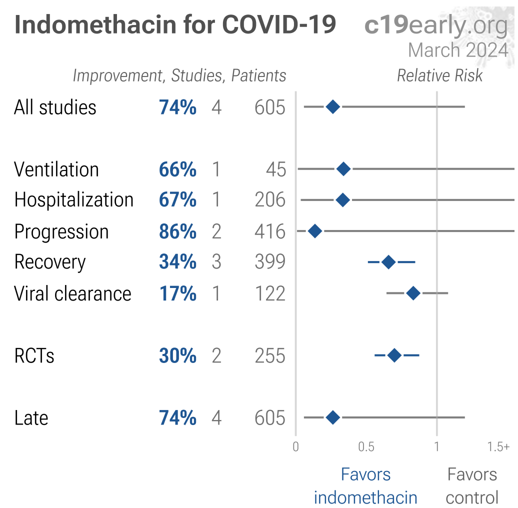
# Indomethacin for COVID-19: real-time meta analysis of 4 studies

@CovidAnalysis, March 2024, Version 3
https://c19early.org/inmeta.html


## Abstract




Statistically significant lower risk is seen for recovery. 2 studies (both from the same team) show statistically significant improvements.

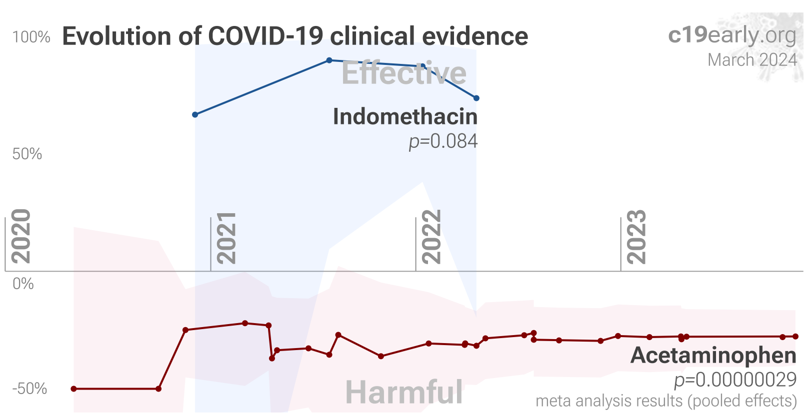
Meta analysis using the most serious outcome reported shows 74% [-20-94%] lower risk, without reaching statistical significance. Results are worse for Randomized Controlled Trials.

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 [Alkotaji], which may not respond to other treatments.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments may be more effective. There has been no early treatment studies to date.

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

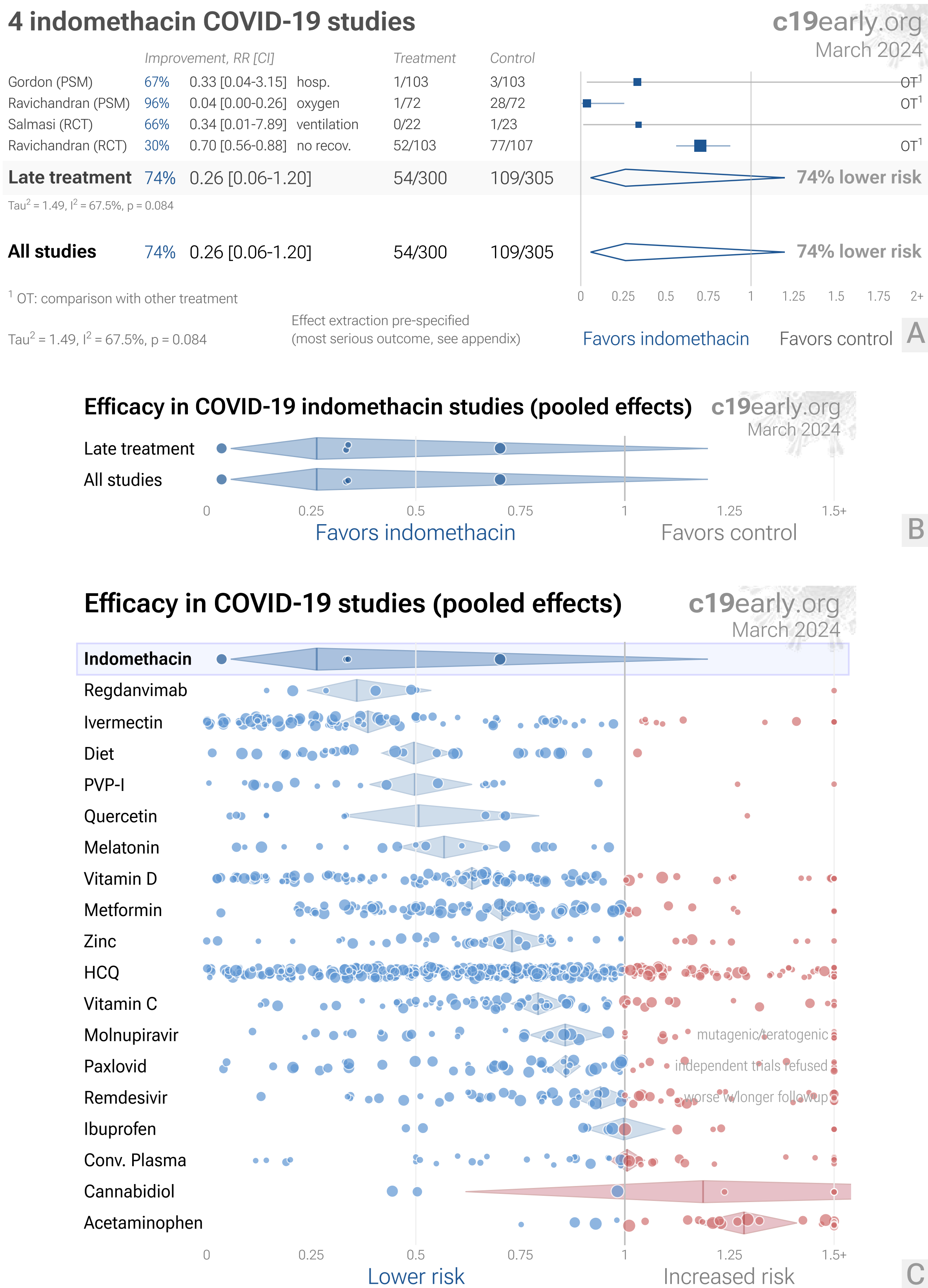




### HIGHLIGHTS

Indomethacin reduces risk for COVID-19 with low confidence for recovery and in pooled analysis, and very low confidence for progression and viral clearance.

We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.


4 indomethacin COVID-19 studies
c19early.org
March 2024
Improvement, RR [CI]
Treatment
Control
Gordon (PSM) 67% 0.33 [0.04-3.15] hosp. 1/103 3/103 OT1
Ravichandran (PSM) 96% 0.04 [0.00-0.26] oxygen 1/72 28/72 OT1
Salmasi (RCT) 66% 0.34 [0.01-7.89] ventilation 0/22 1/23
Ravichandran (RCT) 30% 0.70 [0.56-0.88] no recov. 52/103 77/107 OT1
Late treatment 74% 0.26 [0.06-1.20] 54/300 109/305 74% lower risk
Tau2 = 1.49, I2 = 67.5%, p = 0.084
All studies 74% 0.26 [0.06-1.20] 54/300 109/305 74% lower risk
1 OT: comparison with other treatment
Tau2 = 1.49, I2 = 67.5%, p = 0.084
Effect extraction pre-specified
(most serious outcome, see appendix)
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
Favors indomethacin
Favors control
A
Efficacy in COVID-19 indomethacin studies (pooled effects)
c19early.org
March 2024
Late treatment
All studies
0 0.25 0.5 0.75 1 1.25 1.5+
Favors indomethacin
Favors control
B
Efficacy in COVID-19 studies (pooled effects)
c19early.org
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Indomethacin
Regdanvimab
Ivermectin
Diet
PVP-I
Quercetin
Melatonin
Vitamin D
Metformin
Zinc
HCQ
Vitamin C
Molnupiravir
Paxlovid
Remdesivir
Ibuprofen
Conv. Plasma
Cannabidiol
Acetaminophen
mutagenic/teratogenic
independent trials refused
worse w/longer followup
0 0.25 0.5 0.75 1 1.25 1.5+
Lower risk
Increased risk
C

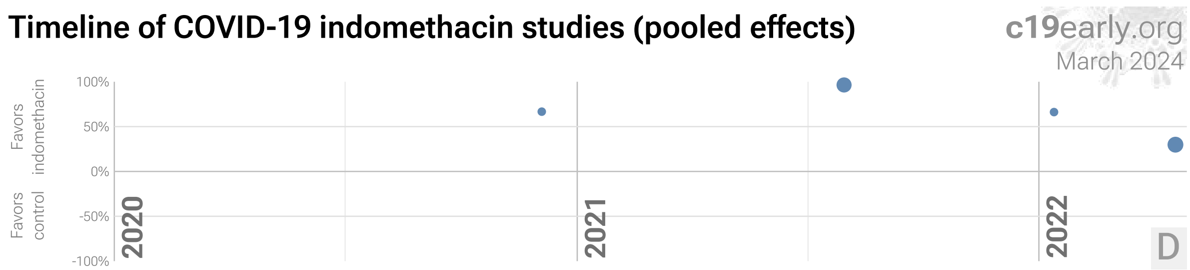



***Figure 1.*** **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. 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 issues *Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

**Many treatments are expected to modulate infection.** SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors *Note A, Malone, Murigneux, Lv, Lui*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk *c19early.org (B)*, 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 2 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

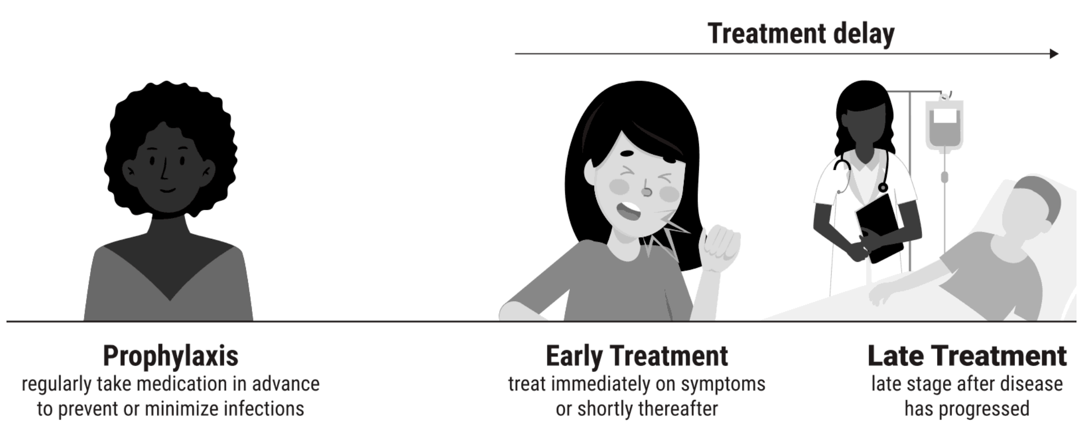



***Figure 2.*** Treatment stages.

## Preclinical Research

An *In Silico* study supports the efficacy of indomethacin [Chakraborty].

2 *In Vitro* studies support the efficacy of indomethacin [Souza, Wang].

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 [Wrotek]. Viral particle sensing occurs via pattern recognition receptors like 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 promotes improved immune system function 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.

*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 3. 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.

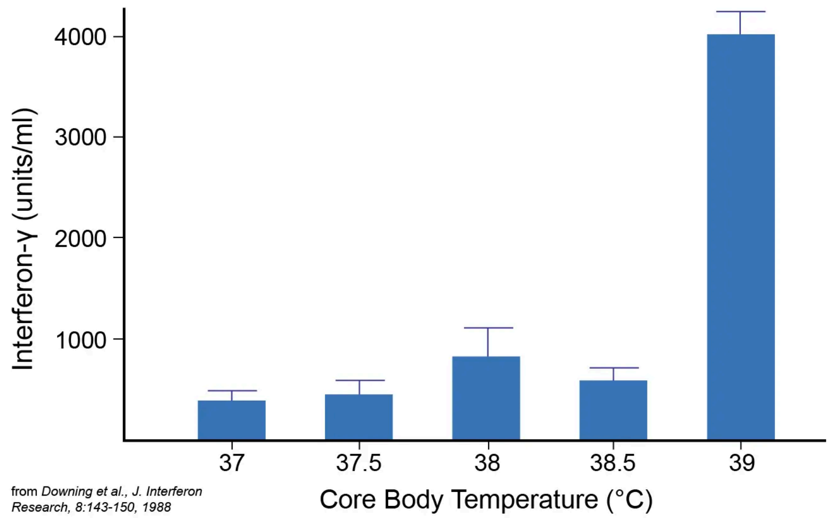



***Figure 3.*** **10 fold increase in interferon-γ production when core body temperature reached 39°C, from** *Downing et al.*

*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 infectious virus production. 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 4.

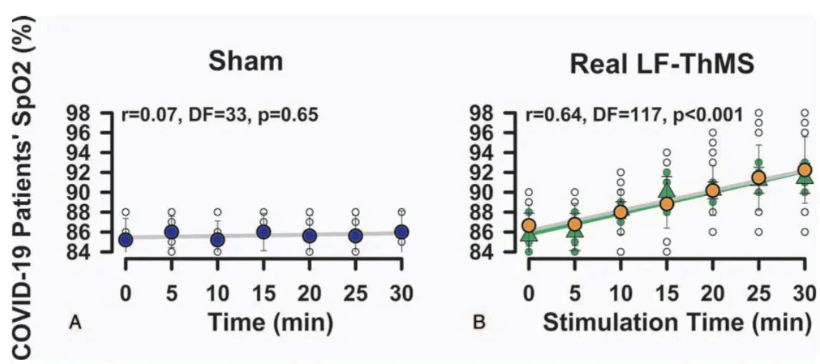



***Figure 4.*** **Rapidly increasing $SpO_2$ in COVID-19 patients with localized thoracic hyperthermia, from** *Dominguez-Nicolas et al.*

*Ramirez et al.* compared COVID-19 mortality in Finland and Estonia, where sauna 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* compared army hospital vs. sanitarium treatment of the 1918 Spanish influenza, showing lower progression to pneumonia and lower mortality with sanitarium treatment, which involves hydrothermotherapy, sunlight, and fresh air.

In summary, fever is a key component of the acute phase 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, we note that it is not universally beneficial, for example extreme and prolonged cases may be harmful.

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 *c19early.org (C)*.

## Results

Table 1 summarizes the results for all studies, for Randomized Controlled Trials, and for specific outcomes. Figure 5, 6, 7, 8, 9, and 10 show forest plots for random effects meta-analysis of all studies with pooled effects, ventilation, hospitalization, progression, recovery, and viral clearance.

| | *Improvement* | *Studies* | *Patients* | *Authors* |
|---|---|---|---|---|
| All studies | **74%** [-20-94%] | 4 | 605 | 333 |
| Randomized Controlled Trials | **30%** [13-44%] ** | 2 | 255 | 16 |
| Recovery | **34%** [15-49%] ** | 3 | 399 | 22 |

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

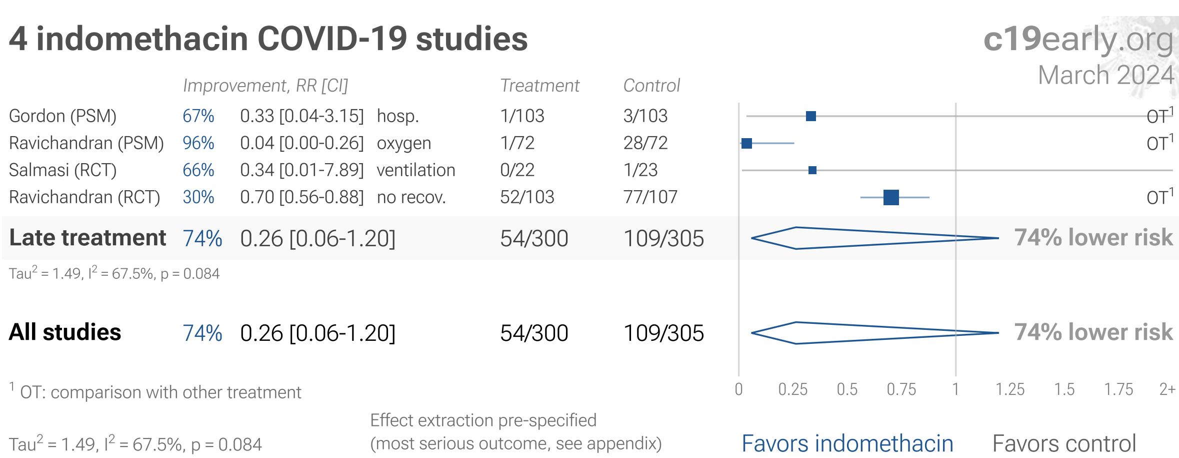



***Figure 5.*** **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

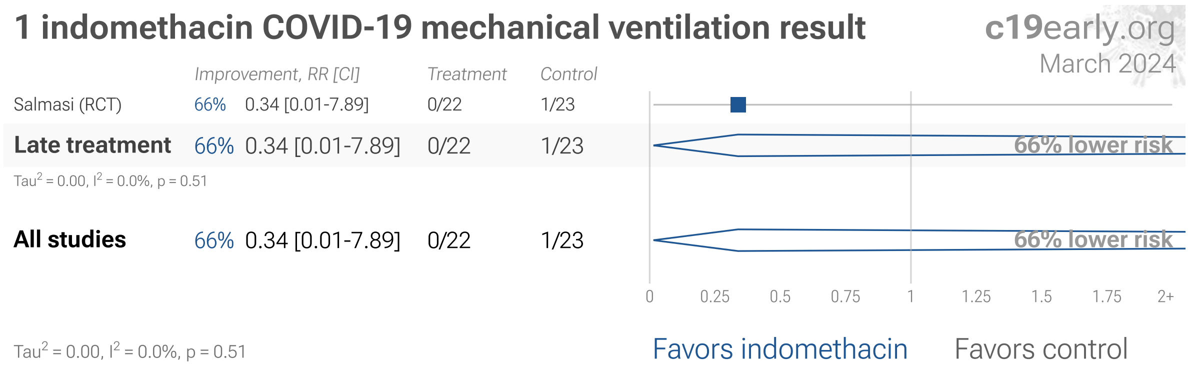



***Figure 6.*** Random effects meta-analysis for ventilation.

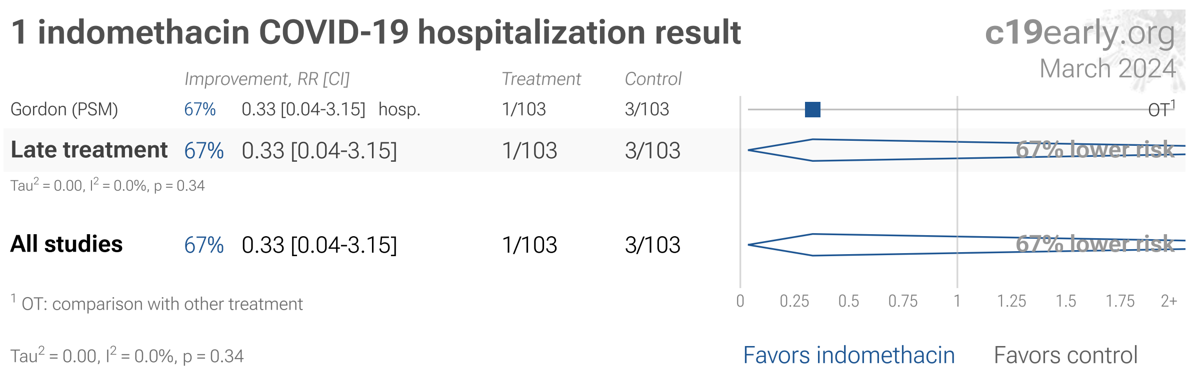



***Figure 7.*** Random effects meta-analysis for hospitalization.

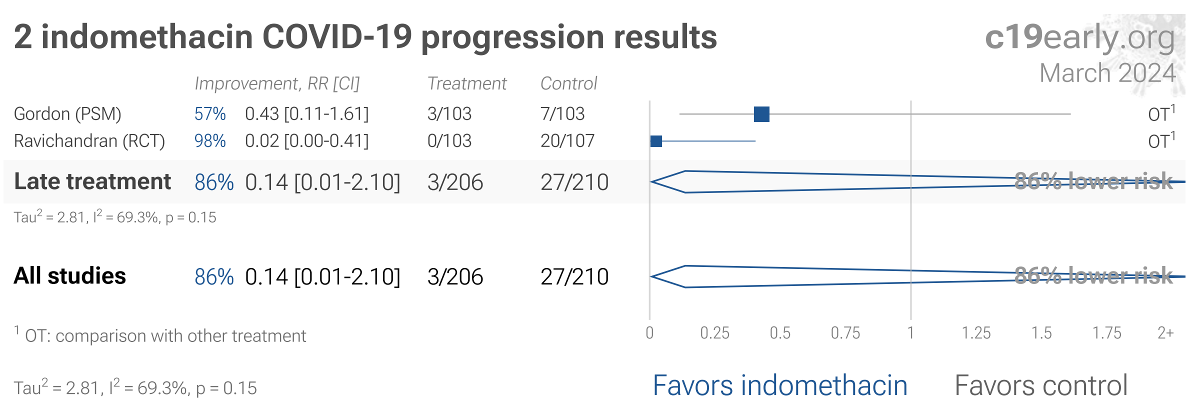



***Figure 8.*** Random effects meta-analysis for progression.

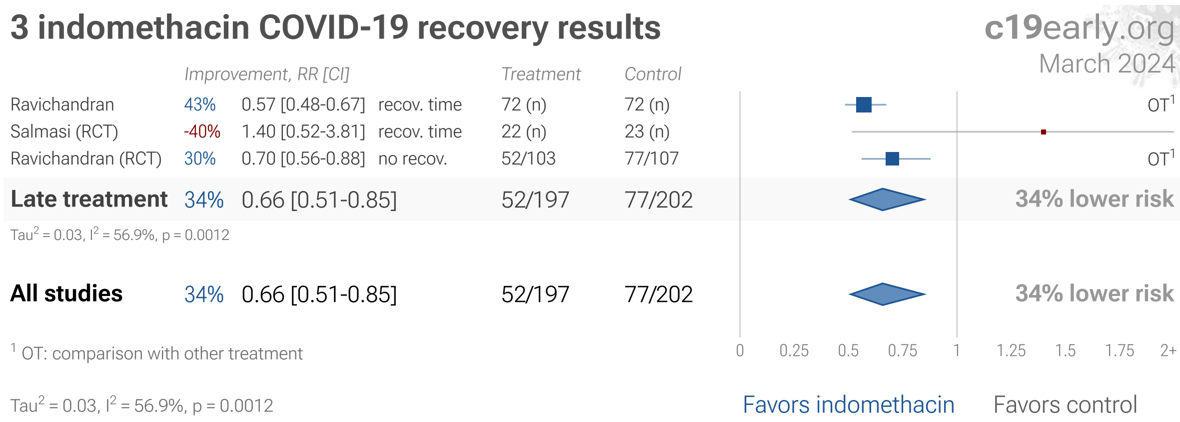



***Figure 9.*** Random effects meta-analysis for recovery.

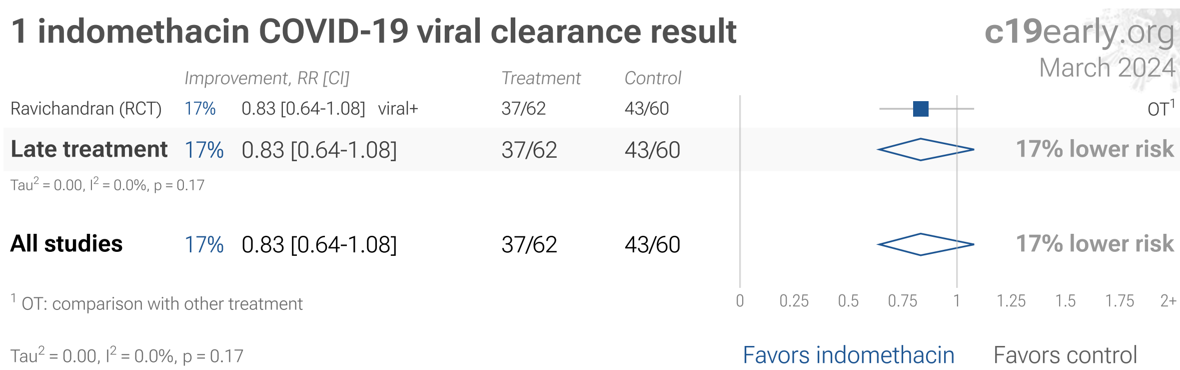



***Figure 10.*** Random effects meta-analysis for viral clearance.

## Randomized Controlled Trials (RCTs)

Figure 11 shows a comparison of results for RCTs and non-RCT studies. Figure 12 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1.

**RCTs have many potential biases.** Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases *Jadad*, and analysis of double-blind RCTs has identified extreme levels of bias *Gøtzsche*. 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, 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 66 treatments we have analyzed, 63% 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.

**Non-RCT studies have been shown to be reliable.** Evidence shows that non-RCT trials 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.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *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 Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see *Deaton, Nichol*.

**Using all studies identifies efficacy 5.7+ months faster for COVID-19.** Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

**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.

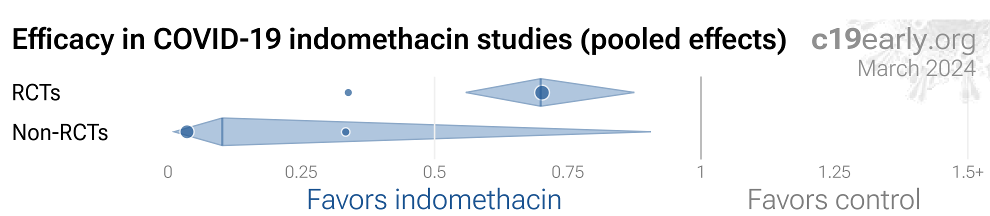



***Figure 11.*** **Results for RCTs and non-RCT studies.**

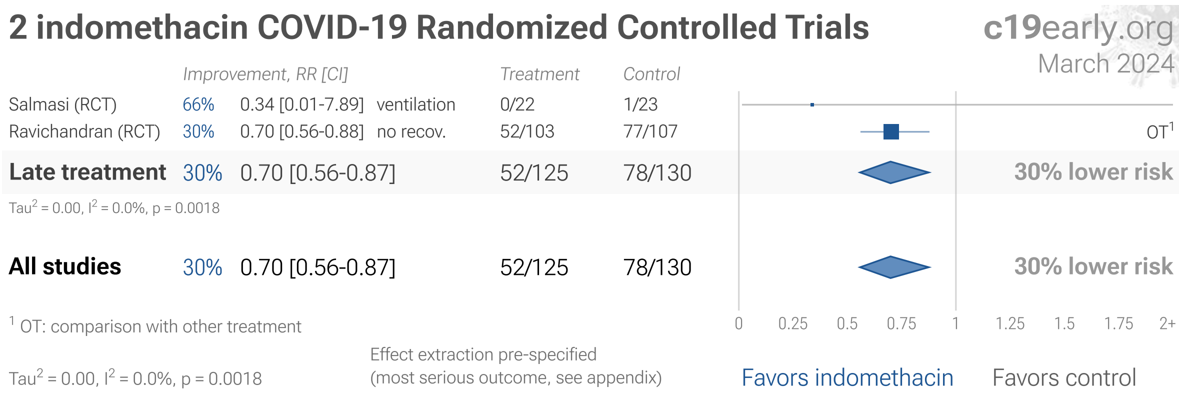



***Figure 12.*** **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction 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 [McLean, Treanor]. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* 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* report only 2.5 hours improvement for inpatient treatment.

| *Treatment delay* | *Result* |
|---|---|
| Post exposure prophylaxis | 86% fewer cases [Ikematsu] |
| <24 hours | -33 hours symptoms [Hayden] |
| 24-48 hours | -13 hours symptoms [Hayden] |
| Inpatients | -2.5 hours to improvement [Kumar] |

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

Figure 13 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

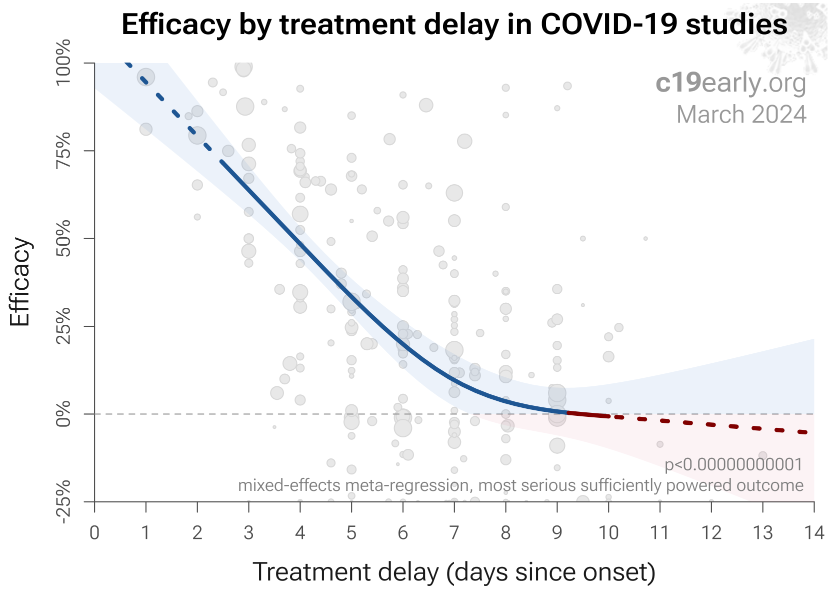



***Figure 13.*** **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

**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 (as in *López-Medina*).

**Effect measured.** Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

**Variants.** There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics [*Faria, Karita, Nonaka, Zavascki*]. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective [*Peacock, Willett*].

**Regimen.** Effectiveness may depend strongly on the dosage and treatment regimen.

**Other treatments.** The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

**Medication quality.** The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

**Pooled outcome analysis.** We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 14. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral replication or early stage disease could show no efficacy in pooled analysis if most studies only examine viral clearance. While we present pooled results, we also present individual outcome analyses, which may be more informative for specific use cases.

**Pooled outcomes identify efficacy faster.** Currently, 44 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 treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

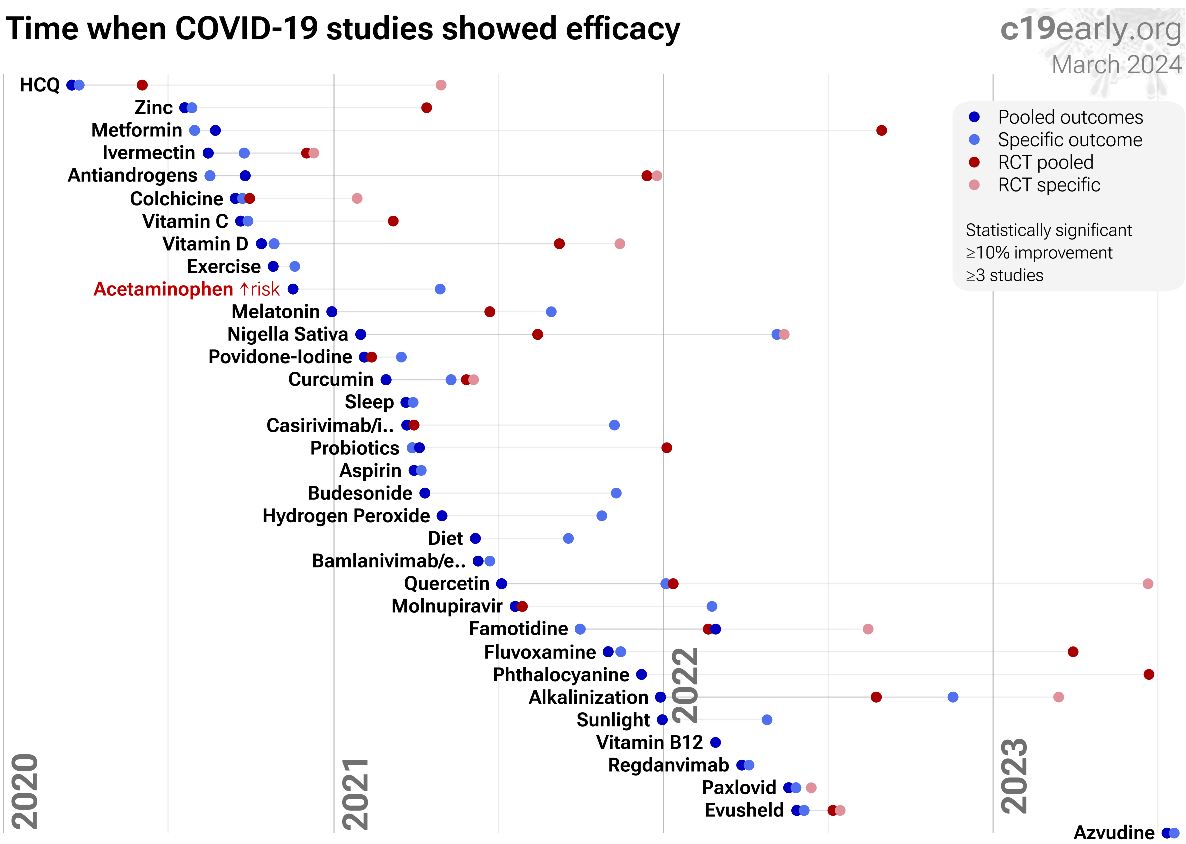



***Figure 14.*** **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

**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. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

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.

## 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 *Boulware, Meeus, Meneguesso*. 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 15 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.

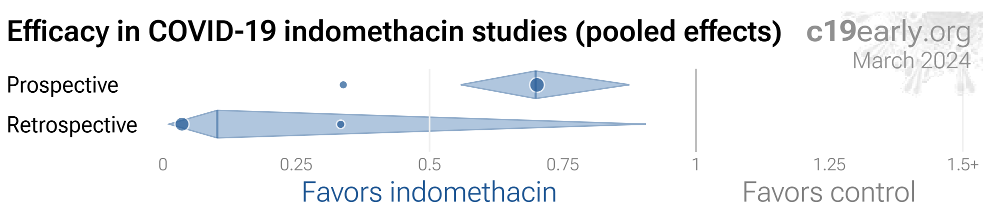



***Figure 15.*** **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

**Funnel plot analysis.** Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 16 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

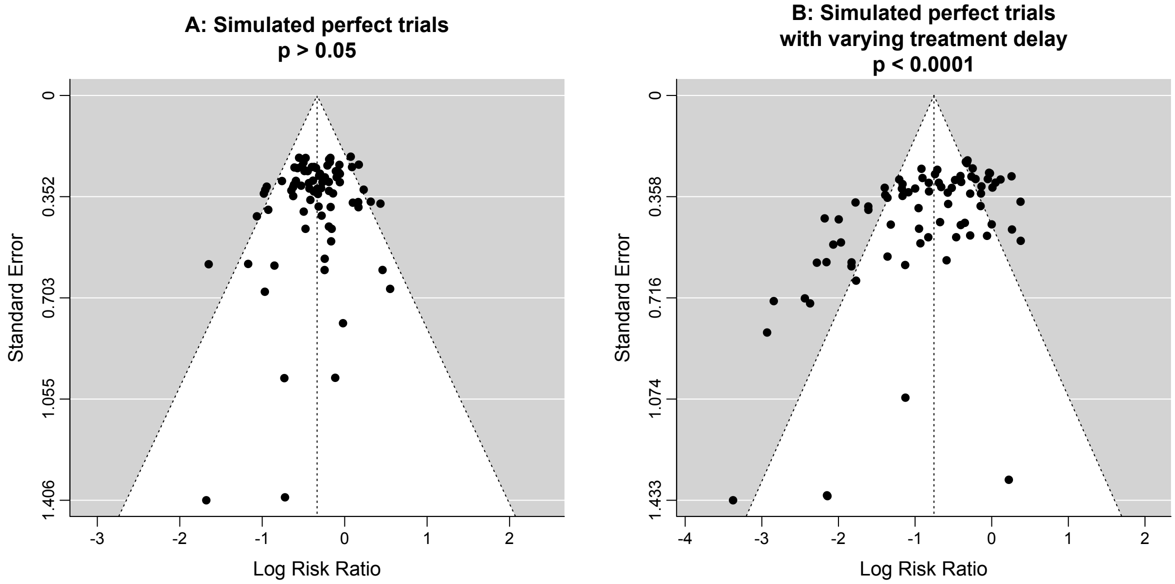



***Figure 16.*** **Example funnel plot analysis for simulated perfect trials.**

**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 by 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 affiliated with special interests 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 *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. 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, vaccine, 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.

## Conclusion

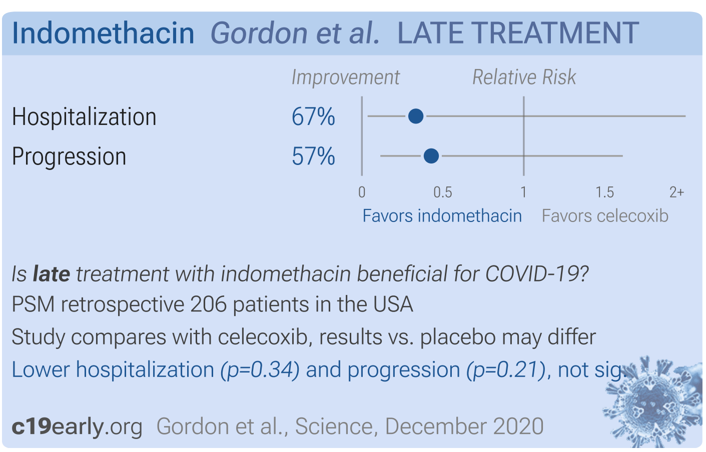
Statistically significant lower risk is seen for recovery. 2 studies (both from the same team) show statistically significant improvements. Meta analysis using the most serious outcome reported shows 74% [-20-94%] lower risk, without reaching statistical significance. Results are worse for Randomized 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 [Alkotaji], which may not respond to other treatments.

## Study Notes

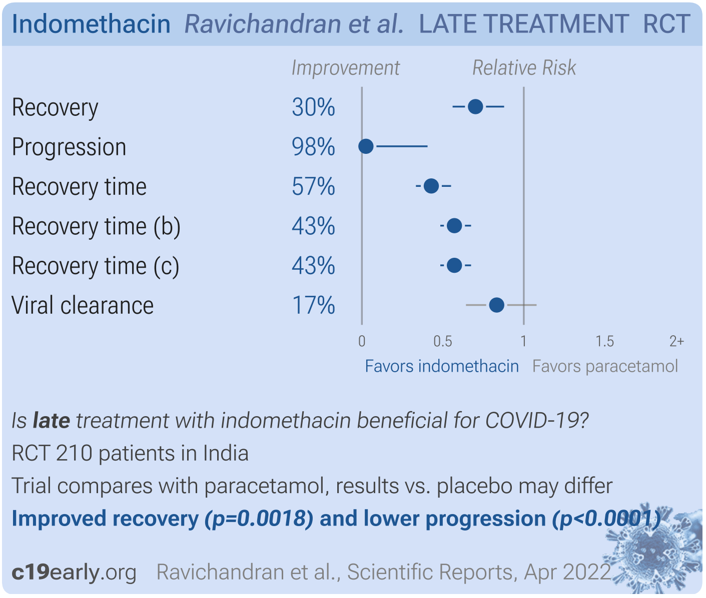
### Gordon




*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.

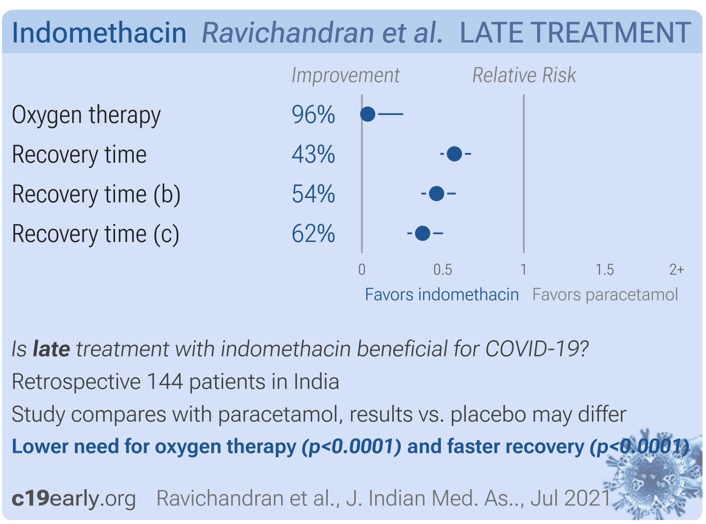
Authors predict indomethacin will have antiviral activity for SARS-CoV-2 and perform a retrospective study of patients in the USA that started treatment within 21 days after COVID-19 infection - 103 with indomethacin, and 103 using a celecoxib, a clinically similar drug without predicted antiviral activity.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

### Ravichandran



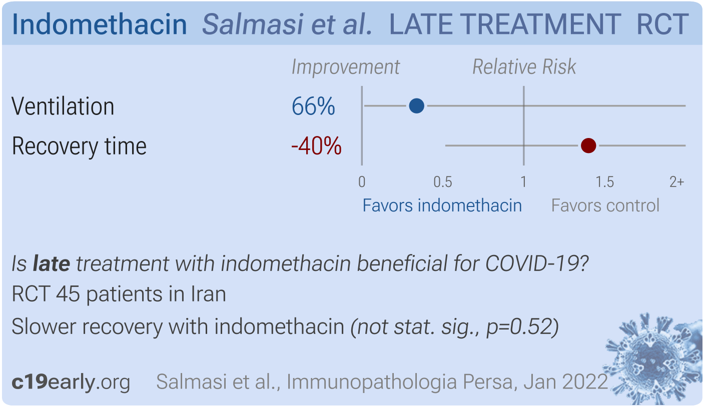

*Ravichandran*: RCT with 103 indomethacin and 107 paracetamol patients, showing lower progression and improved recovery with indomethacin. Notably, improvements include faster resolution of cough. *Alkotaji* previously hypothesised the benefit of indomethacin for reducing cough via bradykinin inhibition.

### Ravichandran




*Ravichandran (B)*: PSM retrospective 72 indomethacin and 72 paracetamol patients in India, showing lower progression and improved recovery with indomethacin.

**Salmasi**




*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. 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 both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used 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 test status. 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. 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]. Reported confidence intervals and *p*-values were used when available, using adjusted values 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 [Sweeting]. 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 (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

Forest plots are computed using PythonMeta [Deng] 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 (4.1.2) using the metafor (3.0-2) and rms (6.2-0) 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 0.8.0 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 [McLean, Treanor].

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, 311 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.

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