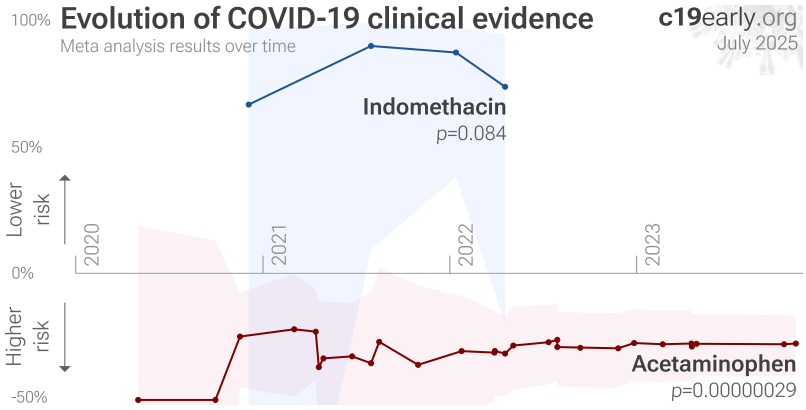
Meta analysis using the most serious outcome reported shows 74% [-20-94%] lower risk, without reaching statistical significance. Results are worse for Randomized Controlled Trials.

Currently there is limited data, with only 605 patients in trials to date. Studies to date are from only 3 different groups.

Concerns have been raised over potential harm with the use of NSAIDs for COVID-19 due to the suppression of beneficial immune and inflammatory responses during early infection, and delaying further care. There are currently no early treatment studies for indomethacin. Early treatment results for NSAID ibuprofen suggest higher risk. Indomethacin may be beneficial for cough [1], which may not respond to other treatments.

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Indomethacin currently has no early treatment studies. All data and sources to reproduce this analysis are in the appendix.

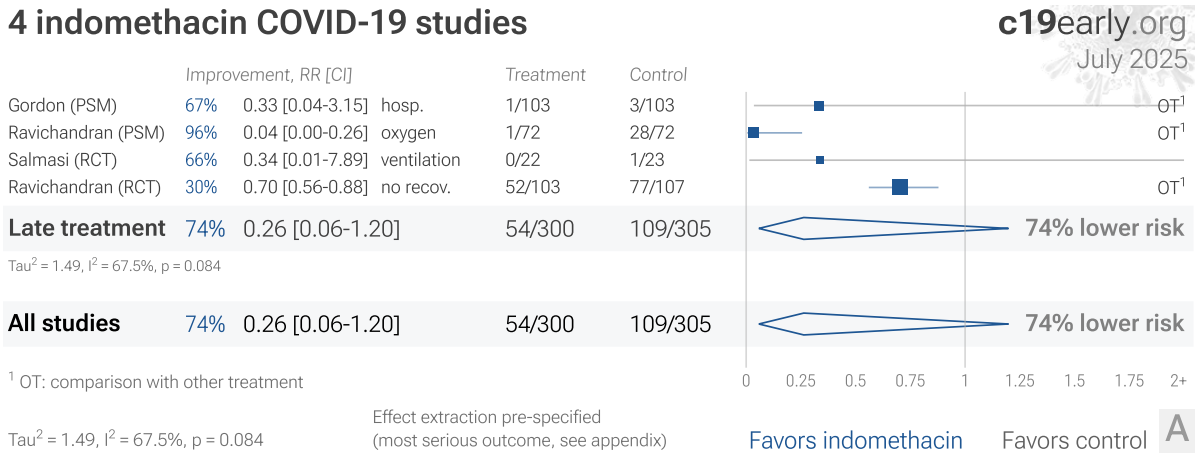




INDOMETHACIN FOR COVID-19 — HIGHLIGHTS

Indomethacin reduces risk with low confidence for recovery and in pooled analysis, and very low confidence for progression and viral clearance.

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.



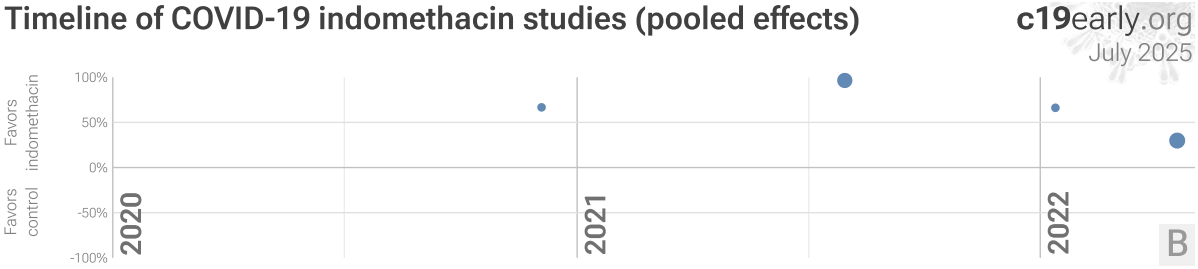


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the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

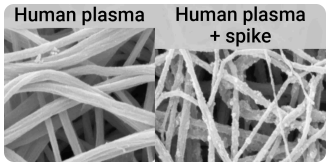


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[2].**

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.

Analysis

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

Treatment timing

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. Currently all indomethacin studies use late treatment.

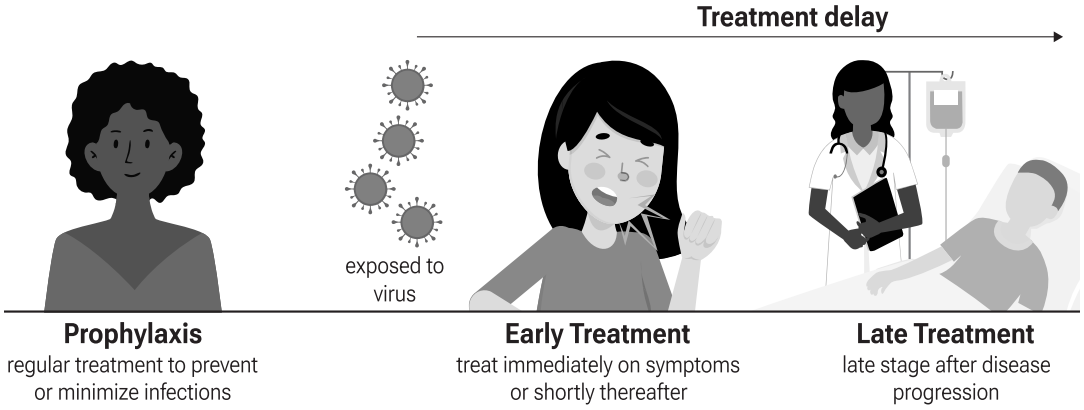


Figure 3. Treatment stages.

Preclinical Research

3 *In Silico* studies support the efficacy of indomethacin [31-33].

4 *In Vitro* studies support the efficacy of indomethacin [31,34-36].

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.

Potential Harm of NSAIDs

Stuart et al. performed a retrospective study of 142,925 outpatients in the UK showing significantly higher risk of hospitalization or death with prescription of NSAIDs for respiratory tract infections, OR 3.19 [2.42-4.23]. Practice-level analysis also found a 0.32 percentage point increase in hospitalizations/deaths for every 1 percentage point increase in NSAID prescribing, which increases confidence in an assocation rather than confounding by indication.

NSAIDs may be harmful due to suppression of inflammatory and immune responses needed to clear infections. They inhibit cyclooxygenase enzymes and production of prostaglandins involved in inflammation. This anti-inflammatory effect could hamper the body's ability to fight the infection. NSAIDs may mask symptoms of worsening infection. By reducing pain, fever, and inflammation, they could provide symptomatic relief while the infection progresses unchecked, delaying further medical care. NSAIDs may increase risks of certain complications, for example some evidence links NSAIDs to a higher risk of cardiovascular events.

For COVID-19, the potential harm or benefit may depend strongly on the timing of use, and any direct antiviral effects of the specific NSAID. For example, anti-inflammatory effects may be detrimental at the early stage of COVID-19 infection, but may be helpful in later stages depending on severity.

For indomethacin, there are currently no early treatment results, and late treatment results suggest benefit, without statistical significance.

Beneficial Effects of Fever

Fever is an important component of the acute response to coronavirus infection[38]. The evolutionary conservation of fever for over 600 million years supports a survival benefit[39]. 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[39], 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.

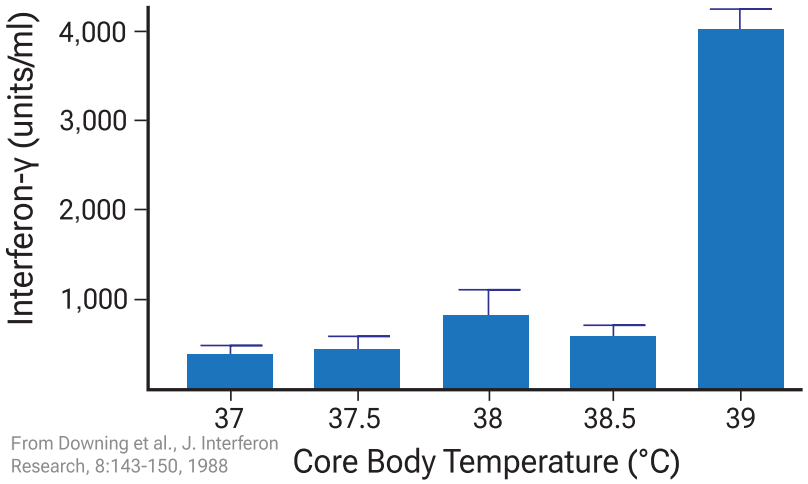


Figure 4. **A 10 fold increase in interferon-γ production was seen when core body temperature reached 39°C, from** *Downing et al.*

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.

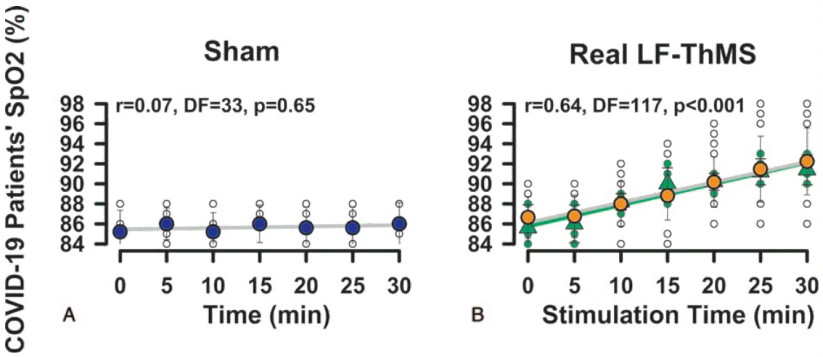


Figure 5. Rapidly increasing SpO_2 in COVID-19 patients with localized thoracic hyperthermia, from *Dominguez-Nicolas et al.*

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.

Fever may also reduce transmissibility. Fever helps clear infection faster by enhancing immune responses and applying cellular stress to pathogens. Faster clearance gives the pathogen less time to amplify within the host to reach contagious levels. Fever may also apply evolutionary pressure resulting in sacrificing replicative fitness at normal temperatures, minimizing infection in other hosts. Further, fever promotes reduced activity, minimizing the opportunity for transmission.

The beneficial effects of fever suggest potential harm from fever-reducing medications in terms of an increased risk of poor outcomes and increased transmission. However, these may be offset by other effects of specific medications, including anticoagulant, anti-inflammatory, or antiviral effects. Notably, studies for COVID-19 show significantly increased risk with acetaminophen [49].

Results

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

	Relative Risk	Studies	Patients
All studies	0.26 [0.06-1.20]	4	605
RCTs	0.70 [0.56-0.87] **	2	255
Recovery	0.66 [0.51-0.85] **	3	399

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

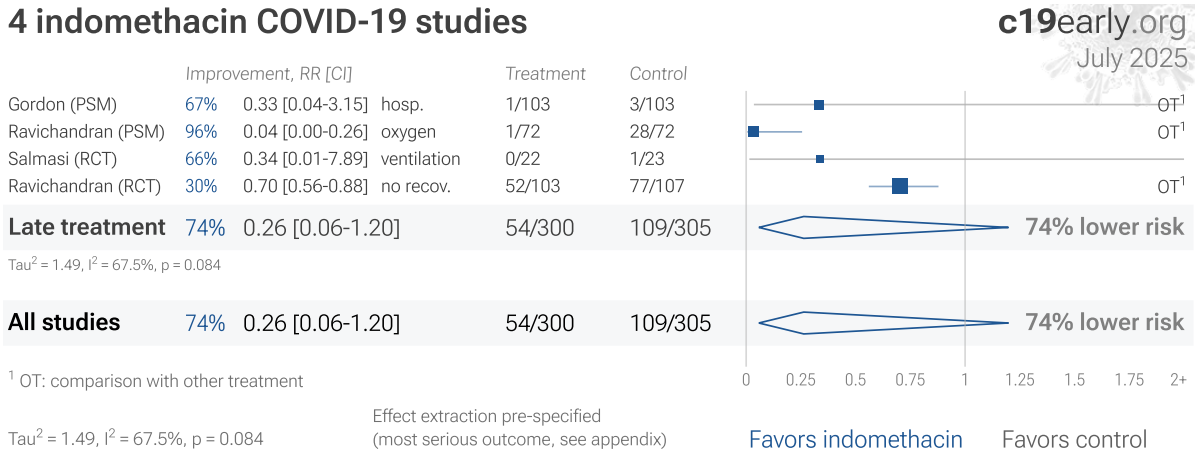


***Figure 6.* Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

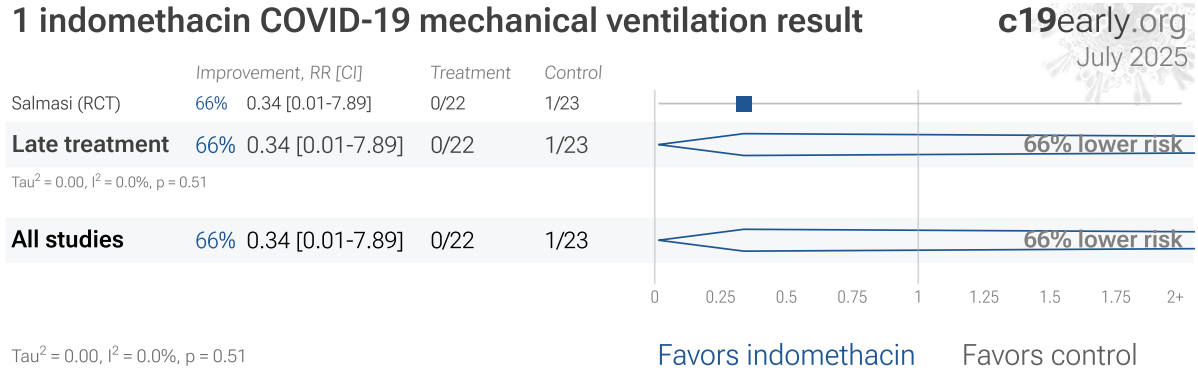


***Figure 7.* Random effects meta-analysis for ventilation.**

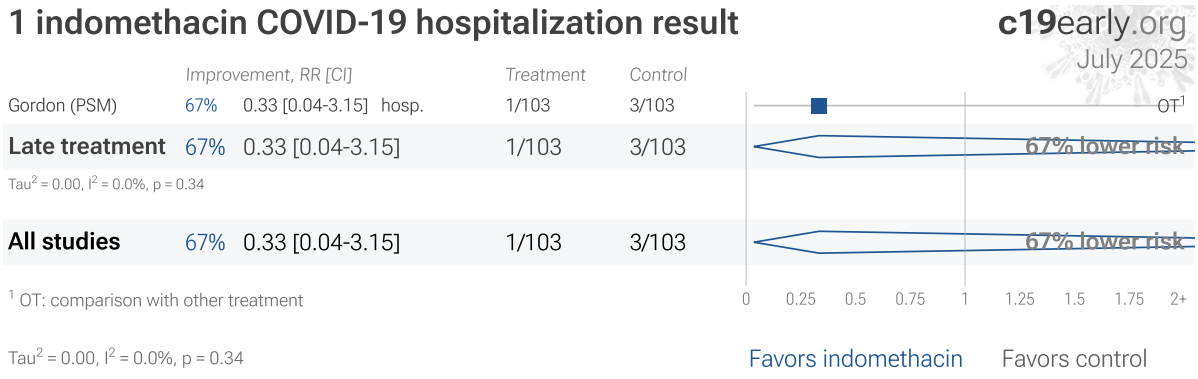


Figure 8. Random effects meta-analysis for hospitalization.

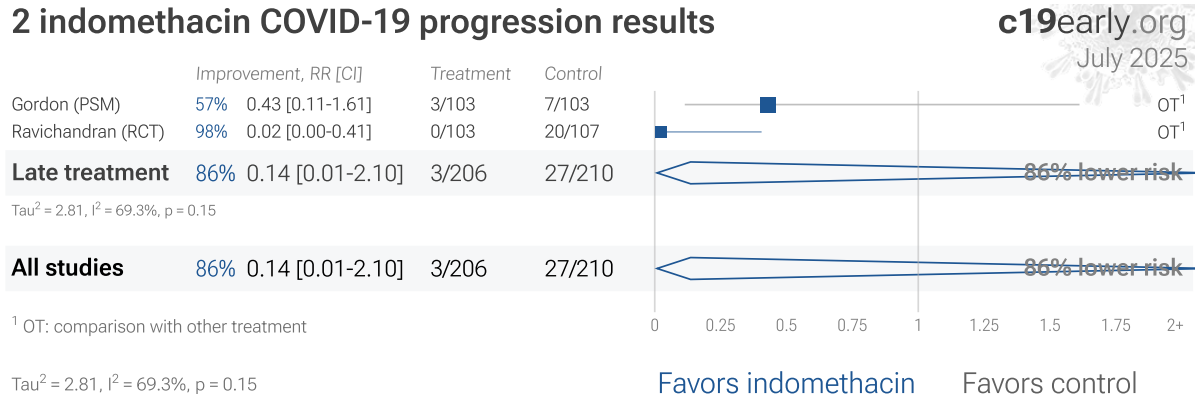


Figure 9. Random effects meta-analysis for progression.

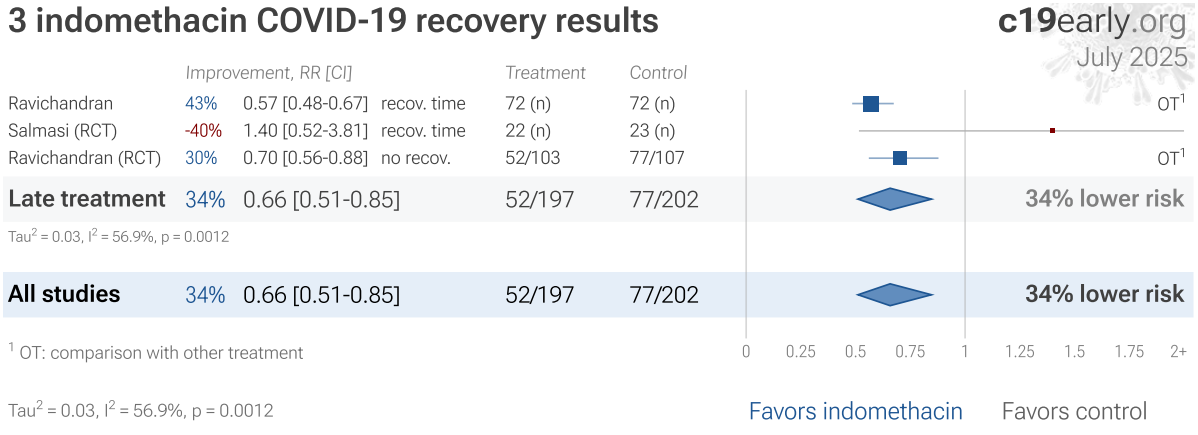


Figure 10. Random effects meta-analysis for recovery.

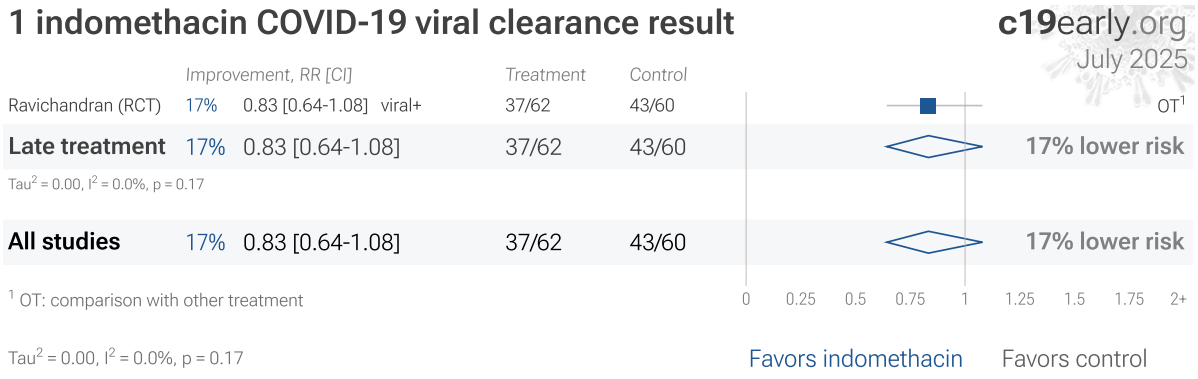


Figure 11. **Random effects meta-analysis for viral clearance.**

Randomized Controlled Trials (RCTs)

Figure 12 shows a comparison of results for RCTs and observational studies. Figure 13 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1.

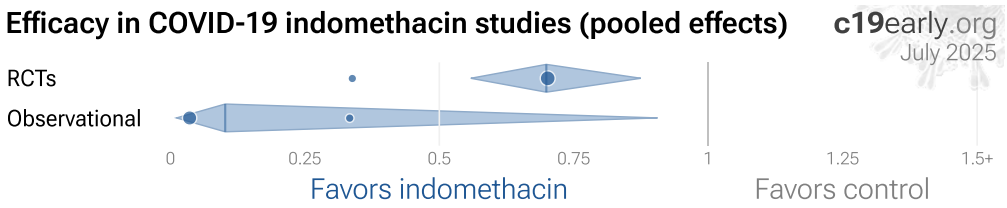


Figure 12. **Results for RCTs and observational studies.**

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[50], and analysis of double-blind RCTs has identified extreme levels of bias[51]. 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.

RCT bias for widely available treatments

RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for indomethacin are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Observational studies have been shown to be reliable

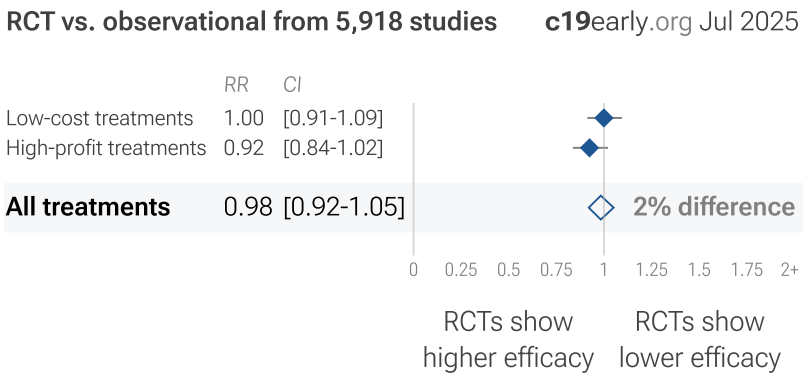


Figure 14. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[53].**

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][56]. 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[58,59].

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.

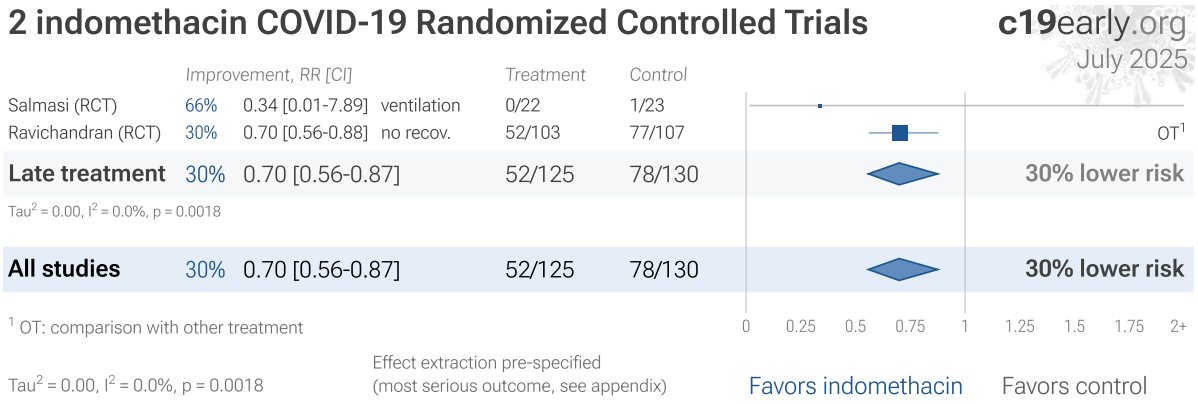


Figure 13. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

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[60,61]. 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[62]
<24 hours	-33 hours symptoms[63]
24-48 hours	-13 hours symptoms[63]
Inpatients	-2.5 hours to improvement[64]

Table 2. **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.

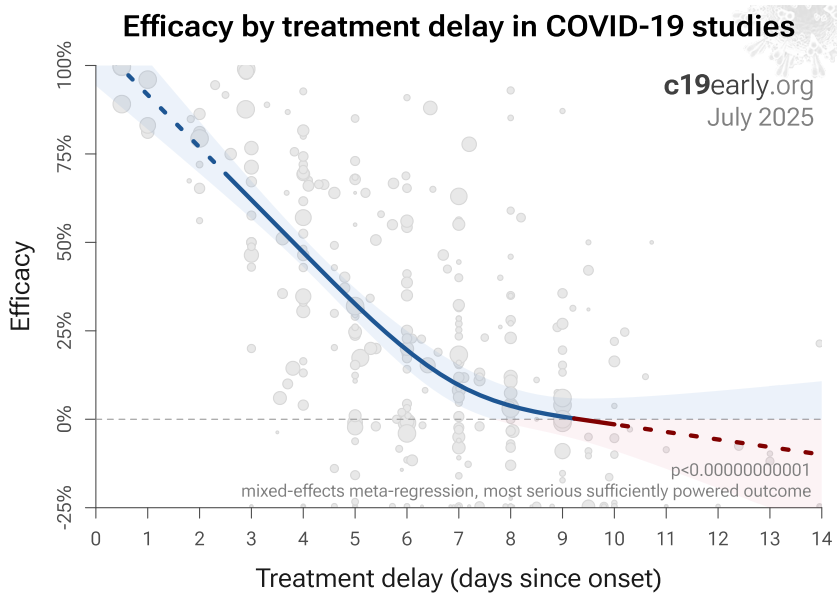


Figure 15. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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[66], for example the Gamma variant shows significantly different characteristics[67-70]. 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[71,72].

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[75-91], 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 $p = 0.0000000033$.

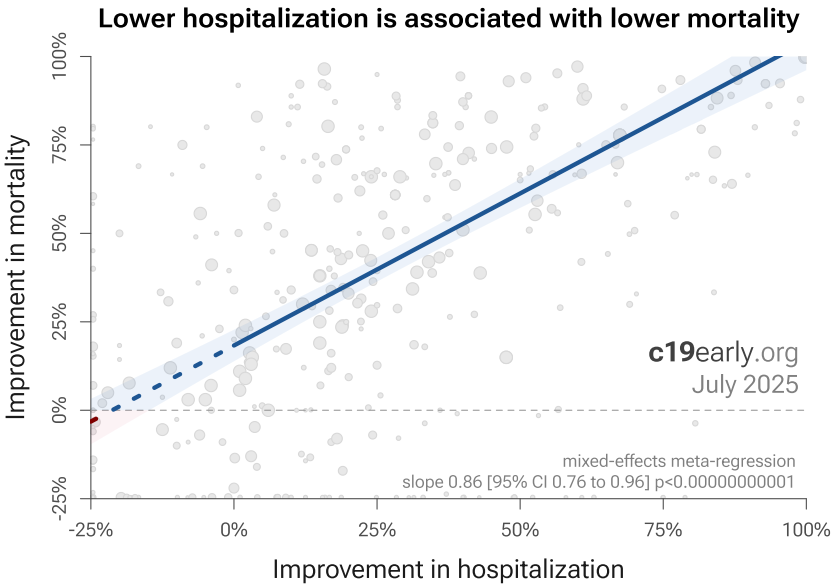


Figure 16. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

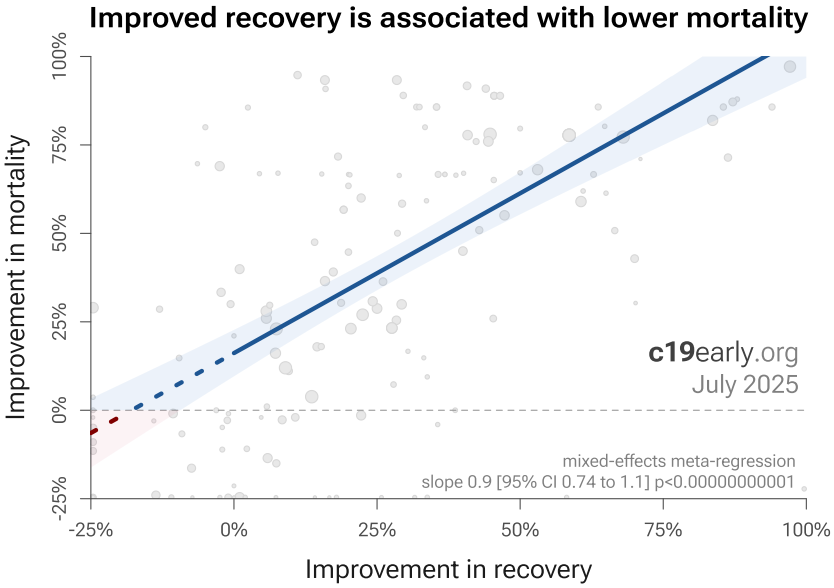


Figure 17. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

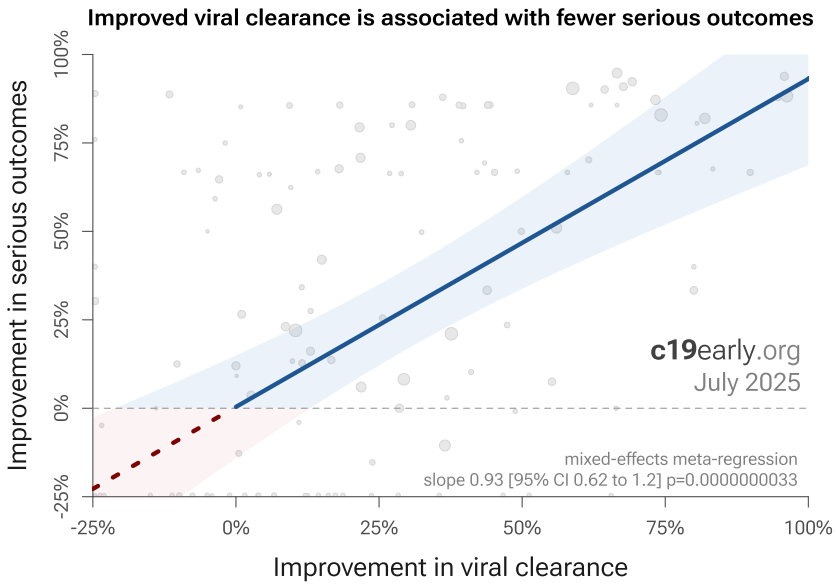


Figure 16. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

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.

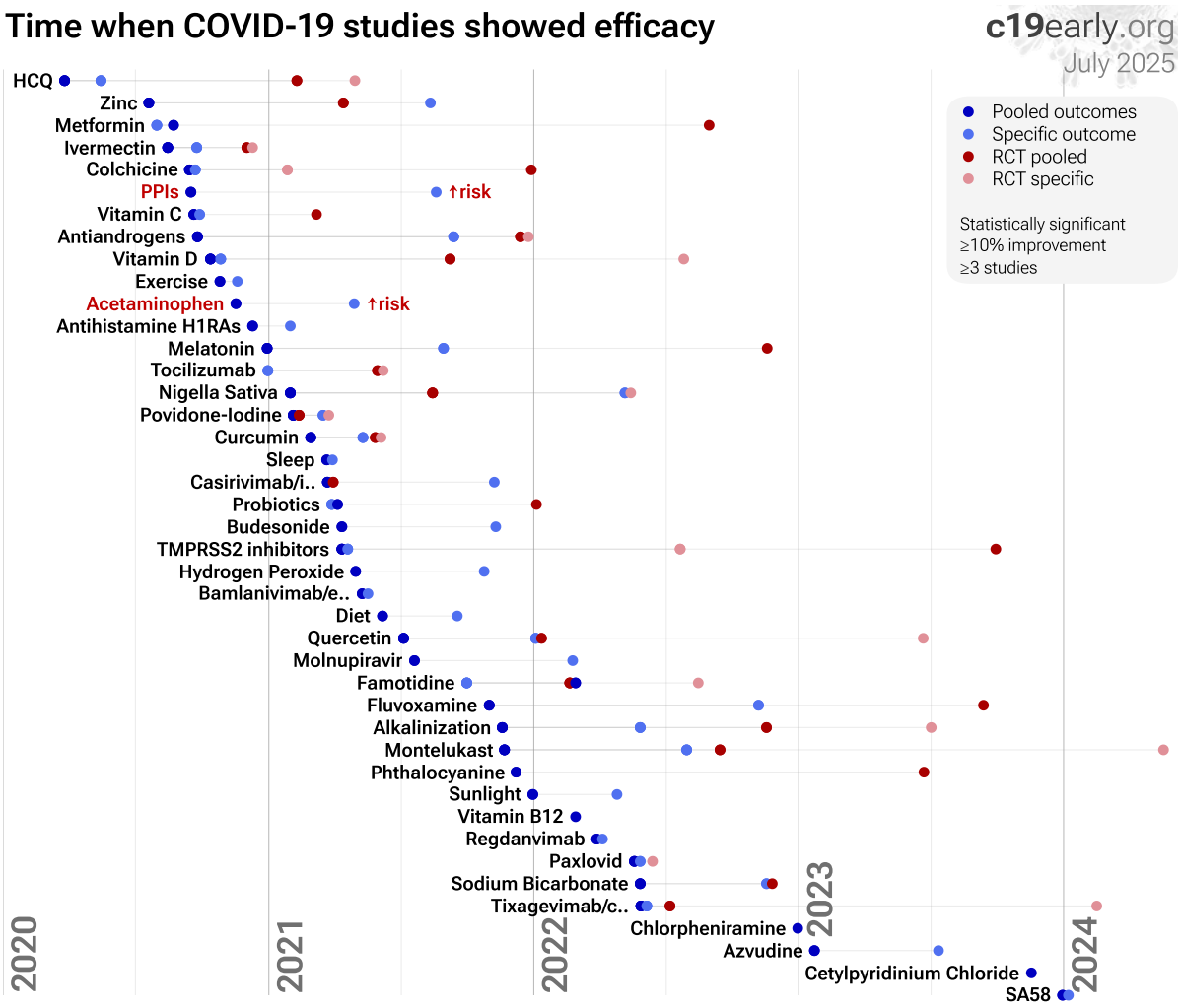


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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, 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[93-96]. For indomethacin, there is currently not enough data to evaluate publication bias with high confidence.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 20 shows a scatter plot of results for prospective and retrospective studies. The median effect size for retrospective studies is 82% improvement, compared to 48% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.

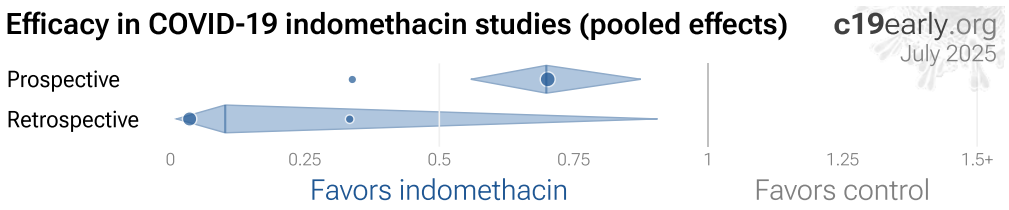


Figure 20. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Conflicts of interest

Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Indomethacin for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 indomethacin trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all indomethacin trials represent the optimal conditions for efficacy.

Limitations

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone [75-91]. 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

3 of the 4 studies compare against other treatments, which may reduce the effect seen. Currently all studies are peer-reviewed.

Reviews

Moshawih et al. present a review covering indomethacin for COVID-19.

Other studies

Additional preclinical or review papers suggesting potential benefits of indomethacin for COVID-19 include [102-118]. 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 indomethacin in the context of multiple COVID-19 treatments, and Figure 22 shows a plot of efficacy vs. cost for COVID-19 treatments.

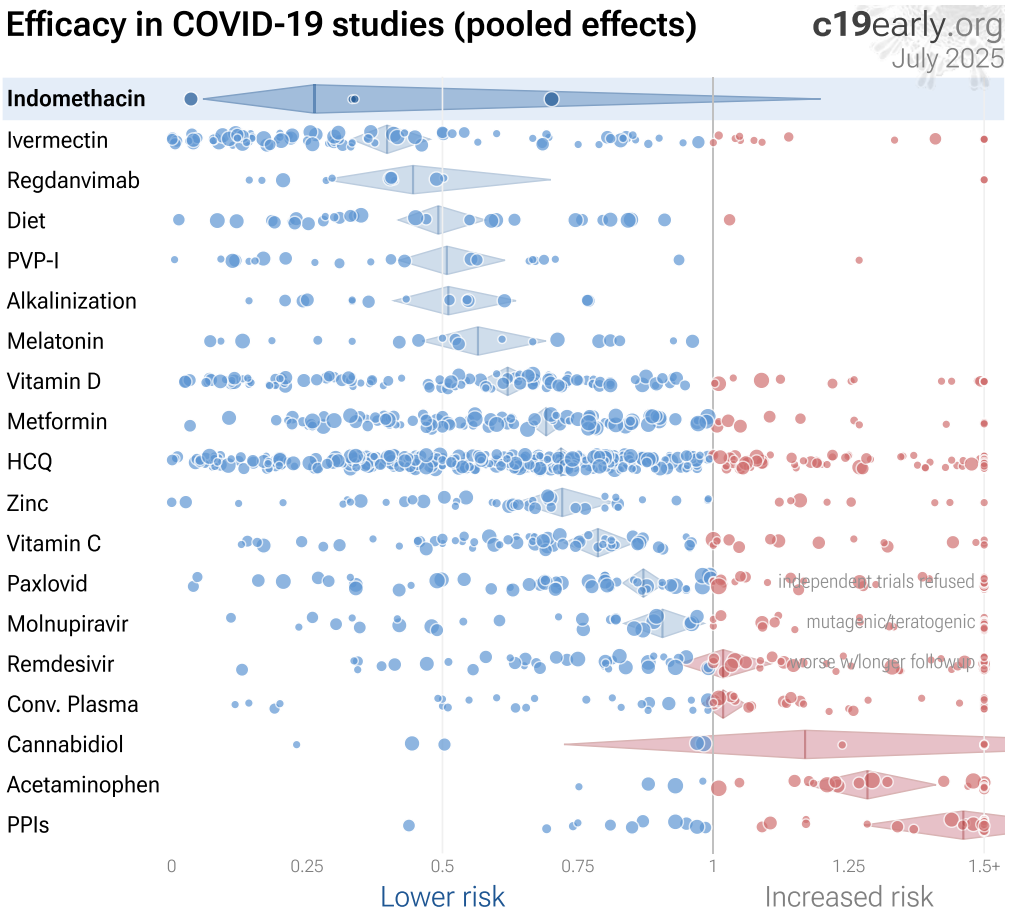


Figure 21. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [119].

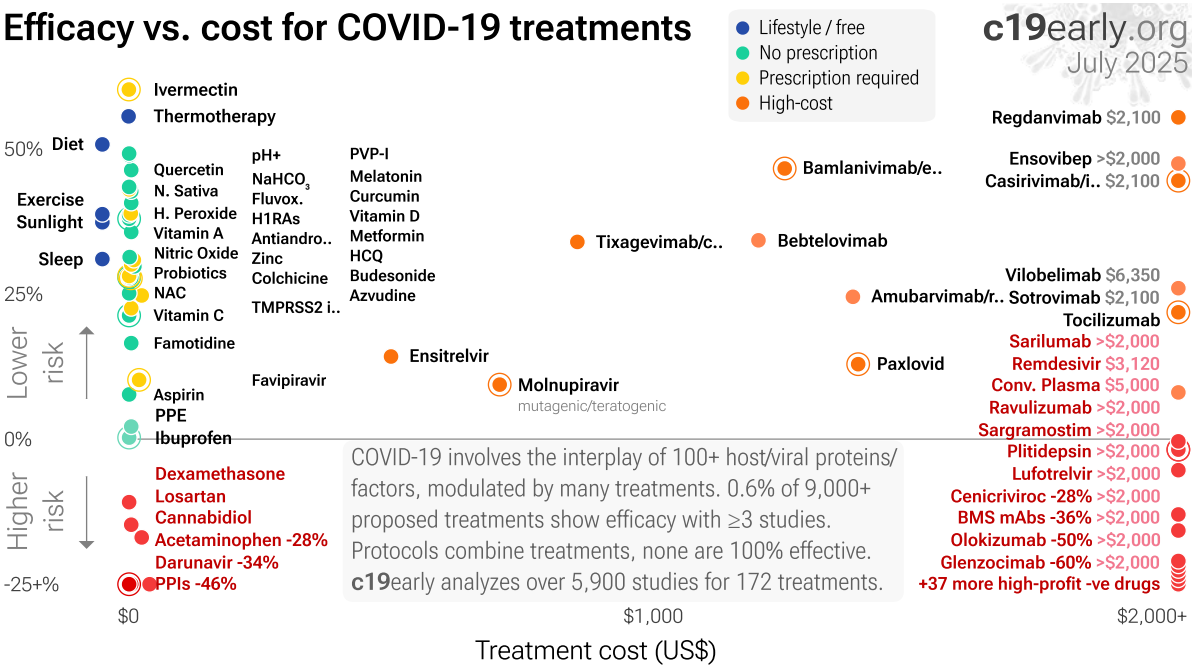


Figure 22. **Efficacy vs. cost for COVID-19 treatments.**

Conclusion

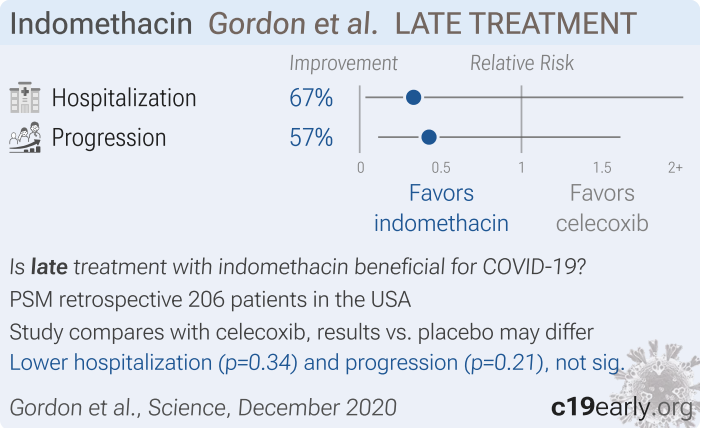
Significantly lower risk is seen for recovery. 2 studies (both from the same team/sponsor) show significant benefit. Meta analysis using the most serious outcome reported shows 74% [-20-94%] lower risk, without reaching statistical significance. Results are worse for Randomized Controlled Trials.

Currently there is limited data, with only 605 patients in trials to date. Studies to date are from only 3 different groups.

Concerns have been raised over potential harm with the use of NSAIDs for COVID-19 due to the suppression of beneficial immune and inflammatory responses during early infection, and delaying further care. There are currently no early treatment studies for indomethacin. Early treatment results for NSAID ibuprofen suggest higher risk. Indomethacin may be beneficial for cough [1], which may not respond to other treatments.

Study Notes

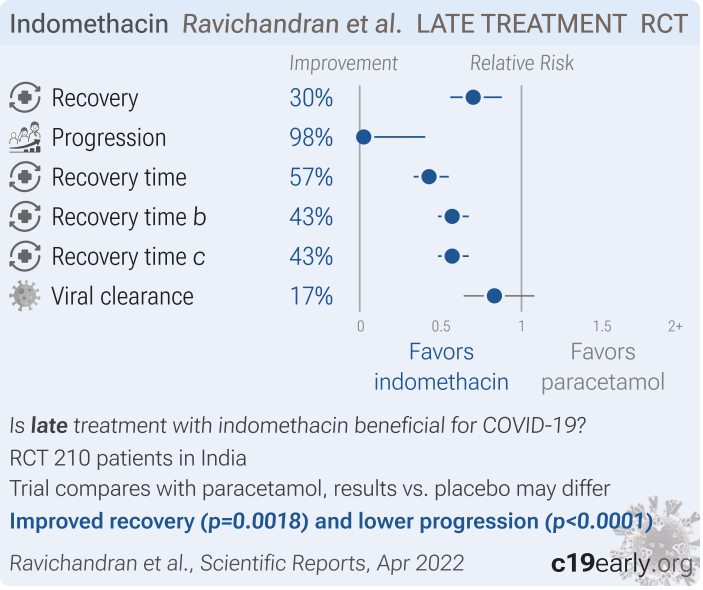
Gordon



Analysis of interactions between viral and human proteins for SARS-CoV-2, SARS-CoV-1, and MERS-CoV and genetic screening to identify host factors that enhance or inhibit viral infection.

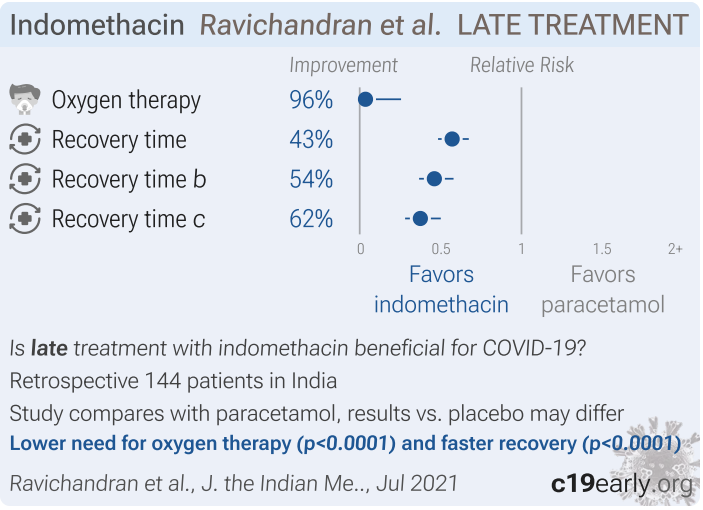
Authors predict indomethacin will have antiviral activity for SARS-CoV-2 and perform a retrospective study of patients in the USA that started treatment within 21 days after COVID-19 infection - 103 with indomethacin, and 103 using a celecoxib, a clinically similar drug without predicted antiviral activity. There were fewer hospital visits and hospitalizations with indomethacin, without statistical significance.

Ravichandran



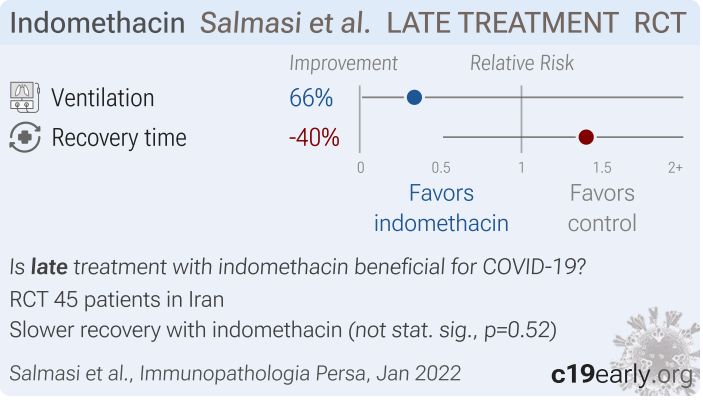
RCT with 103 indomethacin and 107 paracetamol patients, showing lower progression and improved recovery with indomethacin. Notably, improvements include faster resolution of cough.[1] previously hypothesised the benefit of indomethacin for reducing cough via bradykinin inhibition.

Ravichandran



PSM retrospective 72 indomethacin and 72 paracetamol patients in India, showing lower progression and improved recovery with indomethacin.

Salmasi



Very small RCT with 22 indomethacin and 23 control patients, showing no significant difference in outcomes. All patients were treated with HCQ.

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 indomethacin 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 indomethacin for COVID-19 that report a comparison with a control group are included in the main analysis. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

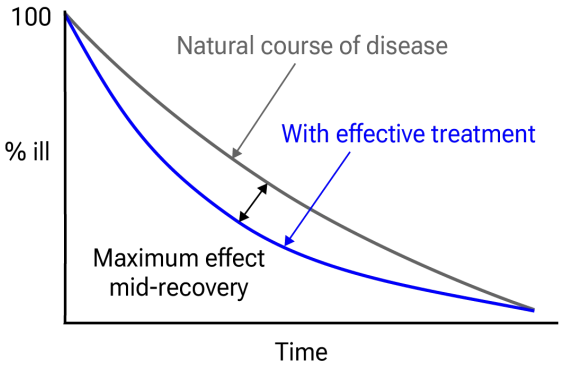


Figure 23. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 [120]. 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 [124]. 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 [125] 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 [60,61].

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/inmeta.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.

Gordon, 12/4/2020, retrospective, USA, peer-reviewed, 200 authors, this trial compares with another treatment - results may be better when compared to placebo.	**risk of hospitalization, 66.7% lower, RR 0.33, *p* = 0.34**, treatment 1 of 103 (1.0%), control 3 of 103 (2.9%), NNT 51, RSS and PSM, propensity score matching.
	risk of progression, 57.1% lower, RR 0.43, *p* = 0.21, treatment 3 of 103 (2.9%), control 7 of 103 (6.8%), NNT 26, RSS and PSM, propensity score matching.
Ravichandran, 4/19/2022, Randomized Controlled Trial, India, peer-reviewed, 8 authors, this trial compares with another treatment - results may be better when compared to placebo, trial CTRI/2021/05/033544.	**risk of no recovery, 29.8% lower, RR 0.70, *p* = 0.002**, treatment 52 of 103 (50.5%), control 77 of 107 (72.0%), NNT 4.7, day 14.
	risk of progression, 97.5% lower, RR 0.02, *p* < 0.001, treatment 0 of 103 (0.0%), control 20 of 107 (18.7%), NNT 5.4, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), SpO2 ≤93.
	recovery time, 57.1% lower, relative time 0.43, *p* < 0.001, treatment median 3.0 IQR 1.0 n=103, control median 7.0 IQR 2.75 n=107, fever.
	recovery time, 42.9% lower, relative time 0.57, *p* < 0.001, treatment median 4.0 IQR 2.0 n=103, control median 7.0 IQR 2.0 n=107, myalgia.

	recovery time, 42.9% lower, relative time 0.57, $p < 0.001$, treatment median 4.0 IQR 1.0 n=103, control median 7.0 IQR 3.0 n=107, cough.
	risk of no viral clearance, 16.7% lower, RR 0.83, $p = 0.19$, treatment 37 of 62 (59.7%), control 43 of 60 (71.7%), NNT 8.3, day 7.
Ravichandran (B), 7/31/2021, retrospective, India, peer-reviewed, 6 authors, this trial compares with another treatment - results may be better when compared to placebo, trial ISRCTN11970082.	risk of oxygen therapy, 96.4% lower, RR 0.04, $p < 0.001$, treatment 1 of 72 (1.4%), control 28 of 72 (38.9%), NNT 2.7, propensity score matching.
	recovery time, 42.9% lower, relative time 0.57, $p < 0.001$, treatment median 4.0 IQR 1.0 n=72, control median 7.0 IQR 1.0 n=72, fever.
	recovery time, 53.8% lower, relative time 0.46, $p < 0.001$, treatment median 3.0 IQR 2.0 n=72, control median 6.5 IQR 3.25 n=72, myalgia.
	recovery time, 62.5% lower, relative time 0.38, $p < 0.001$, treatment median 3.0 IQR 2.0 n=72, control median 8.0 IQR 2.0 n=72, cough.
Salmasi, 1/13/2022, Randomized Controlled Trial, Iran, peer-reviewed, 8 authors, trial IRCT20200427047215N1.	risk of mechanical ventilation, 66.2% lower, RR 0.34, $p = 1.00$, treatment 0 of 22 (0.0%), control 1 of 23 (4.3%), NNT 23, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	recovery time, 40.0% higher, relative time 1.40, $p = 0.52$, treatment 22, control 23.

Supplementary Data

Supplementary Data

Footnotes

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

References

1. **Alkotaji** et al., *Indomethacin: Can It Counteract Bradykinin Effects in COVID-19 Patients?*, Current Pharmacology Reports, doi:10.1007/s40495-021-00257-6.
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. **Metwaly** et al., *Discovery of potential FDA-approved SARS-CoV-2 Papain-like protease inhibitors: A multi-phase in silico approach*, Journal of Chemical Research, doi:10.1177/17475198241298547.
32. **Agamah** et al., *Network-based multi-omics-disease-drug associations reveal drug repurposing candidates for COVID-19 disease phases*, ScienceOpen, doi:10.58647/DRUGARXIV.PR000010.v1.
33. **Chakraborty** et al., *In-silico screening and in-vitro assay show the antiviral effect of Indomethacin against SARS-CoV-2*, Computers in Biology and Medicine, doi:10.1016/j.compbiomed.2022.105788.
34. **Tramontozzi** et al., *Indomethacin inhibits human seasonal coronaviruses at late stages of viral replication in lung cells: Impact on virus-induced COX-2 expression*, Journal of Virus Eradication, doi:10.1016/j.jve.2024.100387.
35. **Wang (B)** et al., *Combating pan-coronavirus infection by indomethacin through simultaneously inhibiting viral replication and inflammatory response*, iScience, doi:10.1016/j.isci.2023.107631.
36. **Souza** et al., *Analysis of the effects of indomethacin on SARS-CoV-2 infection and the inflammatory response associated with the purinergic system*, Master's Dissertation, repositorio.ufsm.br/handle/1/29252.
37. **Stuart** et al., *NSAID prescribing and adverse outcomes in common infections: a population-based cohort study*, BMJ Open, doi:10.1136/bmjopen-2023-077365.
38. **Wrotek** et al., *Let fever do its job*, Evolution, Medicine, and Public Health, doi:10.1093/emph/eoaa044.
39. **Evans** et al., *Fever and the thermal regulation of immunity: the immune system feels the heat*, Nature Reviews Immunology, doi:10.1038/nri3843.
40. **Los** et al., *Body temperature variation controls pre-mRNA processing and transcription of antiviral genes and SARS-CoV-2 replication*, Nucleic Acids Research, doi:10.1093/nar/gkac513.

41. **Zhou** et al., *Temperature dependence of the SARS-CoV-2 affinity to human ACE2 determines COVID-19 progression and clinical outcome*, Computational and Structural Biotechnology Journal, doi:10.1016/j.csbj.2020.12.005.

42. **Downing** et al., *Hyperthermia in Humans Enhances Interferon-γ Synthesis and Alters the Peripheral Lymphocyte Population*, Journal of Interferon Research, doi:10.1089/jir.1988.8.143.

43. **Herder** et al., *Elevated temperature inhibits SARS-CoV-2 replication in respiratory epithelium independently of IFN-mediated innate immune defenses*, PLOS Biology, doi:10.1371/journal.pbio.3001065.

44. **Dominguez-Nicolas** et al., *Low-field thoracic magnetic stimulation increases peripheral oxygen saturation levels in coronavirus disease (COVID-19) patients*, Medicine, doi:10.1097/MD.0000000000027444.

45. **Ramirez** et al., *Hydrothermotherapy in prevention and treatment of mild to moderate cases of COVID-19*, Medical Hypotheses, doi:10.1016/j.mehy.2020.110363.

46. **Ruble**, W., *Sanitarium Treatment of Influenza* Life and Health, May 1919, 34:5, documents.adventistarchives.org/Periodicals/LH/LH19190501-V34-05.pdf.

47. **Stewart**, H., *Diathermy in the Treatment of Pneumonia*, Proceedings of the Royal Society of Medicine, 19:53-56, www.ncbi.nlm.nih.gov/pmc/articles/PMC1948555/.

48. **Xie** et al., *Molecular Basis of High-Blood-Pressure-Enhanced and High-Fever-Temperature-Weakened Receptor-Binding Domain/Peptidase Domain Binding: A Molecular Dynamics Simulation Study*, International Journal of Molecular Sciences, doi:10.3390/ijms26073250.

49. ***c19early.org (B)***, c19early.org/acemeta.html.

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

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

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

53. ***c19early.org (C)***, c19early.org/insupp.html#fig_rctobs.

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

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

56. ***c19early.org (D)***, c19early.org/rctobs.html.

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

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

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

60. **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.

61. **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.

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

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

64. **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.

65. **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.

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

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

68. **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.

69. **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.

70. **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.

71. **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.

72. **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.

73. **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.

74. **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.

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

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

77. **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.

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

79. **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.

80. **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.

81. **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.

82. **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.

83. **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.

84. **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.

85. **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.

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

87. **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.

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

89. **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.

90. **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.

91. **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.

92. **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.

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

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

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

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

97. **Moshawih** et al., *Evaluating NSAIDs in SARS-CoV-2: Immunomodulatory mechanisms and future therapeutic strategies*, Heliyon, doi:10.1016/j.heliyon.2024.e25734.

98. **Ravichandran** et al., *An open label randomized clinical trial of Indomethacin for mild and moderate hospitalised Covid-19 patients*, Scientific Reports, doi:10.1038/s41598-022-10370-1.

99. **Salmasi** et al., *Efficacy of oral indomethacin in the treatment of COVID-19 infection; a randomized clinical trial*, Immunopathologia Persa, doi:10.34172/ipp.2022.xx.

100. **Ravichandran (B)** et al., *Use of indomethacin in COVID-19 patients: experience from two medical centres*, Journal of the Indian Medical Association, 119:7, sapiensfoundation.org/wp-content/uploads/2021/08/Use-of-Indomethacin-in-Covid-19-patients-JIMA-2021.pdf.

101. **Gordon** et al., *Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms*, Science, doi:10.1126/science.abe9403.

102. **Pendharkar** et al., *Analysis of Indomethacin as a potential drug for COVID-19 using CoV-DrugX Pipeline*, Center for Open Science, doi:10.31219/osf.io/txmra.

103. **Abner**, M., *Intranasal lavage with hypochlorous acid safely reduces the symptoms in the ambulatory patient with COVID-19*, medRxiv, doi:10.1101/2023.07.17.23292426.

104. **Rosa-Baez** et al., *Cross-trait GWAS in COVID-19 and systemic sclerosis reveals novel genes implicated in fibrotic and inflammation pathways*, Rheumatology, doi:10.1093/rheumatology/keaf028.

105. **Girgis** et al., *Indole-based compounds as potential drug candidates for SARS-CoV-2*, MDPI AG, doi:10.20944/preprints202308.0746.v1.

106. **Lei** et al., *Small molecules in the treatment of COVID-19*, Signal Transduction and Targeted Therapy, doi:10.1038/s41392-022-01249-8.

107. **Gordon (B)** et al., *A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing*, bioRxiv, doi:10.1101/2020.03.22.002386.

108. **Farag** et al., *Identification of FDA Approved Drugs Targeting COVID-19 Virus by Structure-Based Drug Repositioning*, American Chemical Society (ACS), doi:10.26434/chemrxiv.12003930.v1.

109. **Girgis (B)** et al., *Indole-Based Compounds as Potential Drug Candidates for SARS-CoV-2*, Molecules, doi:10.3390/molecules28186603.

110. **Wei** et al., *Total network controllability analysis discovers explainable drugs for Covid-19 treatment*, Biology Direct, doi:10.1186/s13062-023-00410-9.

111. **Kushwaha** et al., *A comprehensive review on the global efforts on vaccines and repurposed drugs for combating COVID-19*, European Journal of Medicinal Chemistry, doi:10.1016/j.ejmech.2023.115719.

112. **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.

113. **Homolak** et al., *Widely available lysosome targeting agents should be considered as potential therapy for COVID-19*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2020.106044.

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

115. **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.

116. **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.

117. **Mortezaei** et al., *Variations of SARS-CoV-2 in the Iranian Population and Candidate Putative Drug-like Compounds to Inhibit the Mutated Proteins*, Heliyon, doi:10.1016/j.heliyon.2022.e09910.

118. **Heimfarth** et al., *Drug repurposing and cytokine management in response to COVID-19: A review*, International Immunopharmacology, doi:10.1016/j.intimp.2020.106947.

119. **c19early.org (E)**, c19early.org/timeline.html.

120. **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.

121. **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.

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

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

124. **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.

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