Indomethacin for COVID-19: real-time meta analysis of 4 studies
@CovidAnalysis, November 2023
https://c19early.org/inmeta.html

- 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.

- 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 57 treatments.
### 4 indomethacin COVID-19 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Improvement, RR [CI]</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon (PSM)</td>
<td>67%</td>
<td>0.33 [0.04-3.15] hosp.</td>
<td>1/103</td>
</tr>
<tr>
<td>Ravichandran (PSM)</td>
<td>96%</td>
<td>0.04 [0.00-0.25] oxygen</td>
<td>1/72</td>
</tr>
<tr>
<td>Sabnis (RCT)</td>
<td>66%</td>
<td>0.34 [0.01-7.89] ventilation</td>
<td>0/22</td>
</tr>
<tr>
<td>Ravichandran (RCT)</td>
<td>30%</td>
<td>0.70 [0.56-0.88] no recov.</td>
<td>52/103</td>
</tr>
</tbody>
</table>

**Late treatment** 74% 0.26 [0.06-1.20] 54/300 109/305

- **Tau**² = 1.49, I² = 67.5%, p = 0.084

**All studies** 74% 0.26 [0.06-1.20] 54/300 109/305

- **Tau**² = 1.49, I² = 67.5%, p = 0.084

1 OT: comparison with other treatment

**Effect extraction pre-specified** (most serious outcome, see appendix)

Favors indomethacin

Favors control

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### Efficacy in COVID-19 indomethacin studies (pooled effects)

**Late treatment**

- **Favors indomethacin**

- **Favors control**

**All studies**

- **Favors indomethacin**

- **Favors control**

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### Efficacy in COVID-19 studies (pooled effects)

- **Indomethacin**
- **Ivermectin**
- **PVP-I**
- **Quercetin**
- **Melatonin**
- **Sunlight**
- **Exercise**
- **Fluvoxamine**
- **Vitamin D**
- **Metformin**
- **Zinc**
- **HCQ**
- **Sotrovimab**
- **Vitamin C**
- **Paxlovid**
- **Molnupiravir**
- **Remdesivir**
- **Ibuprofen**
- **Conv. Plasma**
- **Vitamin B9**
- **Cannabidiol**
- **Acetaminophen**

- **Lower risk**
- **Increased risk**

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**c19early.org**

November 2023
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. 0.7% of 5,722 proposed treatments show efficacy. D. Timeline of results in indomethacin studies.

Introduction

We analyze all significant studies concerning the use 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).

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.
Results

Table 1 summarizes the results for all studies, after exclusions, and for specific outcomes. Figure 3, 4, 5, 6, 7, and 8 show forest plots for random effects meta-analysis of all studies with pooled effects, ventilation, hospitalization, progression, recovery, and viral clearance.

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Studies</th>
<th>Patients</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>74% [-20-94%]</td>
<td>4</td>
<td>605</td>
</tr>
<tr>
<td>Randomized Controlled Trials</td>
<td>30% [13-44%] **</td>
<td>2</td>
<td>255</td>
</tr>
<tr>
<td>Recovery</td>
<td>34% [15-49%] **</td>
<td>3</td>
<td>399</td>
</tr>
</tbody>
</table>

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

**Figure 3.** 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.

4 indomethacin COVID-19 studies

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<td>1/72</td>
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<td>Salmasi (RCT)</td>
<td>66% 0.34 [0.01-7.89] ventilation</td>
<td>0/22</td>
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Late treatment 74% 0.26 [0.06-1.20] 54/300 109/305

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1 OT: comparison with other treatment

Tau² = 1.49, I² = 67.5%, p = 0.084 Effect extraction pre-specified (most serious outcome, see appendix)

Favors indomethacin Favors control

**Figure 4.** Random effects meta-analysis for ventilation.

1 indomethacin COVID-19 mechanical ventilation result

<table>
<thead>
<tr>
<th>Improvement, RR (CI)</th>
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<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmasi (RCT)</td>
<td>66% 0.34 [0.01-7.89]</td>
<td>0/22</td>
</tr>
</tbody>
</table>

Late treatment 66% 0.34 [0.01-7.89] 0/22 1/23

Tau² = 0.00, I² = 0.0%, p = 0.51

All studies 66% 0.34 [0.01-7.89] 0/22 1/23

Favors indomethacin Favors control

**Figure 4.** Random effects meta-analysis for ventilation.
### 1 indomethacin COVID-19 hospitalization result

<table>
<thead>
<tr>
<th></th>
<th>Improvement, RR [CI]</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Gordon (PSM)</td>
<td>67% 0.33 [0.04-3.15]</td>
<td>1/103</td>
<td>3/103</td>
</tr>
<tr>
<td>Late treatment</td>
<td>67% 0.33 [0.04-3.15]</td>
<td>1/103</td>
<td>3/103</td>
</tr>
</tbody>
</table>

All studies 67% 0.33 [0.04-3.15] 1/103 3/103

Figure 5. Random effects meta-analysis for hospitalization.

### 2 indomethacin COVID-19 progression results

<table>
<thead>
<tr>
<th></th>
<th>Improvement, RR [CI]</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon (PSM)</td>
<td>57% 0.43 [0.11-1.61]</td>
<td>3/103</td>
<td>7/103</td>
</tr>
<tr>
<td>Ravichandran (RCT)</td>
<td>98% 0.02 [0.00-0.41]</td>
<td>0/103</td>
<td>20/107</td>
</tr>
<tr>
<td>Late treatment</td>
<td>86% 0.14 [0.01-2.10]</td>
<td>3/206</td>
<td>27/210</td>
</tr>
</tbody>
</table>

All studies 86% 0.14 [0.01-2.10] 3/206 27/210

Figure 6. Random effects meta-analysis for progression.

### 3 indomethacin COVID-19 recovery results

<table>
<thead>
<tr>
<th></th>
<th>Improvement, RR [CI]</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravichandran</td>
<td>43% 0.57 [0.48-0.67]</td>
<td>72 (n)</td>
<td>72 (n)</td>
</tr>
<tr>
<td>Salmasi (RCT)</td>
<td>-40% 1.40 [0.52-3.81]</td>
<td>22 (n)</td>
<td>23 (n)</td>
</tr>
<tr>
<td>Ravichandran (RCT)</td>
<td>30% 0.70 [0.56-0.88]</td>
<td>52/103</td>
<td>77/107</td>
</tr>
<tr>
<td>Late treatment</td>
<td>34% 0.66 [0.51-0.85]</td>
<td>52/197</td>
<td>77/202</td>
</tr>
</tbody>
</table>

All studies 34% 0.66 [0.51-0.85] 52/197 77/202

Figure 7. Random effects meta-analysis for recovery.
Randomized Controlled Trials (RCTs)

Figure 9 shows a comparison of results for RCTs and non-RCT studies. Figure 10 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1 and Table 2.

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. 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.

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 57 treatments we have analyzed, 64% 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. Conato find that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. Anglemyer summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. Lee shows 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

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

<table>
<thead>
<tr>
<th>Improvement, RR [CI]</th>
<th>Treatment</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ravichandran (RCT)</td>
<td>17% 0.83 [0.64-1.08] viral+</td>
<td>37/62 43/60</td>
</tr>
<tr>
<td>Late treatment</td>
<td>17% 0.83 [0.64-1.08]</td>
<td>37/62 43/60</td>
</tr>
</tbody>
</table>

All studies 17% 0.83 [0.64-1.08] 37/62 43/60 17% lower risk

\[\tau^2 = 0.00, I^2 = 0.0\%, p = 0.17\]

1 OT: comparison with other treatment

<table>
<thead>
<tr>
<th></th>
<th>OT: combination with other treatment</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Favors indomethacin Favors control</td>
</tr>
<tr>
<td>0</td>
<td>0.25 0.5 0.75 1 1.25 1.5 1.75 2+</td>
</tr>
</tbody>
</table>

Favors indomethacin Favors control

\[\tau^2 = 0.00, I^2 = 0.0\%, p = 0.17\]
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 Beaton, Nichol.

Using all studies identifies efficacy 5.7+ months faster for COVID-19. Currently, 39 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 39 treatments with statistically significant efficacy/harm, 24 have been confirmed in RCTs, with a mean delay of 5.7 months. For the 15 unconfirmed treatments, 4 have zero RCTs to date. The point estimates for the remaining 11 are all consistent with the overall results (benefit or harm), with 9 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.

**Efficacy in COVID-19 indomethacin studies (pooled effects)**

![Figure 9. Results for RCTs and non-RCT studies.](c19early.org)

**2 indomethacin COVID-19 Randomized Controlled Trials**

<table>
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<td>0.70 [0.56-0.87] 52/125 78/130</td>
</tr>
<tr>
<td>All studies</td>
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<td>0.70 [0.56-0.87] 52/125 78/130</td>
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![Figure 10. Random effects meta-analysis for all Randomized Controlled Trials.](c19early.org)

<table>
<thead>
<tr>
<th>Effect extraction pre-specified (most serious outcome, see appendix)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favors indomethacin Favors control</td>
</tr>
<tr>
<td>0.25 0.5 0.75 1 1.25 1.5 1.75 2+</td>
</tr>
<tr>
<td>Favors indomethacin Favors control</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment delay</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post exposure prophylaxis</td>
<td>86% fewer cases (^{Ikematsu})</td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>-33 hours symptoms (^{Hayden})</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>-13 hours symptoms (^{Hayden})</td>
</tr>
<tr>
<td>Inpatients</td>
<td>-2.5 hours to improvement (^{Kumar})</td>
</tr>
</tbody>
</table>

Figure 11 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 57 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

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 12. 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, 39 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 89% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.4 months. When restricting to RCTs only, 52% 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.
**Figure 12.** The time when studies showed that treatments were effective, defined as statistically significant improvement of $\geq 10\%$ from $\geq 3$ 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. 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 13 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.

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 14 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 [1]. 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 14. Example funnel plot analysis for simulated perfect trials.
Conlicts of interest. Pharmaceutical drug trials often have conlicts 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 eficacy.

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, conlicts of interest, standard of care, and other factors. We provide analyses by specic 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 conlicts of interest. Trials afiliated 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 conidence 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 beneicial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specied method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater eficacy than individual treatments alone. Therefore standard of care may be critical and beneits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy beneits 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 eective for all current and future variants. Eficacy may vary signicantly with different variants and within different populations. All treatments have potential side eects. Propensity to experience side eects may be predicted in advance by qualied physicians. We do not provide medical advice. Before taking any medication, consult a qualied physician who can compare all options, provide personalized advice, and provide details of risks and beneits based on individual medical history and situations.

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

Indomethacin may be beneficial for cough \textit{Alkotaj}, which may not respond to other treatments.

Study Notes

\textit{Gordon}

Is late treatment with indomethacin beneficial for COVID-19? PSM retrospective 206 patients in the USA.
Study compares with celecoxib, results vs. placebo may differ.
Lower hospitalization \((p=0.34)\) and progression \((p=0.21)\), not sig.

\textit{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

**Indomethacin Ravichandran et al. LATE TREATMENT RCT**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>Recovery time</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Recovery time (b)</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Recovery time (c)</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Viral clearance</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

Is late treatment with indomethacin beneficial for COVID-19?
RCT 210 patients in India
Trial compares with paracetamol, results vs. placebo may differ
Improved recovery (*p*<0.0018) and lower progression (*p*<0.0001)
c19early.org Ravichandran et al., Scientific Reports, Apr 2022

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

**Indomethacin Ravichandran et al. LATE TREATMENT**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen therapy</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Recovery time</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Recovery time (b)</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Recovery time (c)</td>
<td>62%</td>
<td></td>
</tr>
</tbody>
</table>

Is late treatment with indomethacin beneficial for COVID-19?
Retrospective 144 patients in India
Study compares with paracetamol, results vs. placebo may differ
Lower need for oxygen therapy (*p*<0.0001) and faster recovery (*p*<0.0001)
c19early.org Ravichandran et al., J. Indian Med. As., Jul 2021

Ravichandran (B): 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 performed ongoing searches of PubMed, medRxiv, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Collabovid, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms were indomethacin, filtered for papers containing the terms COVID-19 or SARS-CoV-2. Automated searches are performed every few hours with notification of new matches. 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 are used. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms were not used (the next most serious outcome is used — no studies were excluded). 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 outcome is considered more important than PCR testing 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 no room for an effective treatment to do better). If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO₂ is more important than cough. When results provide an odds ratio, we computed the relative risk when possible, or converted 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 including propensity score matching (PSM), the PSM results are used. Adjusted primary outcome 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 (3.11.6) with scipy (1.11.3), pythonmeta (1.26), numpy (1.26.1), statsmodels (0.14.0), and plotly (5.17.0).
Forest plots are computed using PythonMeta with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. 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.

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

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.

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.

<table>
<thead>
<tr>
<th>Gordon, 12/4/2020, retrospective, USA, peer-reviewed, 311 authors, this trial compares with another treatment - results may be better when compared to placebo.</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>risk of progression, 97.5% lower, RR 0.02, p &lt; 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.</td>
</tr>
<tr>
<td></td>
<td>recovery time, 57.1% lower, relative time 0.43, p &lt; 0.001, treatment median 3.0 IQR 1.0 n=103, control median 7.0 IQR 2.75 n=107, fever.</td>
</tr>
<tr>
<td></td>
<td>recovery time, 42.9% lower, relative time 0.57, p &lt; 0.001, treatment median 4.0 IQR 2.0 n=103, control median 7.0 IQR 2.0 n=107, myalgia.</td>
</tr>
<tr>
<td></td>
<td>recovery time, 42.9% lower, relative time 0.57, p &lt; 0.001, treatment median 4.0 IQR 1.0 n=103, control median 7.0 IQR 3.0 n=107, cough.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>
**Supplementary Data**

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