Acetaminophen for COVID-19: real-time meta analysis of 28 studies

@CovidAnalysis, January 2024
https://c19early.org/acemeta.html

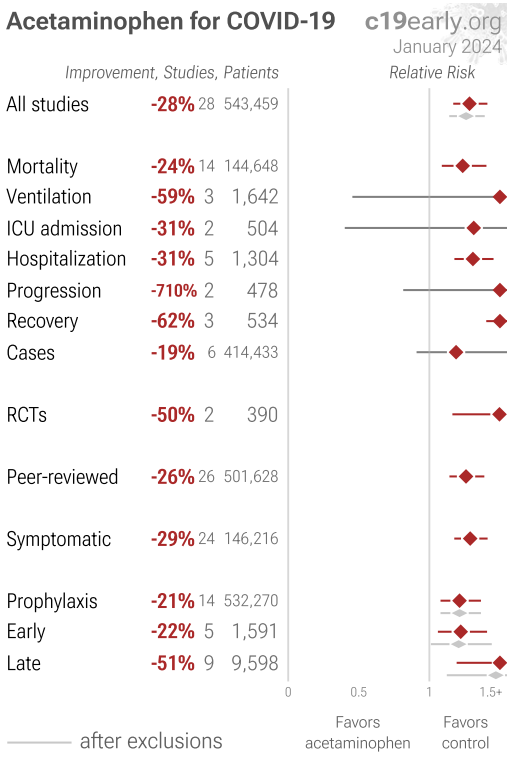
Abstract

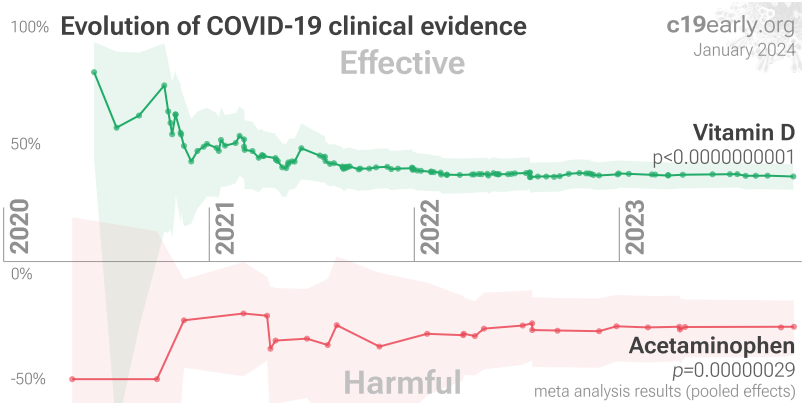
Meta analysis shows 24% [9-40%] higher mortality, and pooled analysis using the most serious outcome reported shows 28% [17-41%] higher risk.

Concerns have been raised over the use of acetaminophen (paracetamol) for COVID-19 *Pandolfi, Sestili*. Studies to date show increased risk. Data is limited, with RCTs to date comparing with indomethacin/ibuprofen.

Potential mechanisms of harm include glutathione depletion, fever suppression, liver toxicity, immunosuppression, cytokine disruption, prostaglandin inhibition, COX inhibition, cell/tissue injury, mitochondrial dysfunction, glycine depletion, disruption of redox balance, increased oxidative stress, trace mineral depletion, microbiome alteration, and endocannabinoid system dysfunction.

All data to reproduce this paper and sources are in the appendix. Acetaminophen is also known as paracetamol.





HIGHLIGHTS

Acetaminophen was the 1st treatment shown harmful with ≥3 clinical studies in November 2020, now known with p = 0.00000029 from 28 studies, but still recommended in 44 countries.

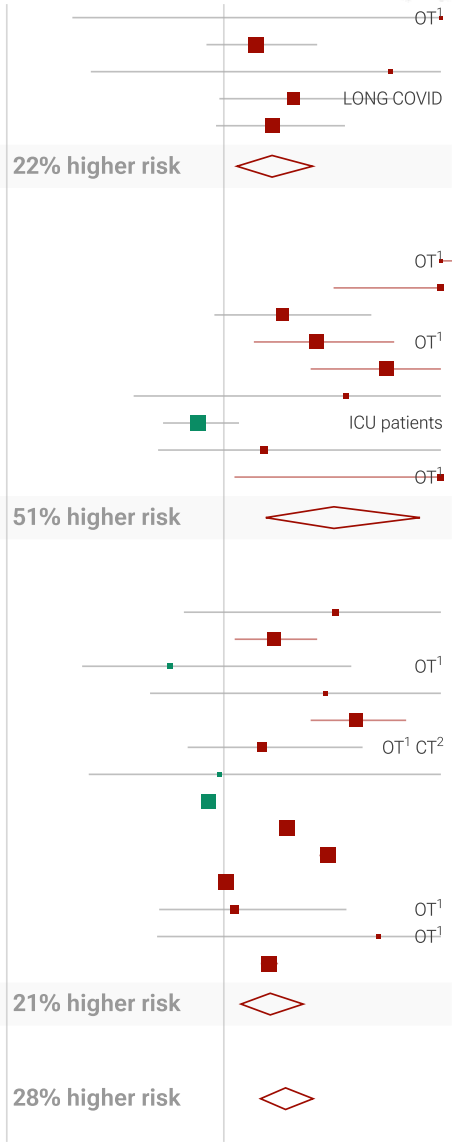
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 63 treatments.

Acetaminophen COVID-19 studies

c19early.org
January 2024

	Improvement	RR [CI]		Treatment	Control
Rinott	-473%	5.73 [0.30-109]	death	3/85	0/49
Lapi (ES)	-15%	1.15 [0.92-1.43]	death/hosp.	n/a	n/a
Sharif	-77%	1.77 [0.39-8.09]	death	9/361	2/142
Chen	-32%	1.32 [0.98-1.78]	PASC	98/232	39/122
Rahman	-23%	1.23 [0.96-1.56]	hosp.	84/244	100/356
Early treatment	**-22%**	1.22 [1.06-1.41]		194/922	141/669
$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.0056$					
	Improvement	RR [CI]		Treatment	Control
Ravichandran (PSM)	-2700%	28.00 [3.91-200]	oxygen	28/72	1/72
Manjani	-220%	3.20 [1.51-6.82]	death	64/388	7/136
Lerner	-27%	1.27 [0.96-1.68]	death	5,783 (all patients)	
Ravichandran (RCT)	-43%	1.43 [1.14-1.78]	no recov.	77/107	52/103
Lapi	-75%	1.75 [1.40-2.18]	death/hosp.	n/a	n/a
Abolhassani	-56%	1.56 [0.58-4.18]	death	3/6	8/25
Baldia (ICU)	12%	0.88 [0.72-1.07]	death	1,166 (n)	1,480 (n)
Stufano	-19%	1.19 [0.70-2.02]	PASC	11/23	23/57
Sobhy (DB RCT)	-110%	2.10 [1.05-4.20]	ICU	21/90	10/90
Late treatment	**-51%**	1.51 [1.19-1.90]		204/1,852	101/1,963
$Tau^2 = 0.07$, $I^2 = 69.8\%$, $p = 0.00061$					
	Improvement	RR [CI]		Treatment	Control
Blanc	-51%	1.51 [0.82-2.84]	cases	60 (n)	119 (n)
Kolin	-23%	1.23 [1.05-1.43]	cases	397,064 (all patients)	
Park (PSM)	25%	0.75 [0.35-1.59]	death	12/397	16/397
Gálvez-Barrón	-47%	1.47 [0.66-3.33]	death	43 (n)	60 (n)
Reese (PSM)	-61%	1.61 [1.40-1.84]	death	20,826 (n)	20,826 (n)
Chandan (PSM)	-18%	1.18 [0.83-1.64]	death	71/8,595	79/8,595
Oh	2%	0.98 [0.38-2.49]	death	58 (n)	7,655 (n)
Leal	7%	0.93 [0.91-0.96]	cases	n/a	n/a
Moreno-Martos	-29%	1.29 [1.27-1.32]	hosp.		
MacFadden	-48%	1.48 [1.44-1.51]	cases	n/a	n/a
Campbell (PSW)	-1%	1.01 [0.99-1.02]	death	2,074 (n)	20,311 (n)
Xie	-5%	1.05 [0.70-1.56]	hosp.	population-based cohort	
Kim (PSM)	-71%	1.71 [0.69-4.24]	death	12/162	7/162
Ritsinger	-21%	1.21 [1.17-1.25]	death	24,641 (n)	20,225 (n)
Prophylaxis	**-21%**	1.21 [1.08-1.37]		95/56,856	102/78,350
$Tau^2 = 0.03$, $I^2 = 98.0\%$, $p = 0.0013$					
All studies	**-28%**	1.28 [1.17-1.41]		493/59,630	344/80,982



A

[1] OT: comparison with other treatment
[2] CT: study uses combined treatment

$Tau^2 = 0.03$, $I^2 = 96.2\%$, $p < 0.0001$

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

Efficacy in COVID-19 acetaminophen studies (pooled effects)

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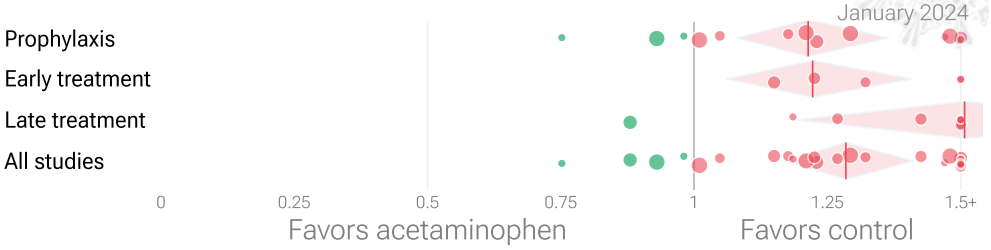
January 2024



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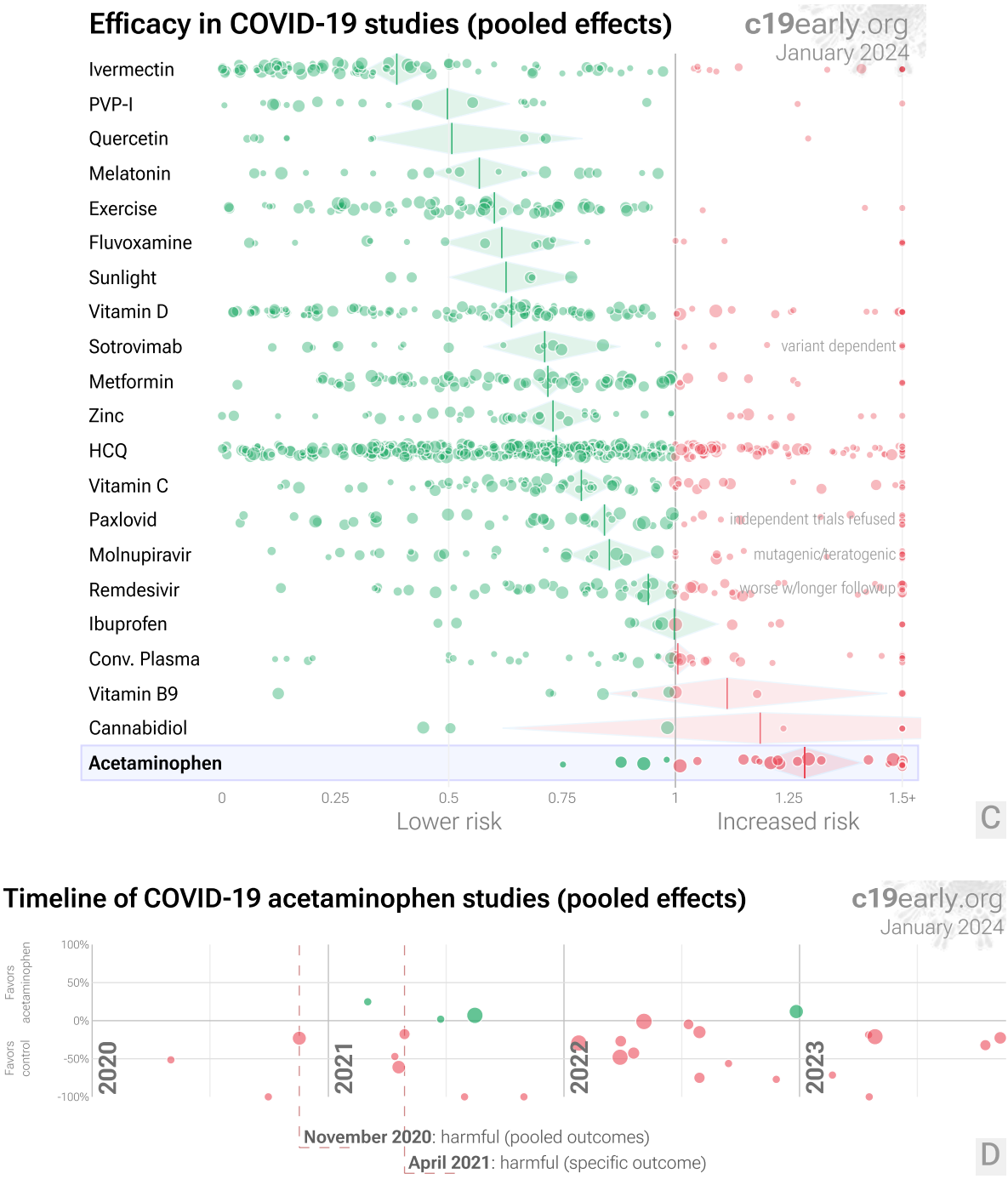


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the 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 6,037 proposed treatments show efficacy *c19early.org*. **D. Timeline of results in acetaminophen studies.** The marked dates indicate the time when a harmful effect was identified with statistical significance from ≥3 studies for pooled outcomes and one or more specific outcome. Harm based on specific outcomes was delayed by 5.4 months, compared to using pooled outcomes.

Introduction

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

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.

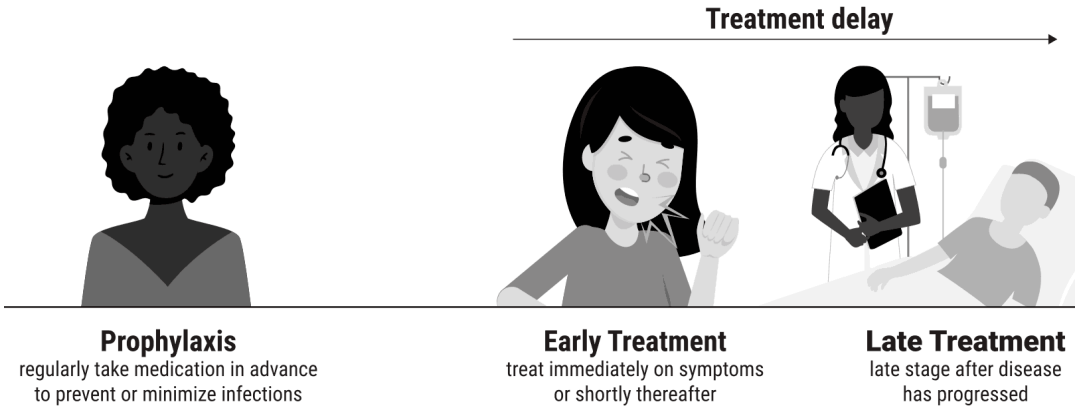


Figure 2. Treatment stages.

Mechanisms of Action

Table 1 shows potential mechanisms by which the treatment of COVID-19 with acetaminophen could be harmful.

Glutathione depletion	Acetaminophen metabolism relies on glutathione, an antioxidant that helps protect cells from damage. Higher or chronic doses of acetaminophen can deplete glutathione levels, which could lead to impaired immune cell function.
Fever suppression	Fever is a natural defense mechanism that helps the body fight off infection. By reducing fever, acetaminophen could potentially prolong infections.
Liver toxicity	Acetaminophen overdose can damage the liver. The liver plays an important role in immune function and inflammation.
Immunosuppression	Some research indicates acetaminophen directly suppresses immune cells such as lymphocytes and macrophages, reducing immune defenses.
Cytokine disruption	Acetaminophen exposure has been found to alter cytokine production, such as reducing IL-6 levels. Cytokines regulate immunity, so this could impair immune responses.
Prostaglandin inhibition	Acetaminophen inhibits prostaglandins, which are signaling molecules that play a role in inflammation and immunity. Reduced prostaglandins could potentially alter immune regulation and make it more difficult for the body to fight off infection.
COX inhibition	Acetaminophen weakly inhibits COX-1/COX-2 enzymes. These generate immune-modulating prostaglandins, so inhibition could alter immunity.
Cell/tissue injury	Acetaminophen is known to cause oxidative injury to cells, even at normal doses. This low-grade damage could potentially trigger inflammatory and immune responses.
Mitochondrial dysfunction	High doses of acetaminophen may impair mitochondrial energy production. Mitochondria play important roles in immune cell activation and function.
Glycine depletion	Conjugating acetaminophen requires glycine, an amino acid that is involved in a number of important biological processes, including immune function. Depletion of glycine could reduce antioxidant production and have immunomodulatory effects.
Disruption of redox balance	Acetaminophen can disrupt the redox balance, which is the balance between antioxidants and free radicals. Free radicals are unstable molecules that can damage cells. If the redox balance is disrupted, it could lead to increased inflammation and impaired immune cell function.
Increased oxidative stress	Beyond glutathione depletion, acetaminophen can increase reactive oxygen species and oxidative stress. Oxidative stress can damage cells and trigger inflammation.
Trace mineral depletion	Acetaminophen increases urinary excretion of trace minerals involved in immunity like zinc, selenium, and manganese.
Microbiome alteration	Acetaminophen exposure might alter the intestinal microbiota, which is the community of bacteria that live in the gut. The intestinal microbiota plays an important role in immune function, so changes to the microbiota could make it more difficult for the body to fight off infection.
Endocannabinoid system dysfunction	Acetaminophen may disrupt endocannabinoid signaling, which helps regulate immune function. This could lead to improper immune responses.

Table 1. **Mechanisms of action for potential harmful effects with acetaminophen treatment.** Submit updates.

Results

Table 2 summarizes the results for all stages combined, with different exclusions, and for specific outcomes. Table 3 shows results by treatment stage. Figure 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, peer reviewed studies, and non-symptomatic vs. symptomatic results.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	-28% [-41--17%] ****	28	543,459	449
After exclusions	-26% [-39--14%] ****	24	542,222	417
Peer-reviewed studies	-26% [-39--14%] ****	26	501,628	404
Randomized Controlled Trials	-50% [-93--16%] **	2	390	14
Mortality	-24% [-40--9%] **	14	144,648	319
Ventilation	-59% [-454-55%]	3	1,642	15
ICU admission	-31% [-331-60%]	2	504	10
Hospitalization	-31% [-45--18%] ****	5	1,304	50
Recovery	-62% [-87--40%] ****	3	534	20
Cases	-19% [-56-9%]	6	414,433	73

Table 2. **Random effects meta-analysis for all stages combined, with different exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	-22% [-41--6%] **	-51% [-90--19%] ***	-21% [-37--8%] **
After exclusions	-21% [-44--1%] *	-47% [-93--12%] **	-21% [-37--8%] **
Peer-reviewed studies	-22% [-41--6%] **	-51% [-90--19%] ***	-17% [-32--3%] *
Randomized Controlled Trials		-50% [-93--16%] **	
Mortality	-127% [-775-41%]	-36% [-104-9%]	-21% [-41--5%] *
Ventilation		-434% [-1345--98%] ***	13% [-83-58%]
ICU admission		-110% [-320--5%] *	40% [-147-85%]
Hospitalization	-23% [-56-4%]	-59% [-130--9%] *	-29% [-37--20%] ****
Recovery		-62% [-87--40%] ****	
Cases			-19% [-56-9%]

Table 3. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

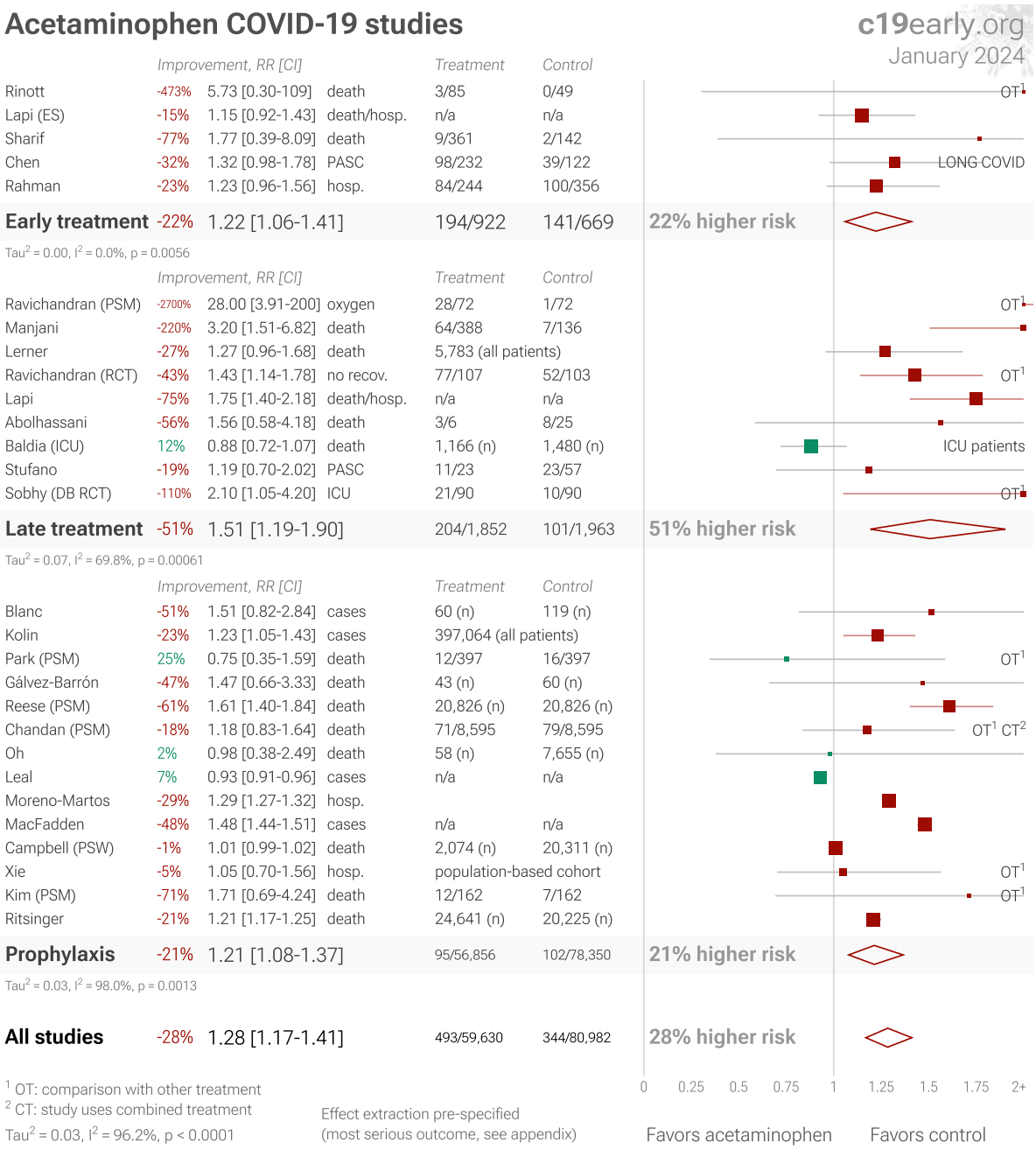


Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

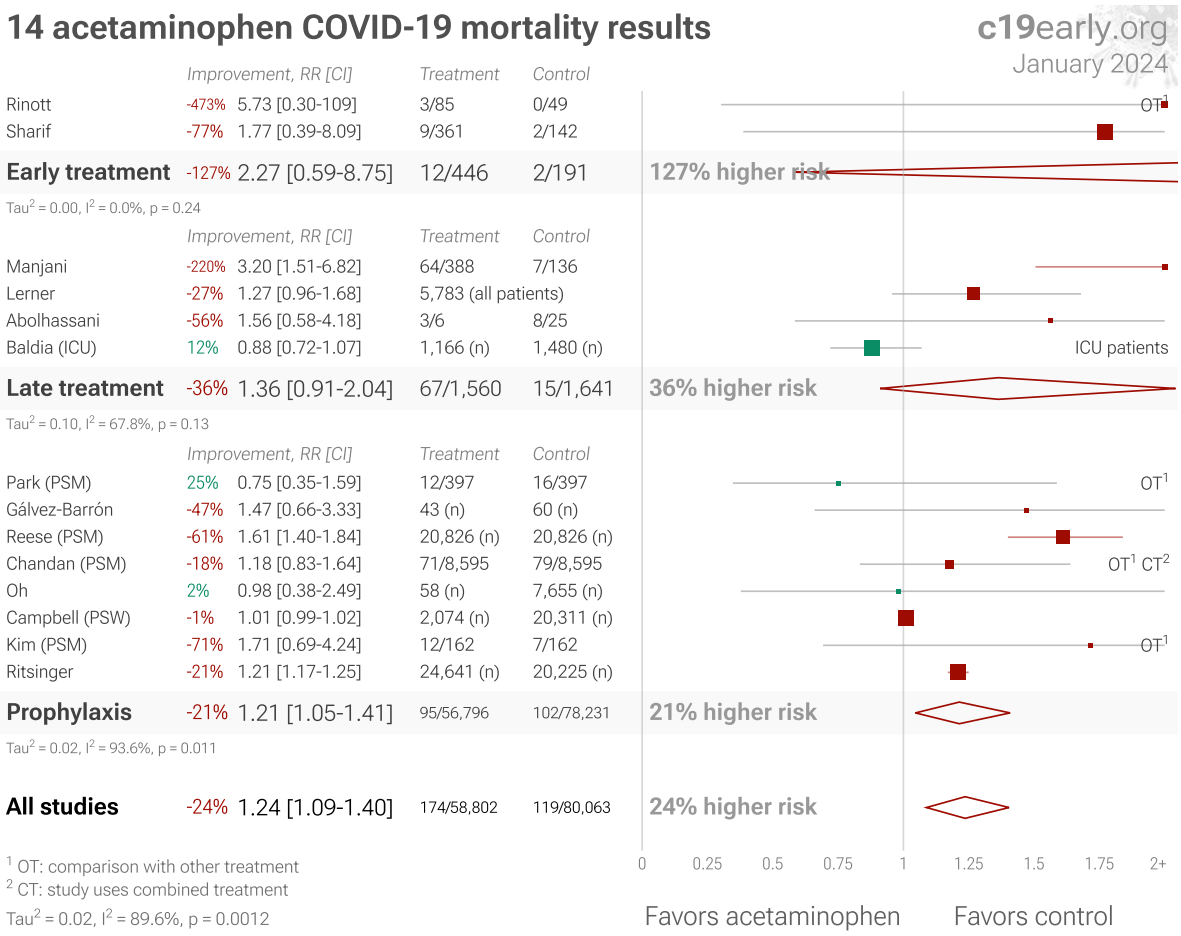


Figure 4. Random effects meta-analysis for mortality results.

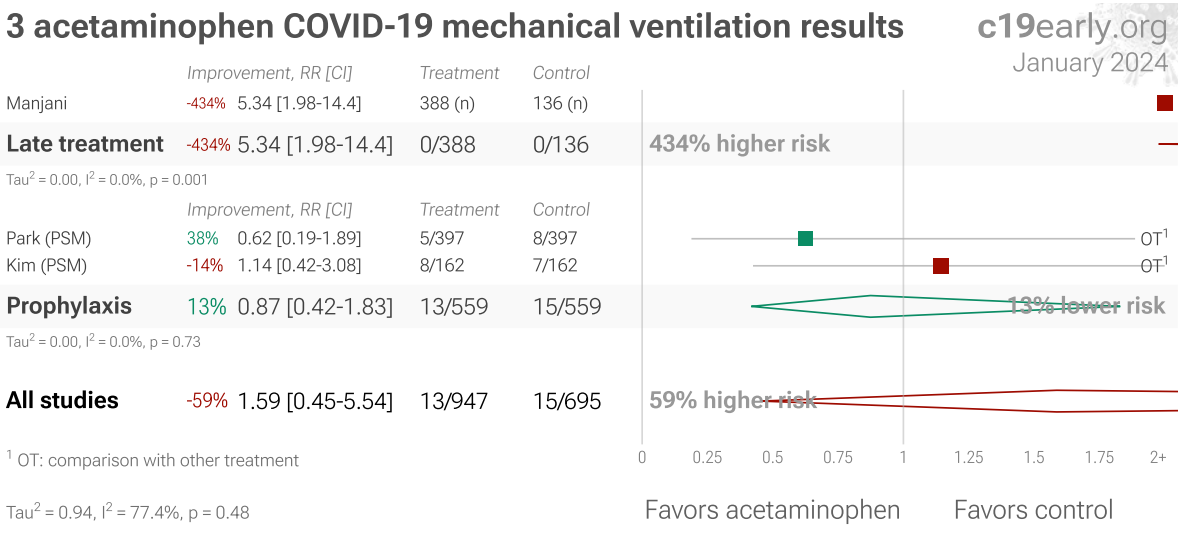


Figure 5. Random effects meta-analysis for ventilation.

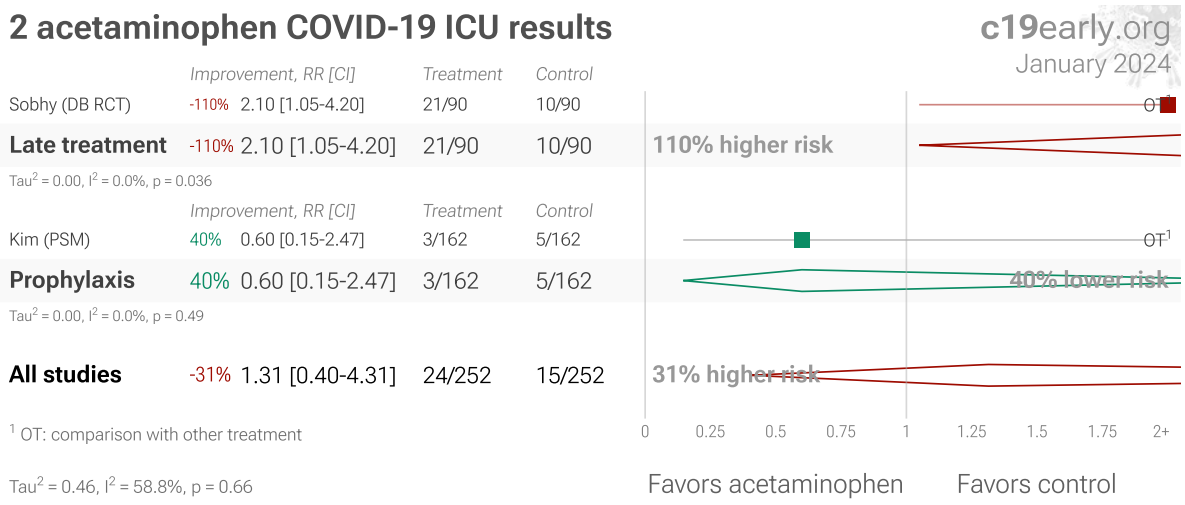


Figure 6. Random effects meta-analysis for ICU admission.

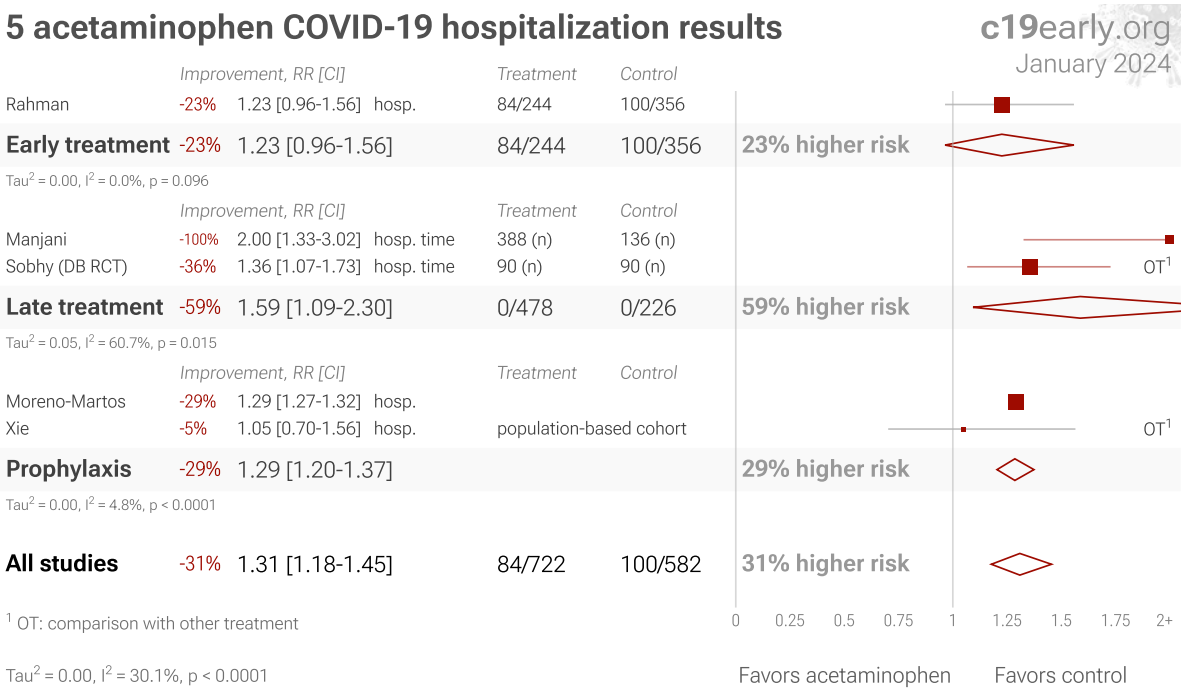


Figure 7. Random effects meta-analysis for hospitalization.

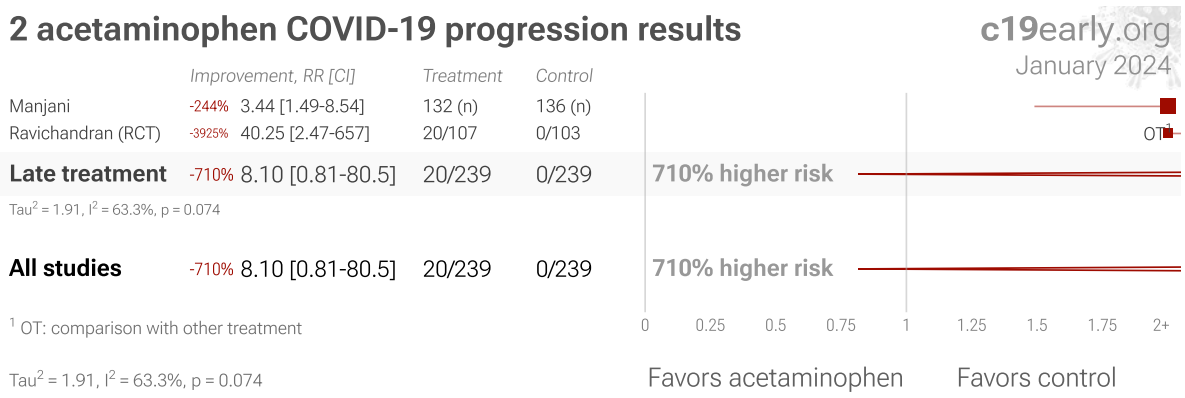


Figure 8. Random effects meta-analysis for progression.

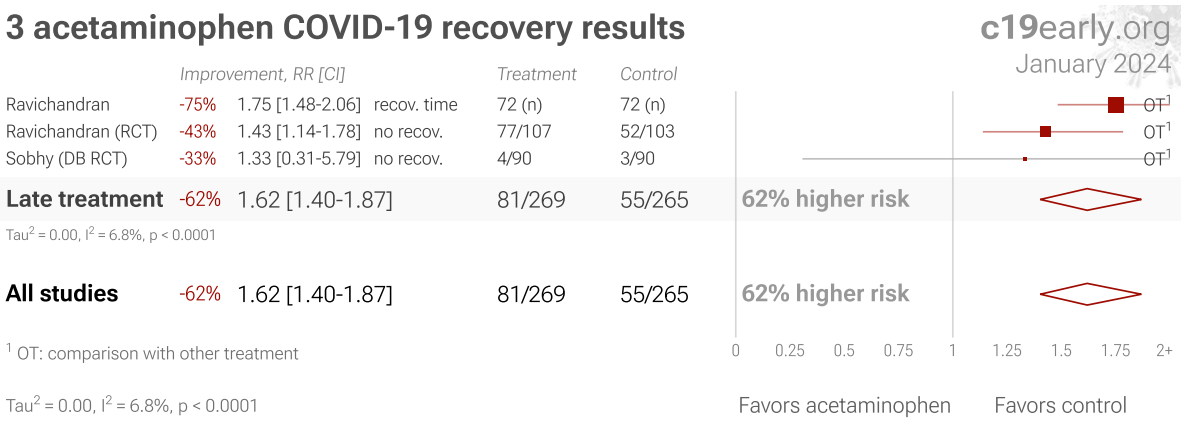


Figure 9. Random effects meta-analysis for recovery.

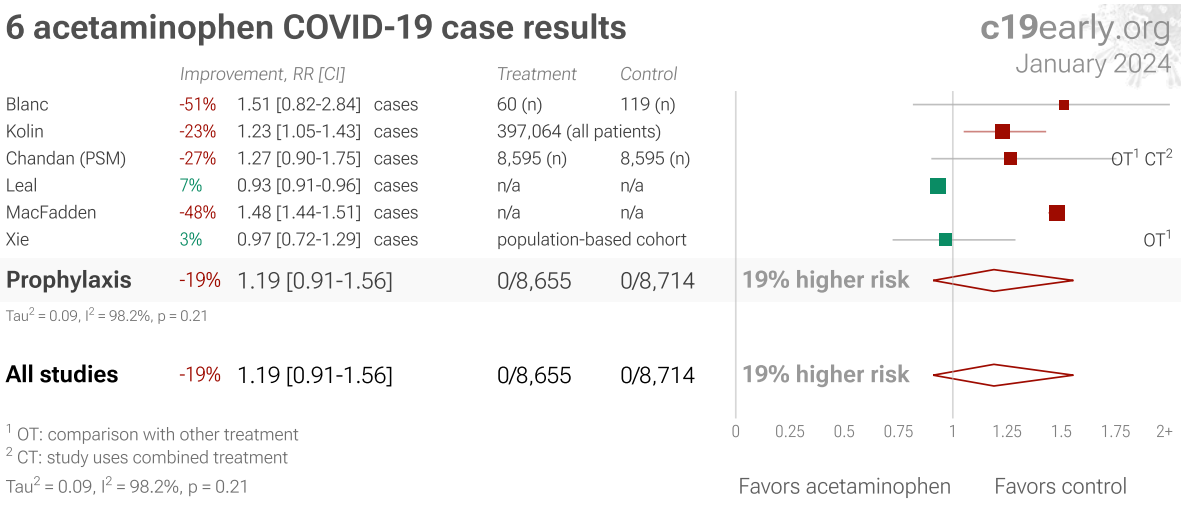


Figure 10. Random effects meta-analysis for cases.

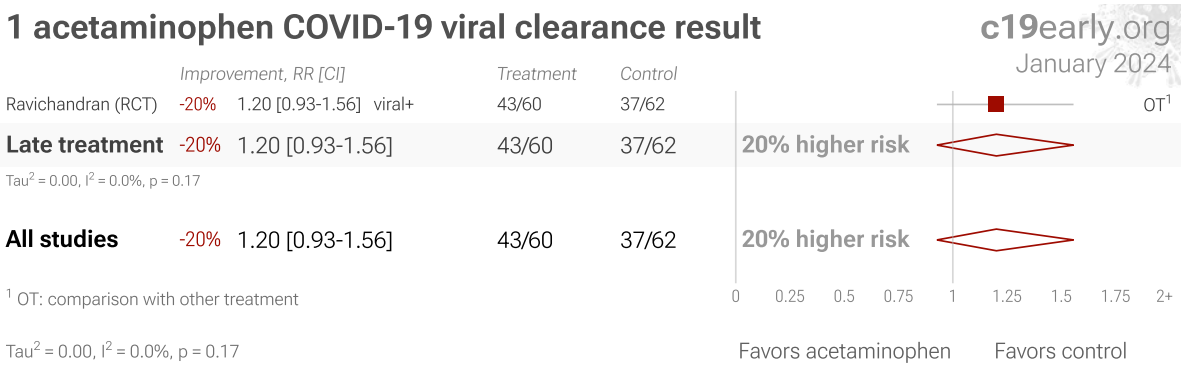


Figure 11. Random effects meta-analysis for viral clearance.

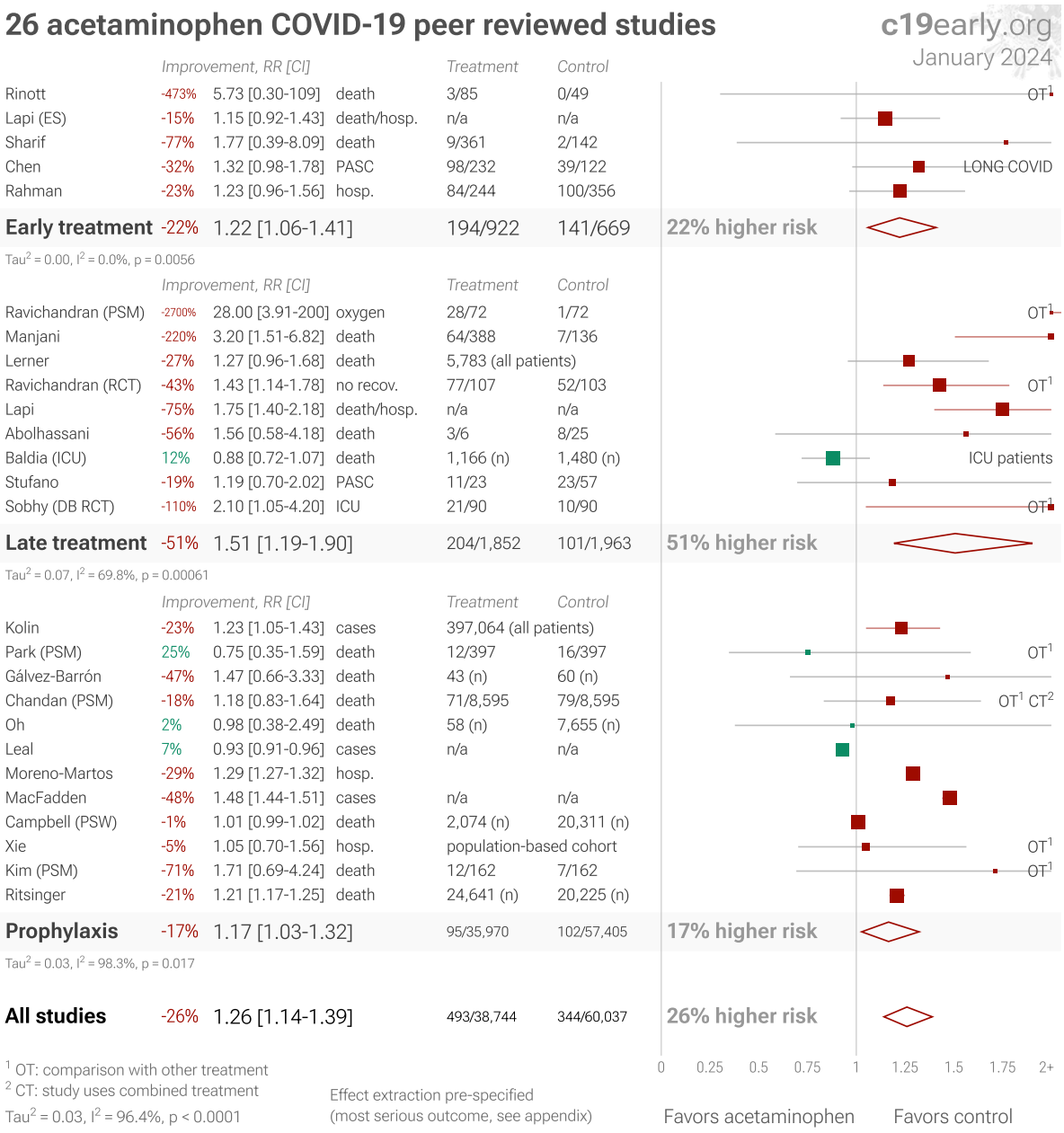


Figure 12. **Random effects meta-analysis for peer reviewed studies.** *Zeraatkar* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

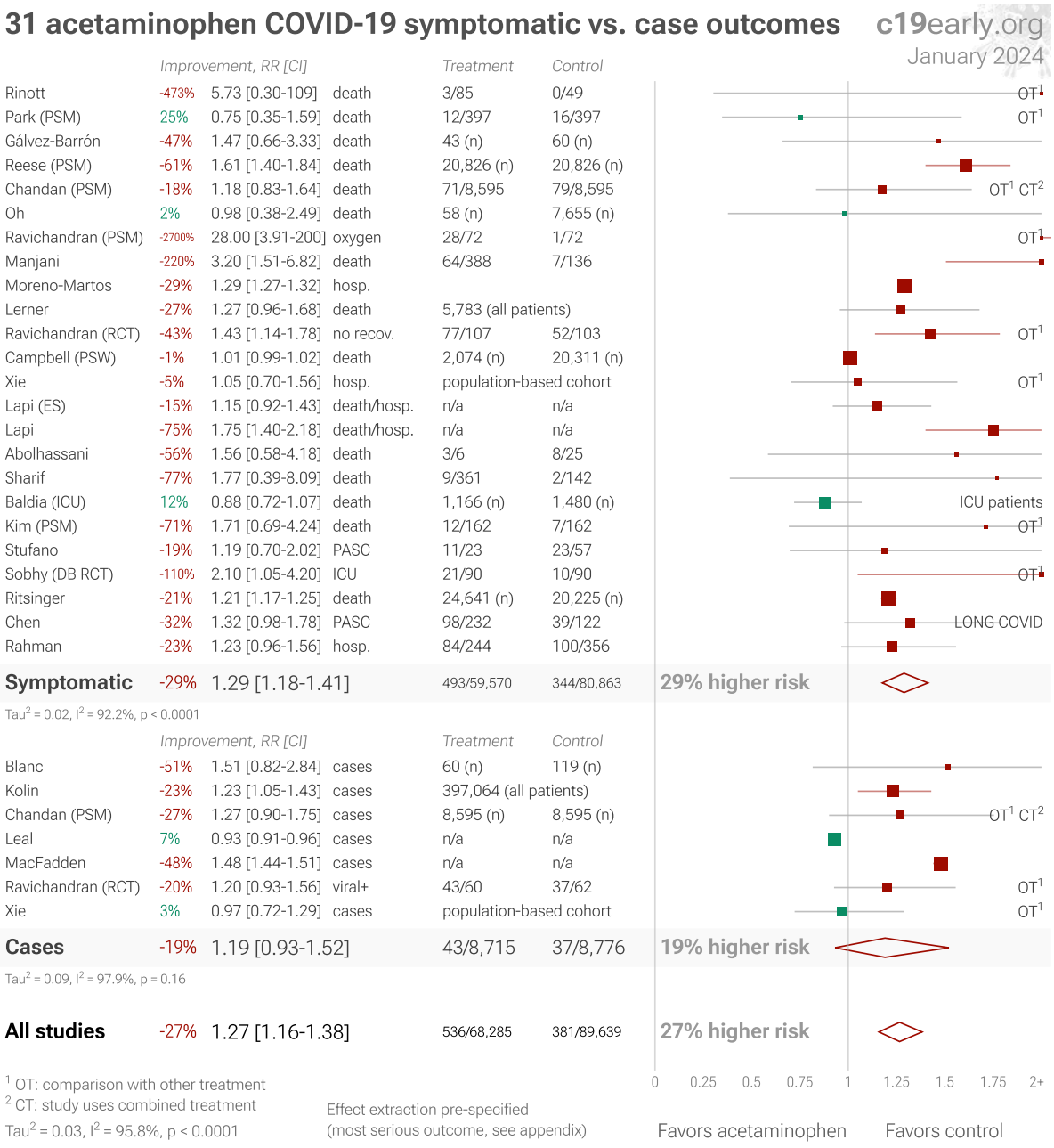


Figure 13. **Random effects meta-analysis for non-symptomatic vs. symptomatic results.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

Randomized Controlled Trials (RCTs)

Figure 14 shows a comparison of results for RCTs and non-RCT studies. Figure 15 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 2 and Table 3.

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.

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 63 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 acetaminophen 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.

Using all studies identifies efficacy 5.5+ months faster for COVID-19. Currently, 42 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 42 treatments with statistically significant efficacy/harm, 25 have been confirmed in RCTs, with a mean delay of 5.5 months. For the 17 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 14 are all consistent with the overall results (benefit or harm), with 11 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.

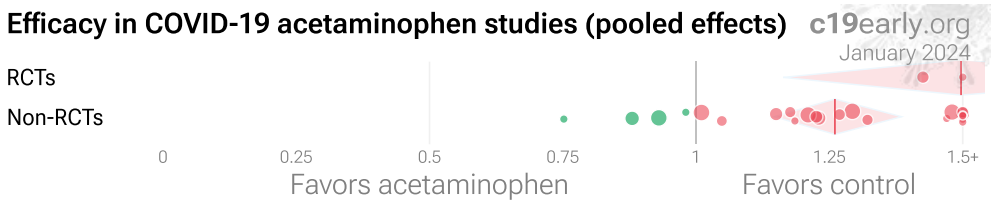


Figure 14. **Results for RCTs and non-RCT studies.**

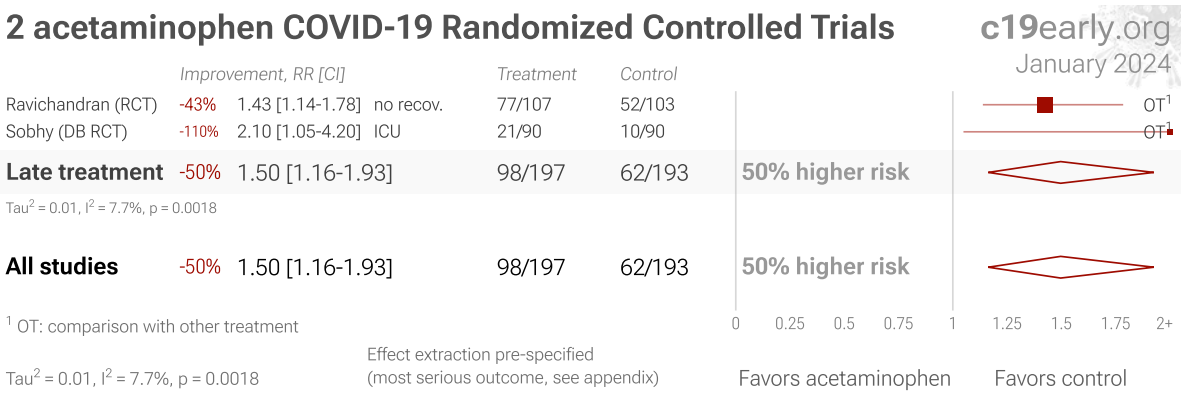


Figure 15. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Exclusions

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

The studies excluded are as below. Figure 16 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Lapi, substantial unadjusted confounding by indication likely.

Rahman, unadjusted results with no group details; significant unadjusted confounding possible.

Rinott, unadjusted differences between groups.

Sharif, unadjusted results with no group details.

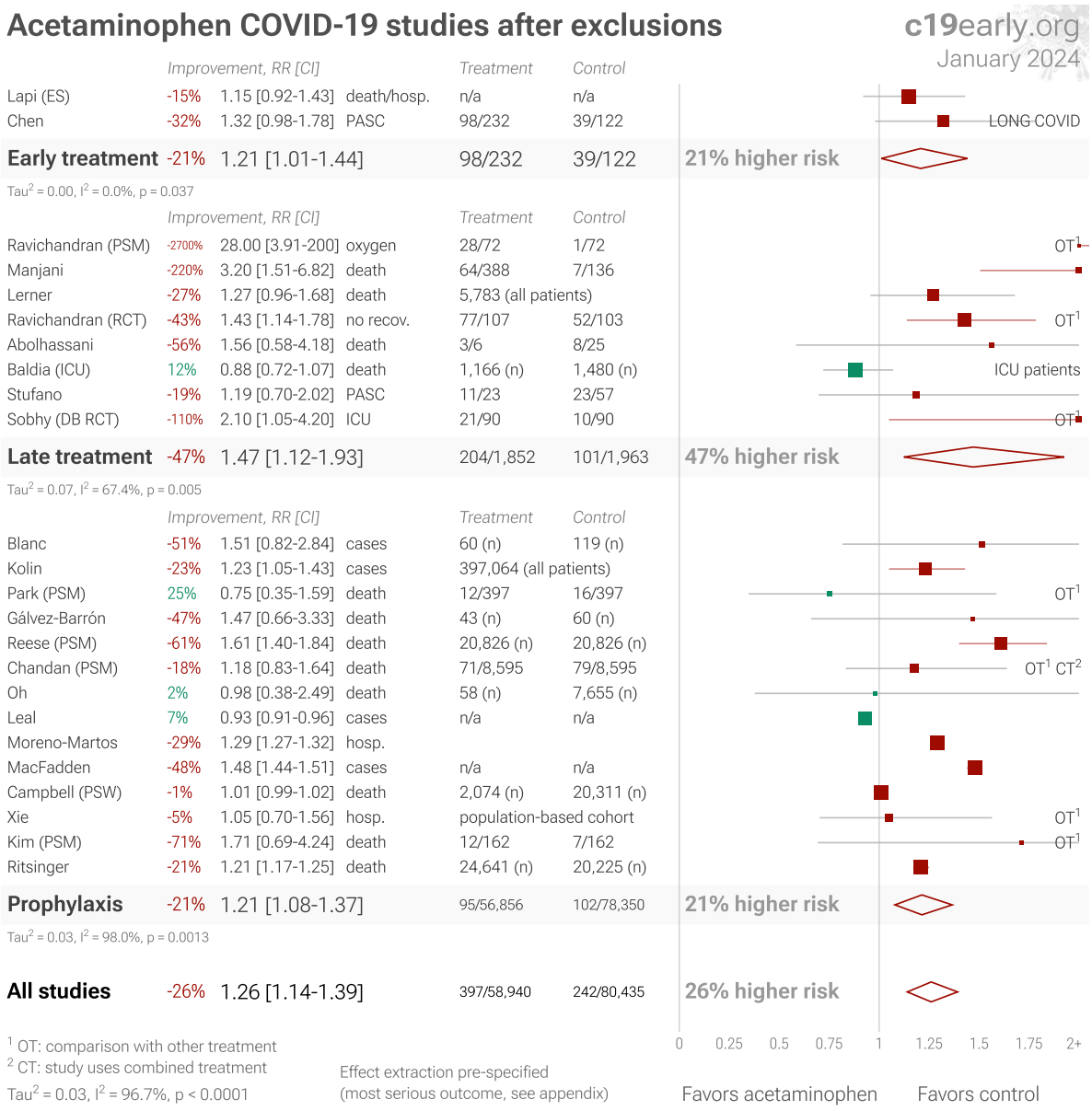


Figure 16. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details 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 4. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 17 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 63 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

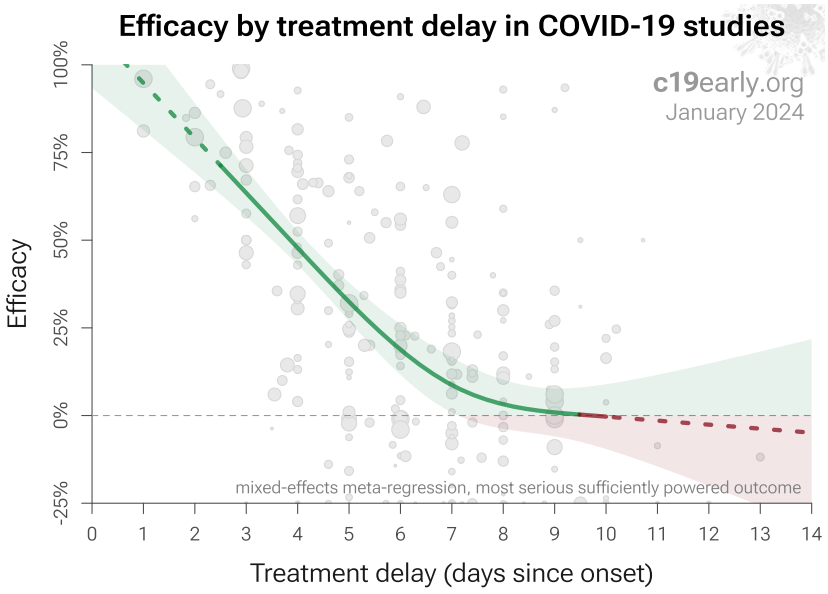


Figure 17. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 63 treatments.

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 18. 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, 42 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 90% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.3 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 3.3 months.

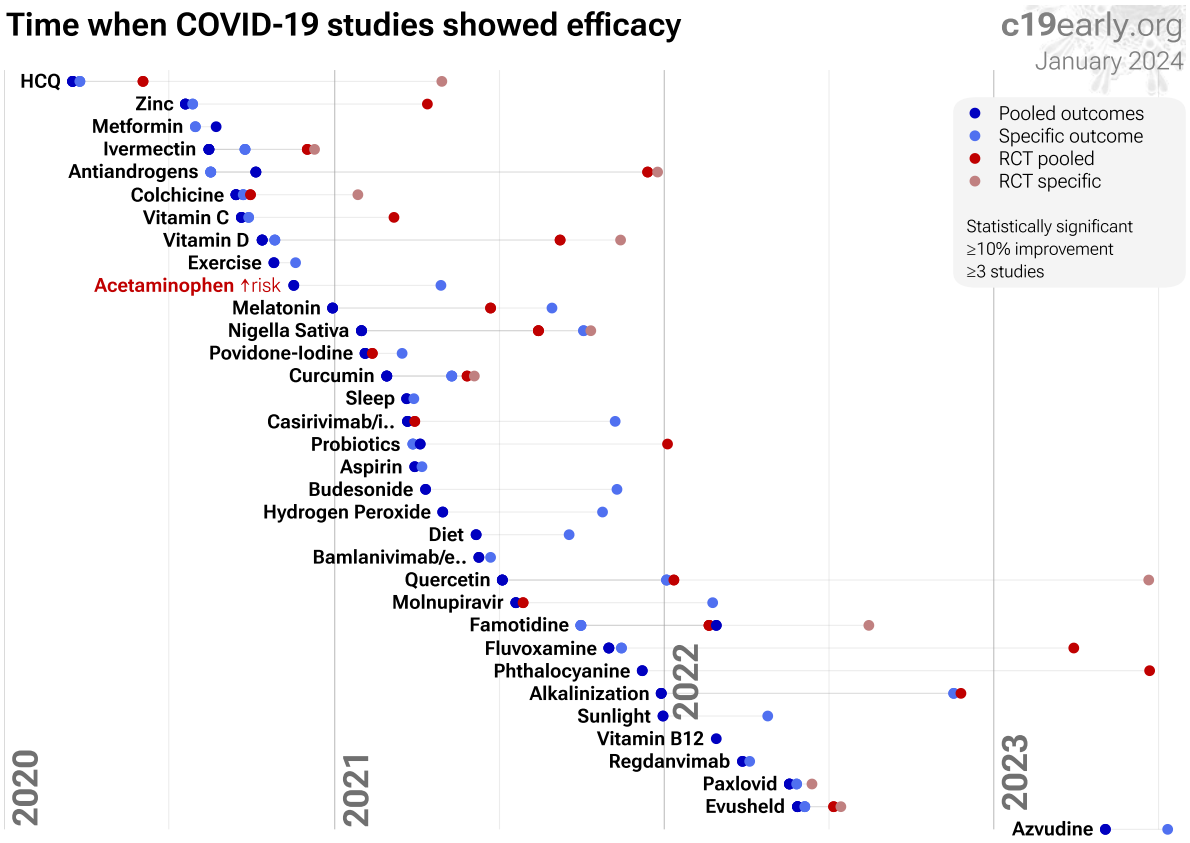


Figure 18. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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 acetaminophen, there is currently not enough data to evaluate publication bias with high confidence.

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 19 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.

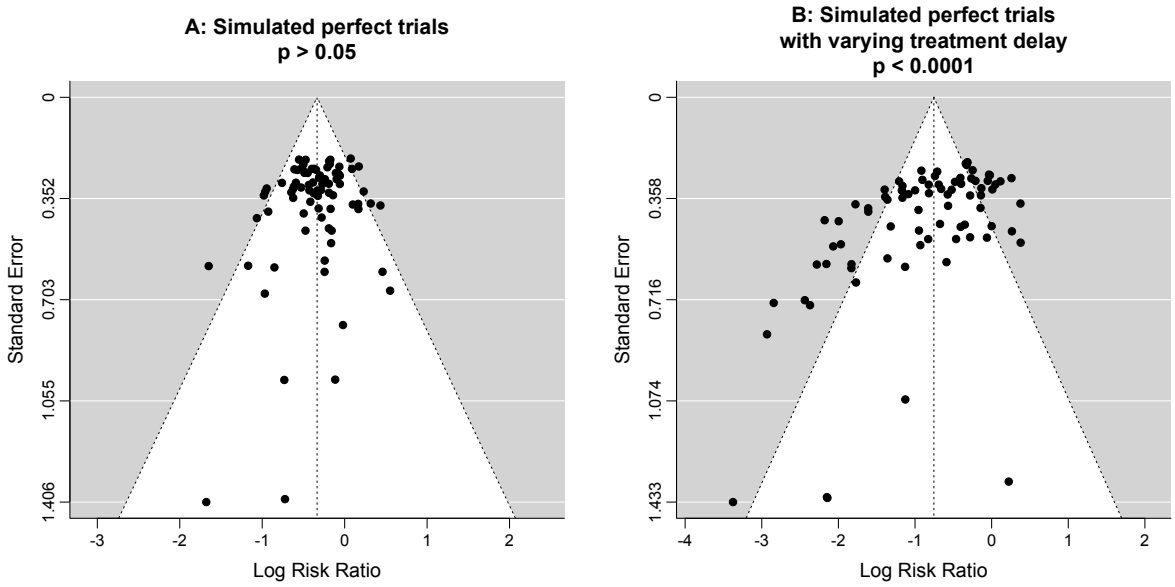


Figure 19. **Example funnel plot analysis for simulated perfect trials.**

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. Acetaminophen for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost.

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, Biancatelli, De Forni, Gasmi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Thairu*. 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. 8 of the 27 studies compare against other treatments, which may reduce the effect seen. 1 of 27 studies combine treatments. The results of acetaminophen alone may differ. None of the RCTs use combined treatment.

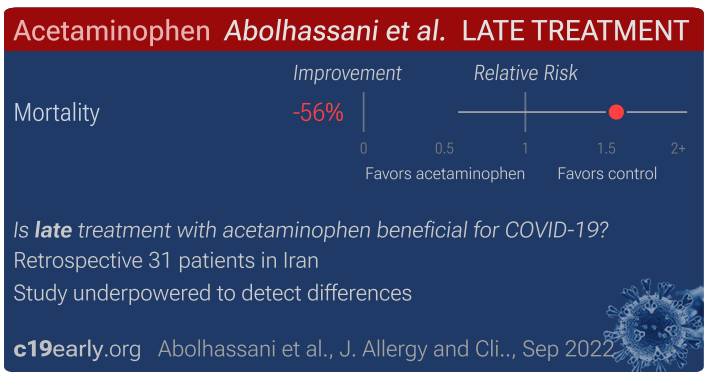
Conclusion

Meta analysis shows 24% [9-40%] higher mortality, and pooled analysis using the most serious outcome reported shows 28% [17-41%] higher risk.

Concerns have been raised over the use of acetaminophen (paracetamol) for COVID-19 *Pandolfi, Sestili*. Studies to date show increased risk. Data is limited, with RCTs to date comparing with indomethacin/ibuprofen.

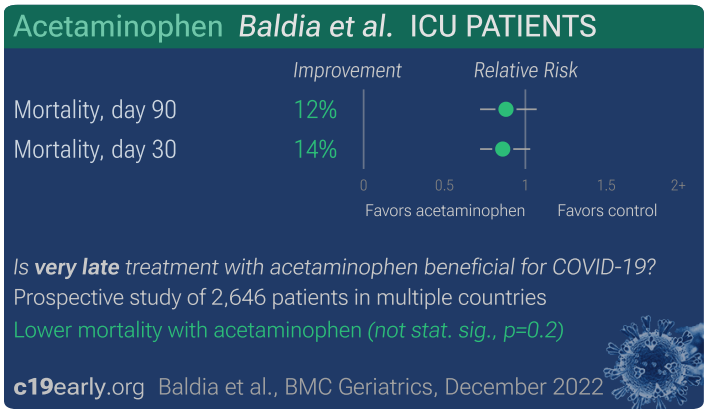
Study Notes

Abolhassani



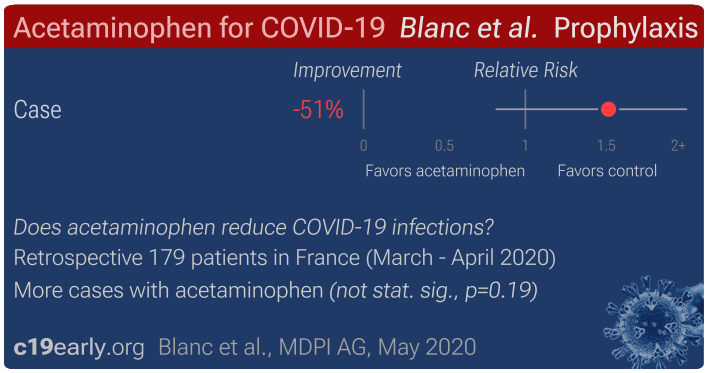
Abolhassani: Retrospective 31 hospitalized patients ≤19 with pre-existing inborn errors of immunity, showing no significant difference in mortality with acetaminophen. Only 6 patients were treated with acetaminophen.

Baldia



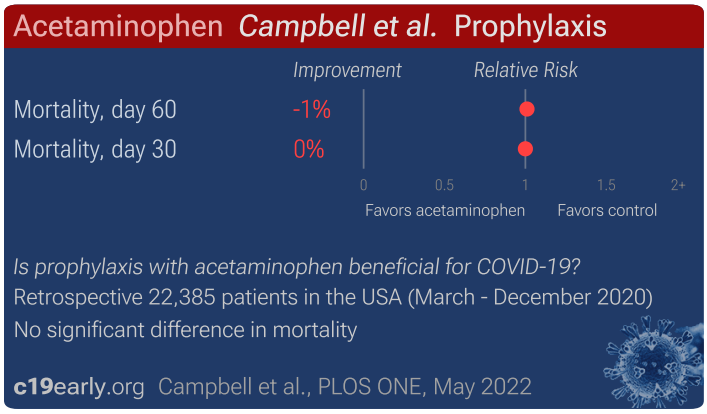
Baldia: Prospective study of 2,646 ICU patients ≥70 years old, showing no significant difference in mortality with acetaminophen use in the 10 days prior to ICU admission.

Blanc



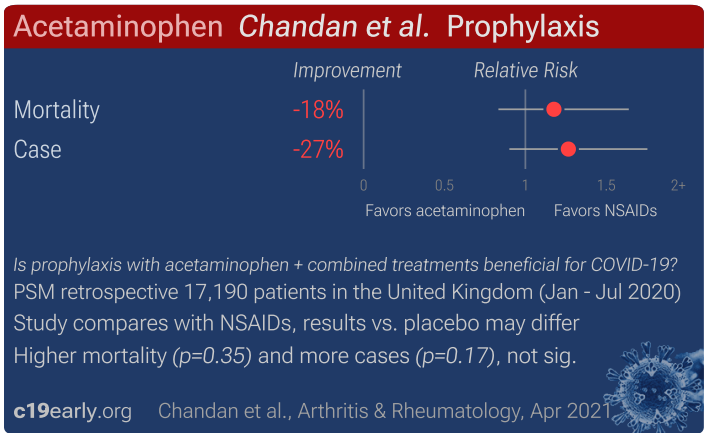
Blanc: Retrospective 179 elderly patients in France, showing higher risk of COVID-19 cases with acetaminophen use, without statistical significance.

Campbell



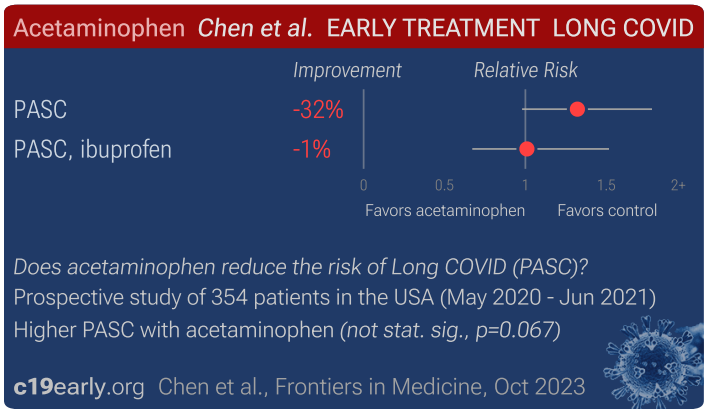
Campbell: Retrospective 28,856 COVID-19 patients in the USA, showing no significant difference in mortality for chronic acetaminophen use vs. sporadic NSAID use. Since acetaminophen is available OTC and authors only tracked prescriptions, many patients classified as sporadic users may have been chronic users.

Chandan



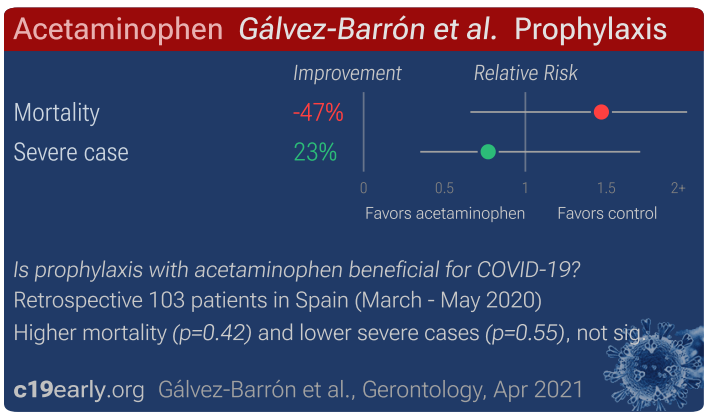
Chandan: Retrospective 12,457 patients prescribed paracetamol with codeine/dihydrocodeine and 13,202 prescribed NSAIDs, showing no significant differences in cases and mortality. Patients prescribed codeine/dihydrocodeine may have different susceptibility to COVID-19.

Chen



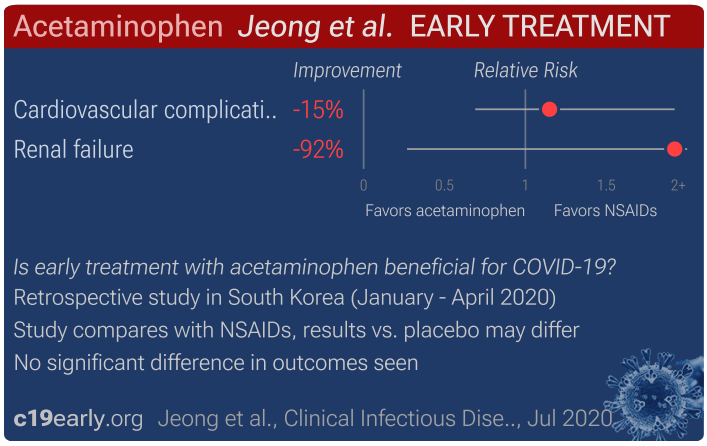
Chen: Prospective study of 494 COVID-19 patients showing higher risk of PASC with acetaminophen use in unadjusted results, without reaching statistical significance (p=0.07). Higher risk is also seen for dexamethasone and remdesivir (statistically significant for dexamethasone), however confounding by indication may be significant for these treatments, with increased use for more severe patients. While details of treatment timing and dose are not available, the result for acetaminophen can be compared with ibuprofen, with comparable indication for use. Notably there is no increased risk with ibuprofen, suggesting higher risk with acetaminophen, consistent with the higher risk seen in meta analysis [c19early.org (B)].

Gálvez-Barrón



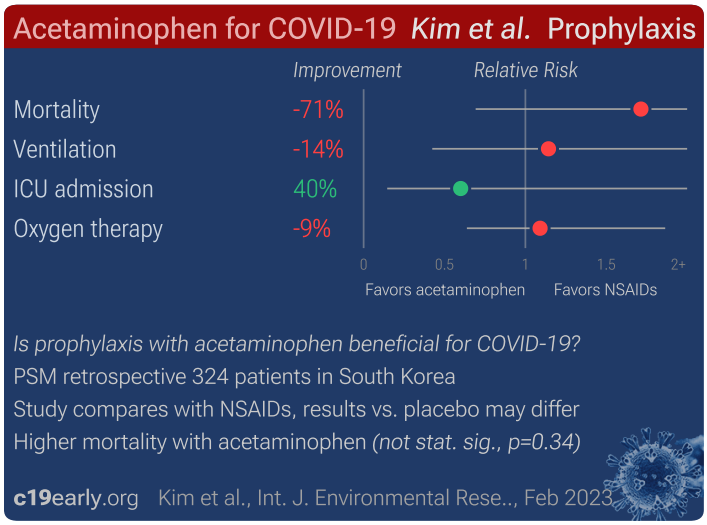
Gálvez-Barrón: Analysis of 103 elderly hospitalized COVID-19 patients in Spain, showing higher mortality with acetaminophen, without statistical significance.

Jeong



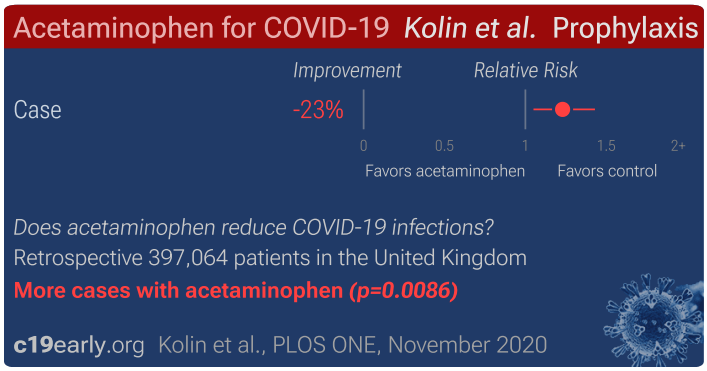
Jeong: Retrospective 1,824 hospitalized COVID-19 patients in South Korea, showing higher progression to combined death, ICU, ventilation, or sepsis (4% versus 0%, group sizes not provided) with paracetamol vs. NSAIDs. Treatment time may vary - exposure was defined as 7 days before and including cohort entry in hospitalized COVID-19 patients.

Kim



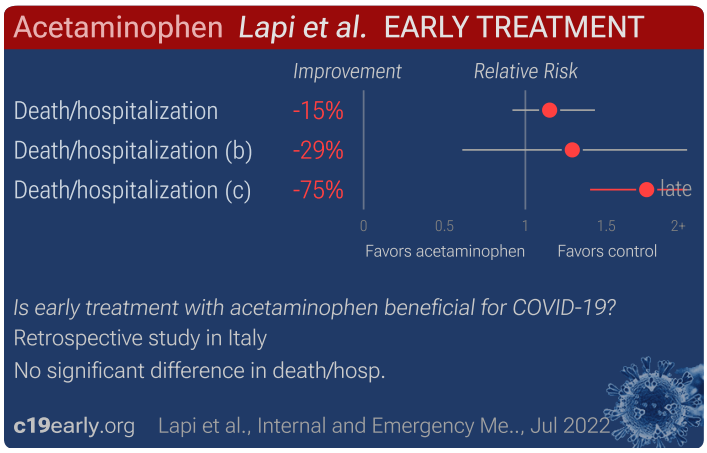
Kim: PSM retrospective in South Korea, showing no significant differences in outcomes with acetaminophen use vs. NSAID use. Adherence and dosage are unknown.

Kolin



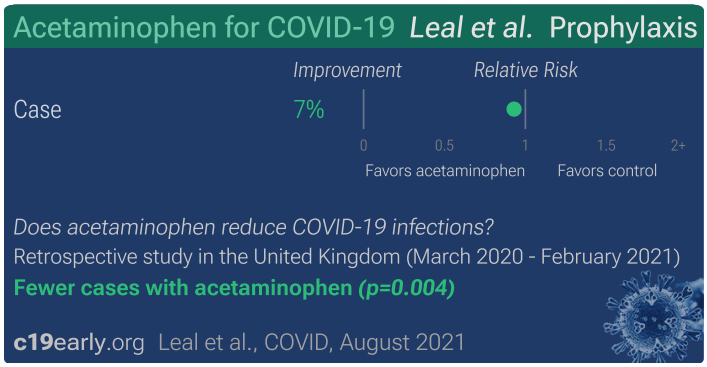
Kolin: 397,064 patient UK Biobank retrospective showing higher risk of COVID-19 with acetaminophen use.

Lapi



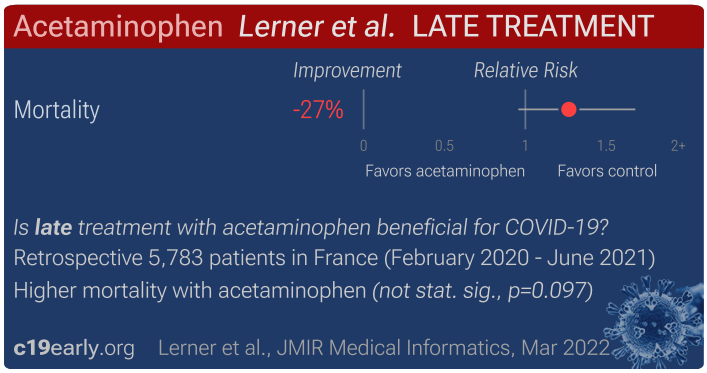
Lapi: Retrospective paracetamol use with a primary care database in Italy, showing no significant difference in hospitalization/death for use 0-3 and 4-7 days from diagnosis, and significantly higher risk for use >7 days from diagnosis. Confounding by indication may have a greater effect on late usage.

Leal



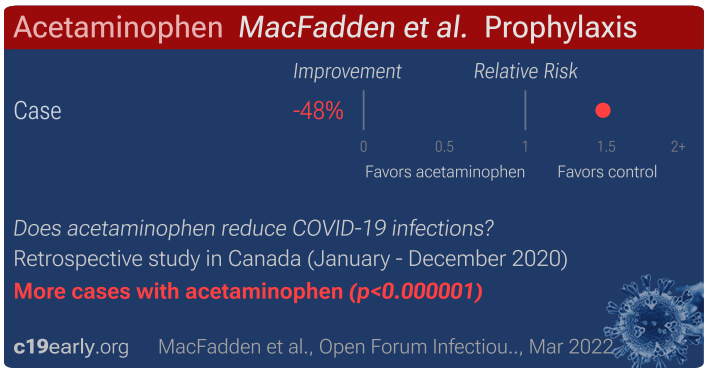
Leal: UK Biobank retrospective showing lower cases with acetaminophen use.

Lerner



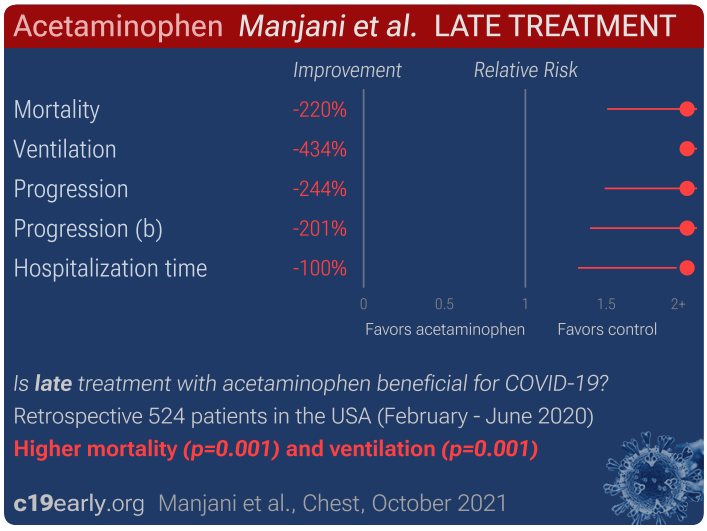
Lerner: Retrospective 5,783 hospitalized patients in France, showing higher mortality with paracetamol use, without statistical significance.

MacFadden



MacFadden: Retrospective 26,121 cases and 2,369,020 controls ≥65yo in Canada, showing higher cases with chronic use of acetaminophen.

Manjani

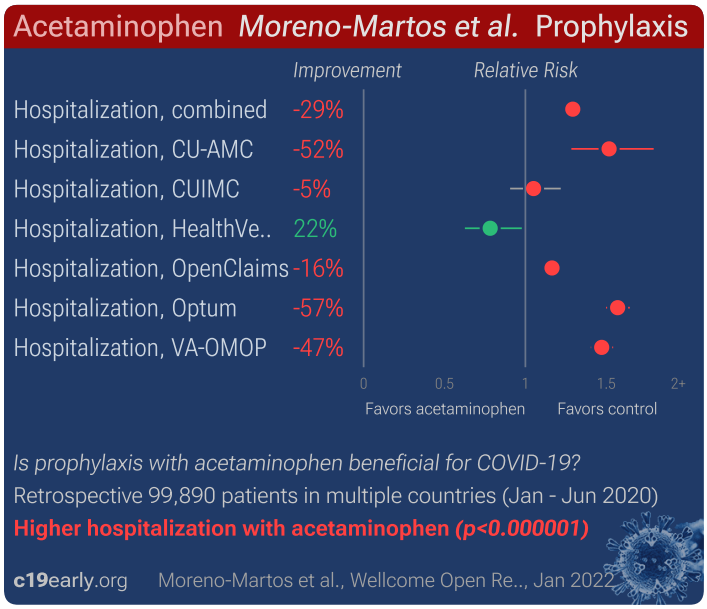


Manjani: Retrospective 524 hospitalized patients in the USA, showing higher mortality and progression with acetaminophen use.

Marcy

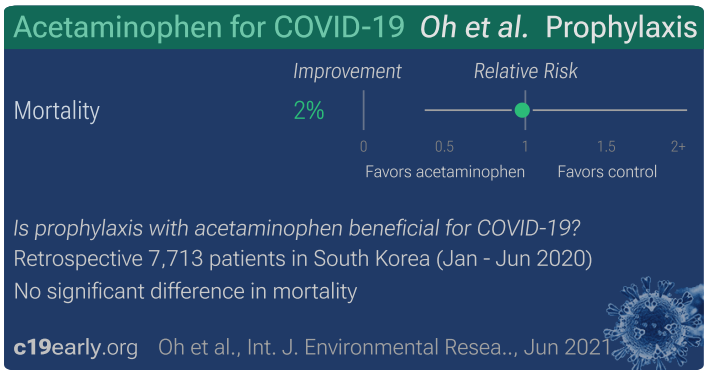
Marcy: Estimated 600 patient acetaminophen early treatment RCT with results expected soon (estimated completion over 5 months ago).

Moreno-Martos



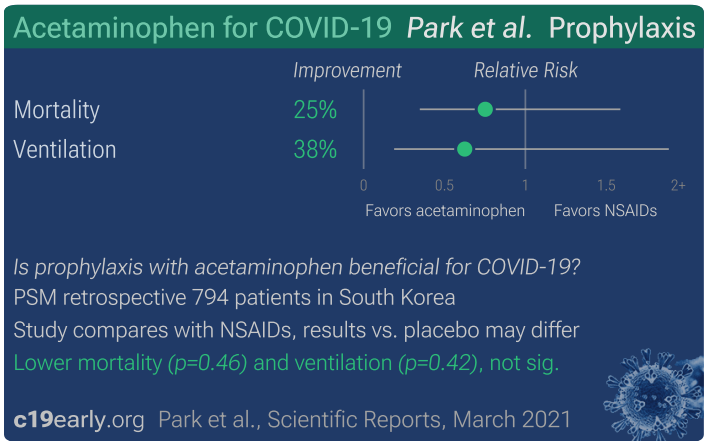
Moreno-Martos: Aanlysis of prescriptions in multiple databases showing higher risk of COVID-19 hospitalization with acetaminophen use for COPD patients. Acetaminophen use was more prevalent in hospitalized patients compared to diagnosed patients (data from tables 1, 5, and S3).

Oh



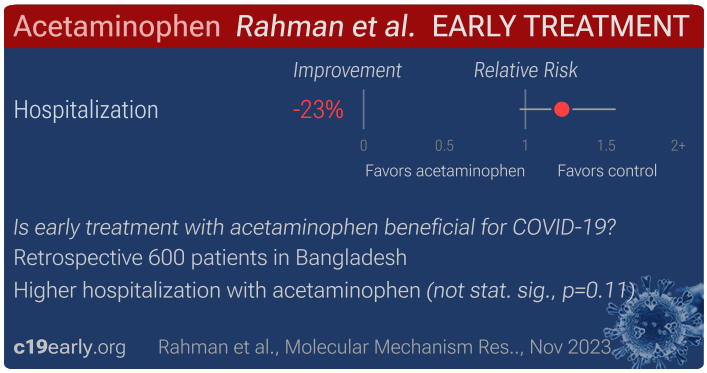
Oh: Retrospective 7,713 COVID-19 patients in Korea, showing no significant difference in mortality with paracetamol use.

Park



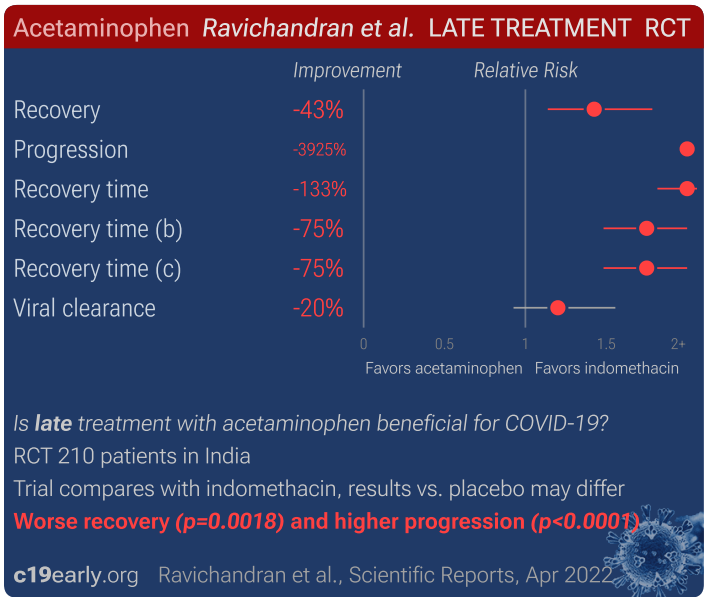
Park: Retrospective 2,365 patients prescribed acetaminophen and 398 prescribed NSAIDs in South Korea, showing no significant differences.

Rahman



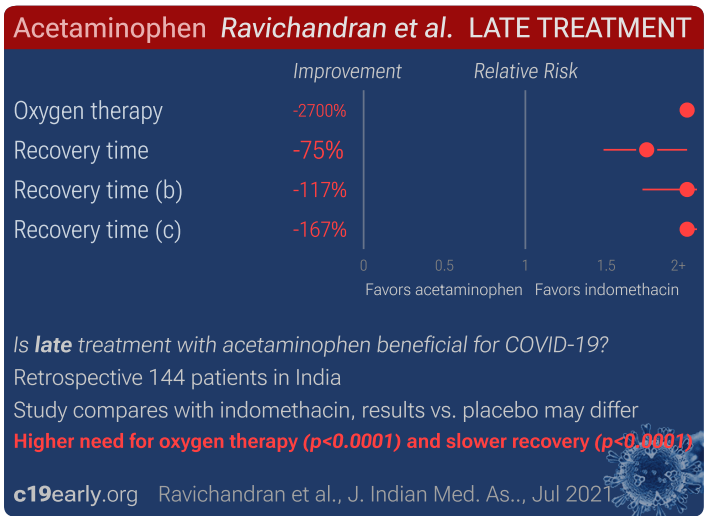
Rahman: Retrospective 416 non-hospitalized and 184 hospitalized COVID-19 patients in Bangladesh, showing higher acetaminophen and lower vitamin C usage for hospitalized patients. Confounding may be significant and baseline details per treatment group are not provided, however fever and symptomatic patients were more common in the non-hospitalized group. Note there is an alignment mismatch in Table 1.

Ravichandran



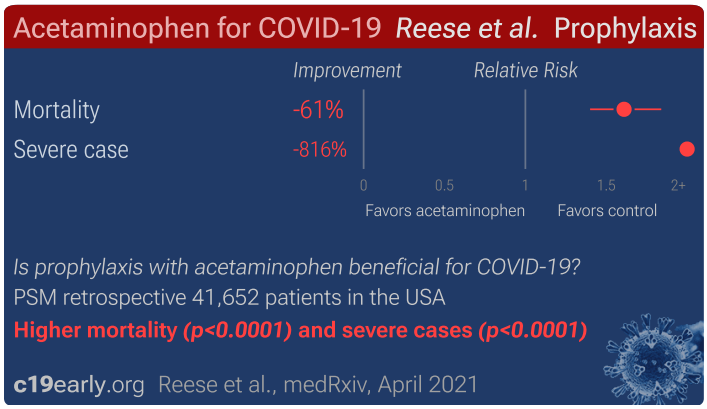
Ravichandran: RCT with 107 paracetamol and 103 indomethacin patients, showing higher progression and worse recovery with paracetamol.

Ravichandran



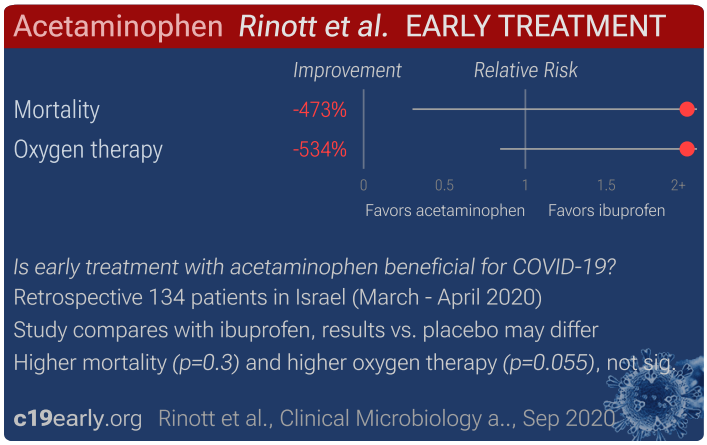
Ravichandran (B): PSM retrospective 72 indomethacin and 72 paracetamol patients in India, showing higher progression and worse recovery with acetaminophen.

Reese



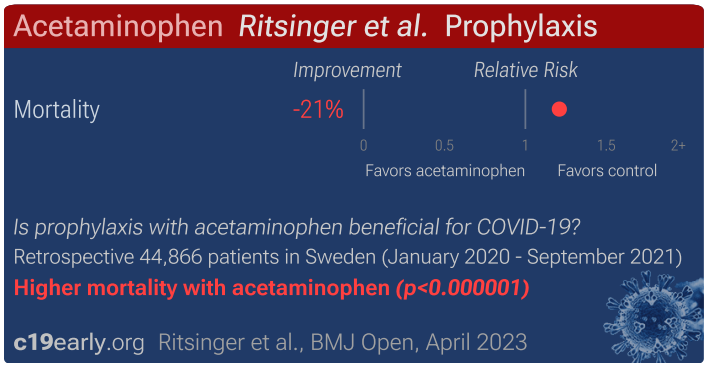
Reese: N3C retrospective 250,533 patients showing significantly higher mortality with acetaminophen use. Note that acetaminophen results were not included in the journal version or v2 of this preprint, which focuses on NSAID analysis.

Rinott



Rinott: Retrospective 89 febrile COVID-19 patients in Israel taking paracetamol and 49 taking ibuprofen, showing higher need for respiratory support with paracetamol. Although not statistically significant, patients in the paracetamol group were older.

Ritsinger

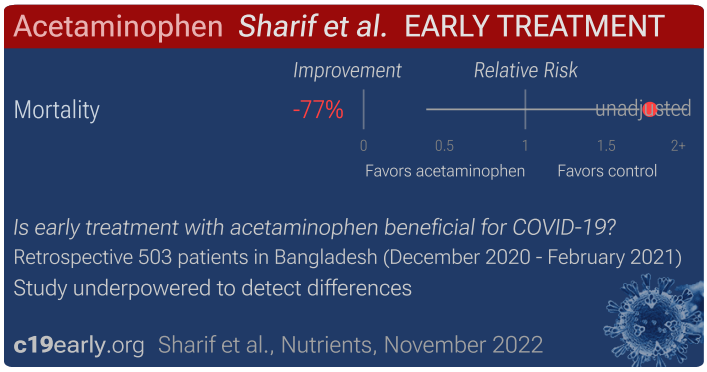


Ritsinger: Retrospective 44,866 hospitalized COVID-19 patients in Sweden, showing higher mortality with vitamin D deficiency and with acetaminophen use.

The study focuses on cardiorenal disease, finding higher risk of mortality with CRD. Authors also show that COVID-19

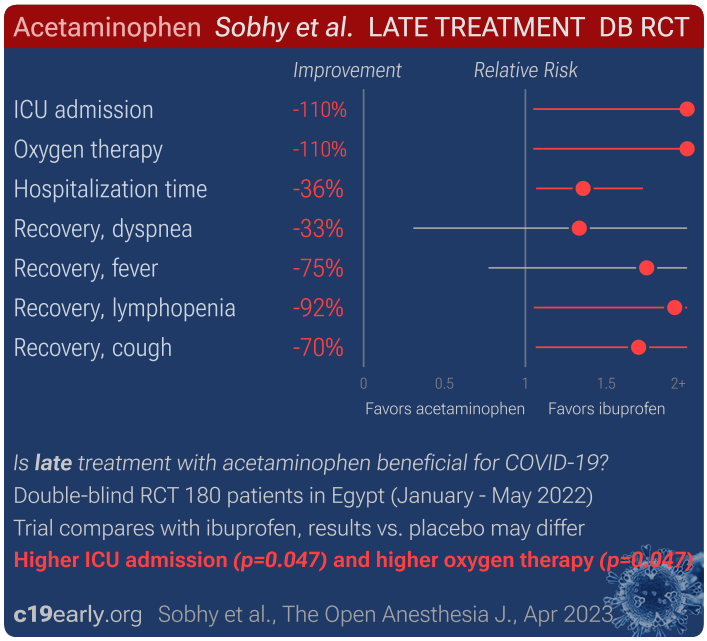
mortality was about 1.5x higher when compared with influenza in the first two pandemic waves, but there was no significant difference in the third wave (HR 1.53 [1.45-1.62] and 1.52 [1.44-1.61] in the first two waves and 1.07 [0.99-1.14] in the third).

Sharif



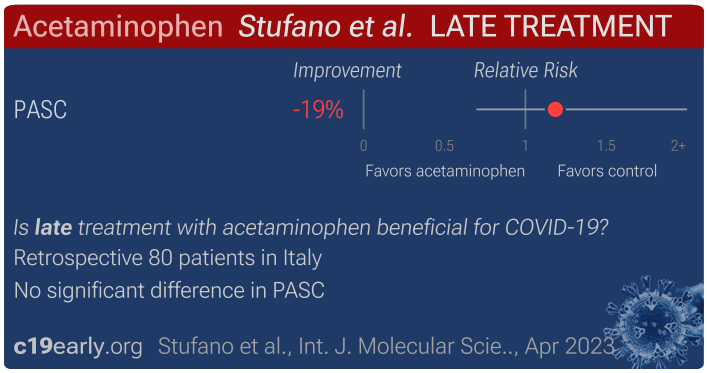
Sharif: Retrospective COVID-19 patients in Bangladesh, showing higher mortality with acetaminophen use in unadjusted results.

Sobhy



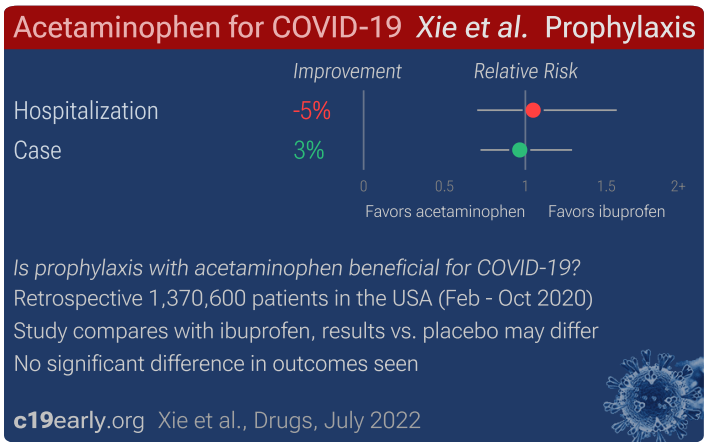
Sobhy: RCT 180 moderate hospitalized COVID-19 patients in Egypt, showing higher ICU admission and longer hospitalization with acetaminophen compared with ibuprofen.

Stufano



Stufano: Retrospective 80 mild COVID-19 patients in Italy, showing no significant difference in long COVID with acetaminophen use during infection.

Xie



Xie: PSM retrospective 1,370,600 osteoarthritis or back pain patients in the US, showing no significant differences in COVID-19 cases and hospitalization for paracetamol vs. ibuprofen.

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 acetaminophen, 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 acetaminophen for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. 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 SpO_2 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 *Deng* 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. Grobid 0.8.0 is used to parse PDF documents.

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 *McLean, Treanor*.

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

Early treatment

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

Chen, 10/16/2023, prospective, USA, peer-reviewed, 17 authors, study period May 2020 - June 2021.	risk of PASC, 32.1% higher, RR 1.32, *p* = 0.07, treatment 98 of 232 (42.2%), control 39 of 122 (32.0%).
	risk of PASC, 0.9% higher, RR 1.01, *p* = 1.00, treatment 16 of 41 (39.0%), control 121 of 313 (38.7%), ibuprofen.
Lapi, 7/30/2022, retrospective, Italy, peer-reviewed, 8 authors, early treatment subset.	risk of death/hospitalization, 15.0% higher, OR 1.15, *p* = 0.22, adjusted per study, early use, RR approximated with OR.
	risk of death/hospitalization, 29.0% higher, OR 1.29, *p* = 0.52, adjusted per study, mid-term use, RR approximated with OR.

Marcy, 8/1/2023, Randomized Controlled Trial, multiple countries, trial NCT04920838 (history) (COVERAGE-A).	Estimated 600 patient RCT with results missing over 5 months.
Rahman, 11/8/2023, retrospective, Bangladesh, peer-reviewed, 5 authors, excluded in exclusion analyses: unadjusted results with no group details; significant unadjusted confounding possible.	risk of hospitalization, 22.6% higher, RR 1.23, $p = 0.11$, treatment 84 of 244 (34.4%), control 100 of 356 (28.1%).
Rinott, 9/30/2020, retrospective, Israel, peer-reviewed, median age 45.0, 5 authors, study period 15 March, 2020 - 15 April, 2020, this trial compares with another treatment - results may be better when compared to placebo, excluded in exclusion analyses: unadjusted differences between groups.	risk of death, 472.9% higher, RR 5.73, $p = 0.30$, treatment 3 of 85 (3.5%), control 0 of 49 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of oxygen therapy, 534.1% higher, RR 6.34, $p = 0.06$, treatment 11 of 85 (12.9%), control 1 of 49 (2.0%).
Sharif, 11/26/2022, retrospective, Bangladesh, peer-reviewed, 14 authors, study period 13 December, 2020 - 4 February, 2021, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 77.0% higher, RR 1.77, $p = 0.74$, treatment 9 of 361 (2.5%), control 2 of 142 (1.4%), unadjusted, ACE.

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.

Abolhassani, 9/13/2022, retrospective, Iran, peer-reviewed, 23 authors.	risk of death, 56.2% higher, RR 1.56, $p = 0.64$, treatment 3 of 6 (50.0%), control 8 of 25 (32.0%).
Baldia, 12/27/2022, prospective, multiple countries, peer-reviewed, median age 75.0, 178 authors, trial NCT04321265 (history).	risk of death, 12.0% lower, OR 0.88, $p = 0.20$, treatment 1,166, control 1,480, adjusted per study, multivariable, day 90, RR approximated with OR.
	risk of death, 14.0% lower, OR 0.86, $p = 0.20$, treatment 1,166, control 1,480, adjusted per study, multivariable, day 30, RR approximated with OR.
Lapi, 7/30/2022, retrospective, Italy, peer-reviewed, 8 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of death/hospitalization, 75.0% higher, OR 1.75, $p < 0.001$, adjusted per study, late use, RR approximated with OR, late treatment result.
Lerner, 3/30/2022, retrospective, France, peer-reviewed, median age 69.2, 7 authors, study period 1 February, 2020 - 15 June, 2021.	risk of death, 26.9% higher, RR 1.27, $p = 0.10$, odds ratio converted to relative risk, weighted and trimmed, day 28, control prevalance approximated with overall prevalence.
Manjani, 10/31/2021, retrospective, USA, peer-reviewed, 6 authors, study period February 2020 - June 2020.	risk of death, 220.5% higher, RR 3.20, $p = 0.001$, treatment 64 of 388 (16.5%), control 7 of 136 (5.1%).
	risk of mechanical ventilation, 434.5% higher, RR 5.34, $p < 0.001$, treatment 388, control 136.

	risk of progression, 244.0% higher, OR 3.44, $p < 0.005$, treatment 132, control 136, triaged to higher level of care, high exposure, RR approximated with OR.
	risk of progression, 201.0% higher, OR 3.01, $p < 0.007$, treatment 256, control 136, triaged to higher level of care, moderate exposure, RR approximated with OR.
	hospitalization time, 100% higher, relative time 2.00, $p < 0.001$, treatment 388, control 136.
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, 42.5% higher, RR 1.43, $p = 0.002$**, treatment 77 of 107 (72.0%), control 52 of 103 (50.5%), day 14.
	risk of progression, 3925.2% higher, RR 40.25, $p < 0.001$, treatment 20 of 107 (18.7%), control 0 of 103 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), SpO2 ≤93.
	recovery time, 133.3% higher, relative time 2.33, $p < 0.001$, treatment median 7.0 IQR 2.75 n=107, control median 3.0 IQR 1.0 n=103, fever.
	recovery time, 75.0% higher, relative time 1.75, $p < 0.001$, treatment median 7.0 IQR 2.0 n=107, control median 4.0 IQR 2.0 n=103, myalgia.
	recovery time, 75.0% higher, relative time 1.75, $p < 0.001$, treatment median 7.0 IQR 3.0 n=107, control median 4.0 IQR 1.0 n=103, cough.
	risk of no viral clearance, 20.1% higher, RR 1.20, $p = 0.19$, treatment 43 of 60 (71.7%), control 37 of 62 (59.7%), 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, 2700.0% higher, RR 28.00, $p < 0.001$**, treatment 28 of 72 (38.9%), control 1 of 72 (1.4%), propensity score matching.
	recovery time, 75.0% higher, relative time 1.75, $p < 0.001$, treatment median 7.0 IQR 1.0 n=72, control median 4.0 IQR 1.0 n=72, fever.
	recovery time, 116.7% higher, relative time 2.17, $p < 0.001$, treatment median 6.5 IQR 3.25 n=72, control median 3.0 IQR 2.0 n=72, myalgia.
	recovery time, 166.7% higher, relative time 2.67, $p < 0.001$, treatment median 8.0 IQR 2.0 n=72, control median 3.0 IQR 2.0 n=72, cough.
Sobhy, 4/19/2023, Double Blind Randomized Controlled Trial, Egypt, peer-reviewed, 6 authors, study period January 2022 - May 2022, this trial compares with another treatment - results may be better when compared to placebo, trial PACTR202202880140319.	**risk of ICU admission, 110.0% higher, RR 2.10, $p = 0.047$**, treatment 21 of 90 (23.3%), control 10 of 90 (11.1%).
	risk of oxygen therapy, 110.0% higher, RR 2.10, $p = 0.047$, treatment 21 of 90 (23.3%), control 10 of 90 (11.1%).

	hospitalization time, 35.7% higher, relative time 1.36, $p = 0.01$, treatment 90, control 90.
	risk of no recovery, 33.3% higher, RR 1.33, $p = 1.00$, treatment 4 of 90 (4.4%), control 3 of 90 (3.3%), day 4, dyspnea.
	risk of no recovery, 75.0% higher, RR 1.75, $p = 0.25$, treatment 14 of 90 (15.6%), control 8 of 90 (8.9%), day 4, fever.
	risk of no recovery, 92.3% higher, RR 1.92, $p = 0.04$, treatment 25 of 90 (27.8%), control 13 of 90 (14.4%), day 4, lymphopenia.
	risk of no recovery, 70.0% higher, RR 1.70, $p = 0.03$, treatment 34 of 90 (37.8%), control 20 of 90 (22.2%), day 4, cough.
Stufano, 4/18/2023, retrospective, Italy, peer-reviewed, 7 authors.	risk of PASC, 18.5% higher, RR 1.19, $p = 0.62$, treatment 11 of 23 (47.8%), control 23 of 57 (40.4%).

Prophylaxis

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

Blanc, 5/2/2020, retrospective, France, preprint, mean age 84.1, 22 authors, study period 2 March, 2020 - 8 April, 2020.	risk of case, 51.4% higher, OR 1.51, $p = 0.19$, treatment 60, control 119, RR approximated with OR.
Campbell, 5/5/2022, retrospective, USA, peer-reviewed, 4 authors, study period 2 March, 2020 - 14 December, 2020.	risk of death, 1.0% higher, OR 1.01, $p = 0.43$, treatment 2,074, control 20,311, adjusted per study, propensity score weighting, multivariable, day 60, RR approximated with OR.
	risk of death, no change, OR 1.00, $p = 0.86$, treatment 2,074, control 20,311, adjusted per study, propensity score weighting, multivariable, day 30, RR approximated with OR.
Chandan, 4/29/2021, retrospective, United Kingdom, peer-reviewed, mean age 65.4, 24 authors, study period 30 January, 2020 - 31 July, 2020, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with codeine or dihydrocodeine) - results of individual treatments may vary.	risk of death, 17.6% higher, HR 1.18, $p = 0.35$, treatment 71 of 8,595 (0.8%), control 79 of 8,595 (0.9%), adjusted per study, inverted to make HR<1 favor treatment, propensity score matching, multivariable.
	risk of case, 26.6% higher, HR 1.27, $p = 0.17$, treatment 8,595, control 8,595, adjusted per study, inverted to make HR<1 favor treatment, propensity score matching, multivariable.
Gálvez-Barrón, 4/14/2021, retrospective, Spain, peer-reviewed, mean age 86.8, 13 authors, study period 12 March, 2020 - 2 May, 2020.	risk of death, 47.0% higher, OR 1.47, $p = 0.42$, treatment 43, control 60, RR approximated with OR.
	risk of severe case, 23.0% lower, OR 0.77, $p = 0.55$, treatment 43, control 60, RR approximated with OR.
Kim, 2/21/2023, retrospective, South Korea, peer-reviewed, mean age 55.8, 4 authors, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 71.4% higher, RR 1.71, $p = 0.34$, treatment 12 of 162 (7.4%), control 7 of 162 (4.3%), propensity score matching.

	risk of mechanical ventilation, 14.3% higher, RR 1.14, *p* = 1.00, treatment 8 of 162 (4.9%), control 7 of 162 (4.3%), propensity score matching.
	risk of ICU admission, 40.0% lower, RR 0.60, *p* = 0.72, treatment 3 of 162 (1.9%), control 5 of 162 (3.1%), NNT 81, propensity score matching.
	risk of oxygen therapy, 9.1% higher, RR 1.09, *p* = 0.87, treatment 24 of 162 (14.8%), control 22 of 162 (13.6%), propensity score matching.
Kolin, 11/17/2020, retrospective, United Kingdom, peer-reviewed, 4 authors.	risk of case, 23.0% higher, RR 1.23, *p* = 0.009.
Leal, 8/16/2021, retrospective, United Kingdom, peer-reviewed, 5 authors, study period 16 March, 2020 - 1 February, 2021.	risk of case, 7.0% lower, OR 0.93, *p* = 0.004, RR approximated with OR.
MacFadden, 3/29/2022, retrospective, Canada, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.	risk of case, 48.0% higher, OR 1.48, *p* < 0.001, RR approximated with OR.
Moreno-Martos, 1/24/2022, retrospective, multiple countries, peer-reviewed, 24 authors, study period January 2020 - June 2020.	risk of hospitalization, 29.3% higher, RR 1.29, *p* < 0.001, treatment 10,367, control 89,523, meta analysis of all databases combined.
	risk of hospitalization, 51.7% higher, RR 1.52, *p* < 0.001, treatment 103 of 178 (57.9%), control 196 of 514 (38.1%), US CU-AMC.
	risk of hospitalization, 5.1% higher, RR 1.05, *p* = 0.57, treatment 87 of 144 (60.4%), control 360 of 626 (57.5%), US CUIMC.
	risk of hospitalization, 21.8% lower, RR 0.78, *p* = 0.02, treatment 64 of 319 (20.1%), control 1,585 of 6,181 (25.6%), NNT 18, US HealthVerity.
	risk of hospitalization, 16.5% higher, RR 1.16, *p* < 0.001, treatment 2,597 of 4,983 (52.1%), control 28,320 of 63,279 (44.8%), US IQVIA OpenClaims.
	risk of hospitalization, 57.0% higher, RR 1.57, *p* < 0.001, treatment 1,090 of 1,868 (58.4%), control 3,414 of 9,188 (37.2%), US Optum EHR.
	risk of hospitalization, 47.2% higher, RR 1.47, *p* < 0.001, treatment 1,397 of 2,875 (48.6%), control 3,214 of 9,735 (33.0%), US VA-OMOP.
Oh, 6/24/2021, retrospective, South Korea, peer-reviewed, 5 authors, study period 1 January, 2020 - 4 June, 2020.	risk of death, 1.9% lower, RR 0.98, *p* = 0.97, treatment 58, control 7,655, adjusted per study, odds ratio converted to relative risk, multivariable, control prevalance approximated with overall prevalence.

Park, 3/3/2021, retrospective, South Korea, peer-reviewed, 5 authors, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 24.8% lower, HR 0.75, $p = 0.46$, treatment 12 of 397 (3.0%), control 16 of 397 (4.0%), NNT 99, inverted to make HR<1 favor treatment, propensity score matching.
	risk of mechanical ventilation, 37.5% lower, HR 0.62, $p = 0.42$, treatment 5 of 397 (1.3%), control 8 of 397 (2.0%), NNT 132, inverted to make HR<1 favor treatment, propensity score matching.
Reese, 4/20/2021, retrospective, USA, preprint, 23 authors.	risk of death, 61.0% higher, HR 1.61, $p < 0.001$, treatment 20,826, control 20,826, propensity score matching, Cox proportional hazards, Table S58.
	risk of severe case, 816.0% higher, OR 9.16, $p < 0.001$, treatment 20,826, control 20,826, propensity score matching, Table S50, RR approximated with OR.
Ritsinger, 4/28/2023, retrospective, Sweden, peer-reviewed, mean age 79.8, 8 authors, study period 1 January, 2020 - 9 September, 2021.	risk of death, 21.0% higher, HR 1.21, $p < 0.001$, treatment 24,641, control 20,225.
Xie, 7/13/2022, retrospective, USA, peer-reviewed, 9 authors, study period 1 February, 2020 - 31 October, 2020, this trial compares with another treatment - results may be better when compared to placebo.	risk of hospitalization, 4.8% higher, HR 1.05, $p = 0.83$, inverted to make HR<1 favor treatment, Open Claims, PharMetrics Plus, both periods combined.
	risk of case, 3.5% lower, HR 0.97, $p = 0.82$, inverted to make HR<1 favor treatment, Open Claims, PharMetrics Plus, both periods combined.

Supplementary Data

Supplementary Data

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