Montelukast for COVID-19: real-time meta analysis of 8 studies

@CovidAnalysis, June 2024, Version 8
https://c19early.org/mkmeta.html

Abstract

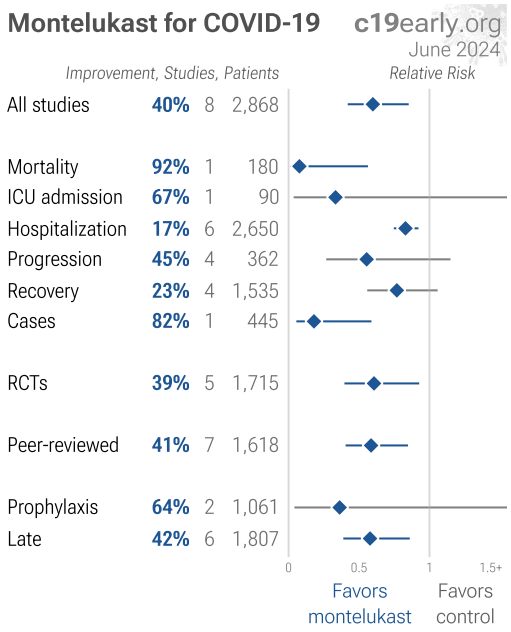
Statistically significant lower risk is seen for mortality, hospitalization, and cases. 4 studies from 4 independent teams in 4 countries show significant improvements.

Meta analysis using the most serious outcome reported shows 40% [15-58%] lower risk. Results are similar for Randomized Controlled Trials and peer-reviewed studies.

Currently there is limited data, with only 33 control events for the most serious outcome in trials to date.

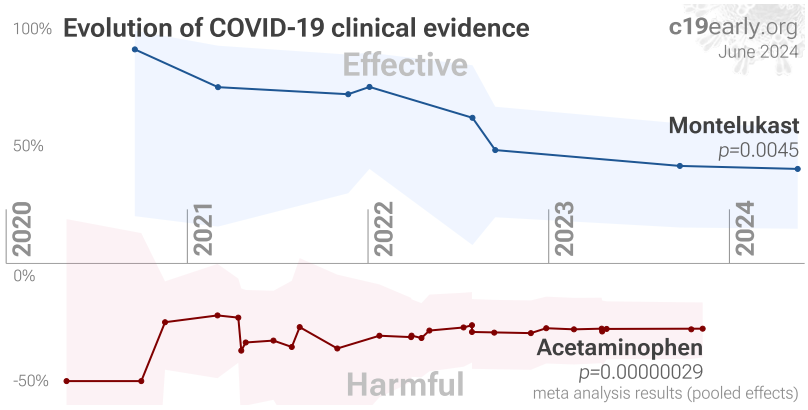
2 RCTs with 664 patients have not reported results (up to 2 years late) [1,2].

Montelukast has a boxed warning for neuropsychiatric side effects [3].



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.



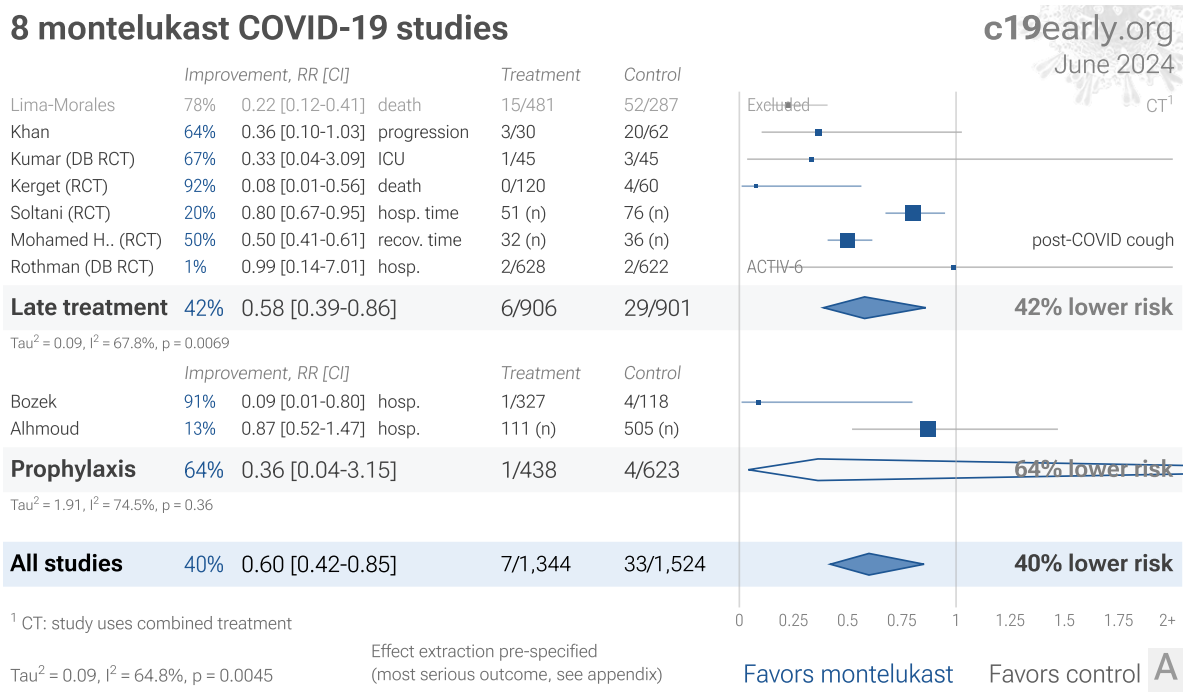
MONTELUKAST FOR COVID-19 — HIGHLIGHTS

Montelukast reduces risk with very high confidence for hospitalization and in pooled analysis, and low confidence for mortality, progression, recovery, and cases.

28th treatment shown effective with ≥3 clinical studies in November 2021, now with p = 0.0045 from 8 studies.

Outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 72 treatments.



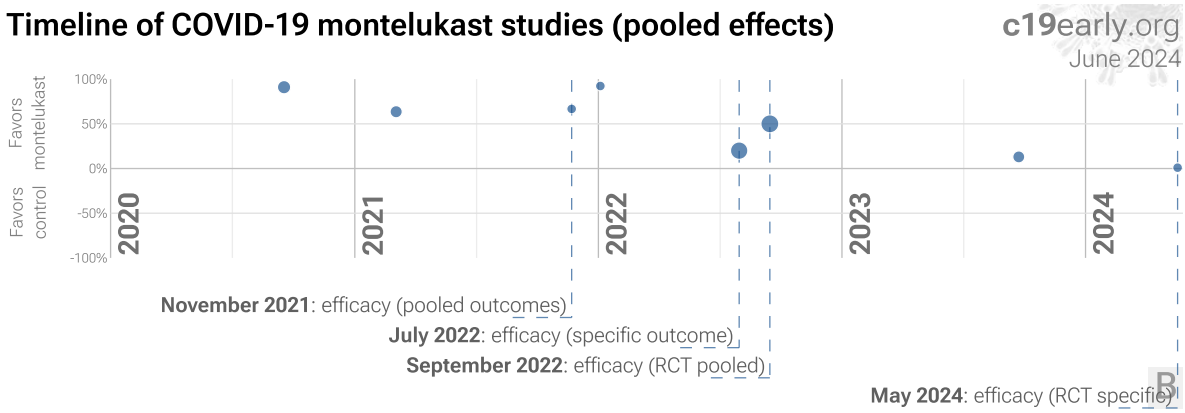


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in montelukast studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, pooled outcomes in RCTs, and one or more specific outcome in RCTs. Efficacy based on RCTs only was delayed by 9.8 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 8.2 months, compared to using pooled outcomes. Efficacy based on specific outcomes in RCTs was delayed by 20.1 months, compared to using pooled outcomes in RCTs.

Introduction

Immediate treatment recommended. SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury[4-9] and cognitive deficits[6], cardiovascular complications[10], organ failure, and death. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors[A,11-15], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19

risk[16], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Analysis. We analyze all significant controlled studies of montelukast 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, and Randomized Controlled Trials (RCTs).

Treatment timing. Figure 2 shows stages of possible treatment for COVID-19. **Prophylaxis** refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. **Early Treatment** refers to treatment immediately or soon after symptoms appear, while **Late Treatment** refers to more delayed treatment.

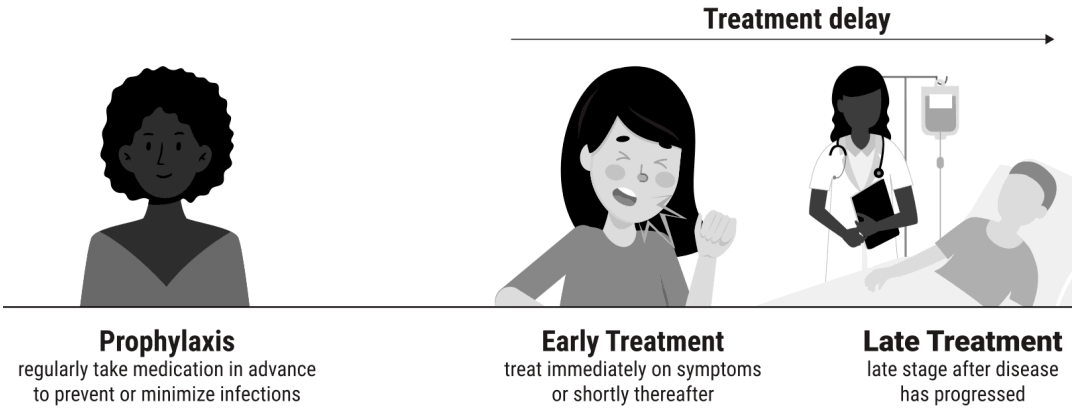


Figure 2. Treatment stages.

Preclinical Research

An *In Silico* study supports the efficacy of montelukast[17].

2 *In Vitro* studies support the efficacy of montelukast[17,18].

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 stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ICU admission, hospitalization, progression, recovery, cases, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**40%** [15-58%] **	8	2,868	87
Peer-reviewed studies	**41%** [15-60%] **	7	1,618	55
Randomized Controlled Trials	**39%** [7-60%] *	5	1,715	59
Hospitalization	**17%** [8-25%] ***	6	2,650	70
Recovery	**23%** [-6-44%]	4	1,535	55
RCT hospitalization	**18%** [7-27%] **	3	1,497	42

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$.

	Late treatment	*Prophylaxis*
All studies	**42%** [14-61%] **	**64%** [-215-96%]
Peer-reviewed studies	**44%** [15-63%] **	**64%** [-215-96%]
Randomized Controlled Trials	**39%** [7-60%] *	
Hospitalization	**17%** [7-25%] ***	**64%** [-215-96%]
Recovery	**23%** [-6-44%]	
RCT hospitalization	**18%** [7-27%] **	

Table 2. **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. * $p<0.05$ ** $p<0.01$ *** $p<0.001$.

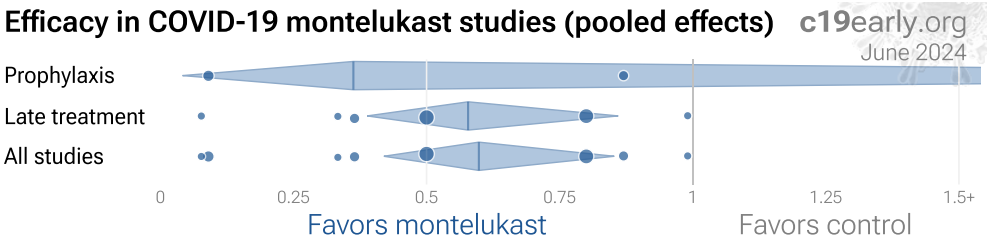


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

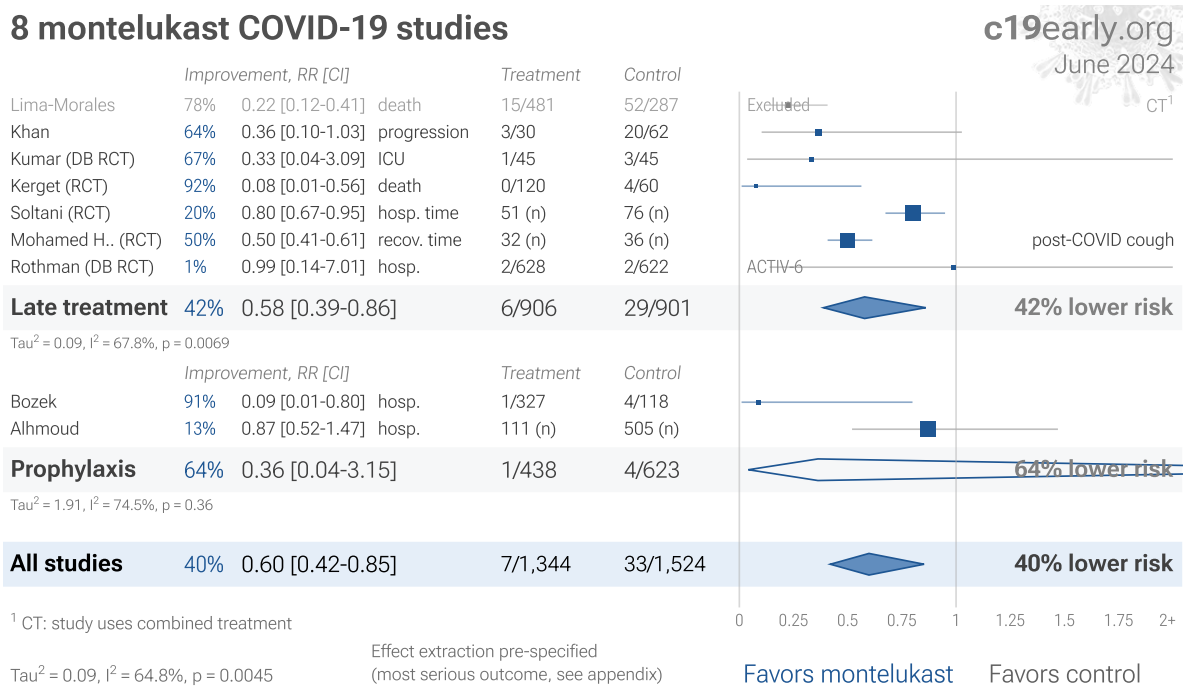


Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

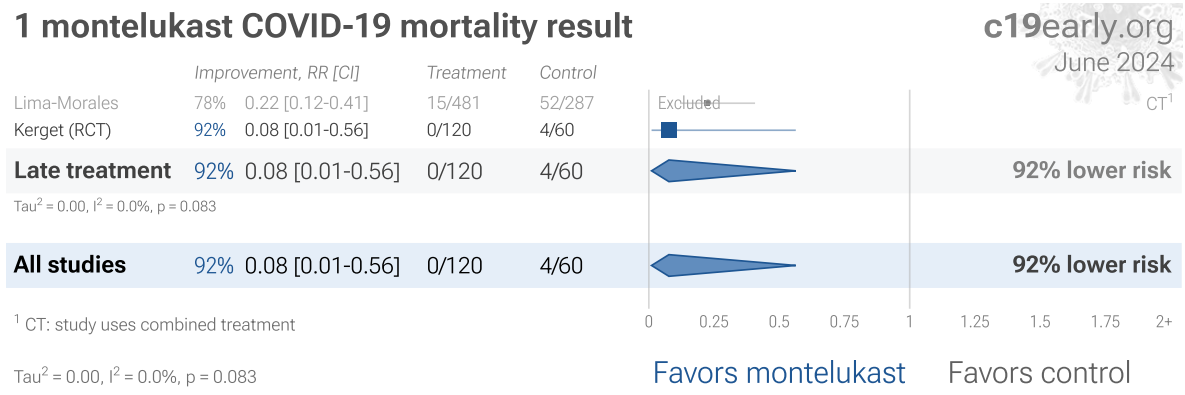


Figure 5. **Random effects meta-analysis for mortality results.**

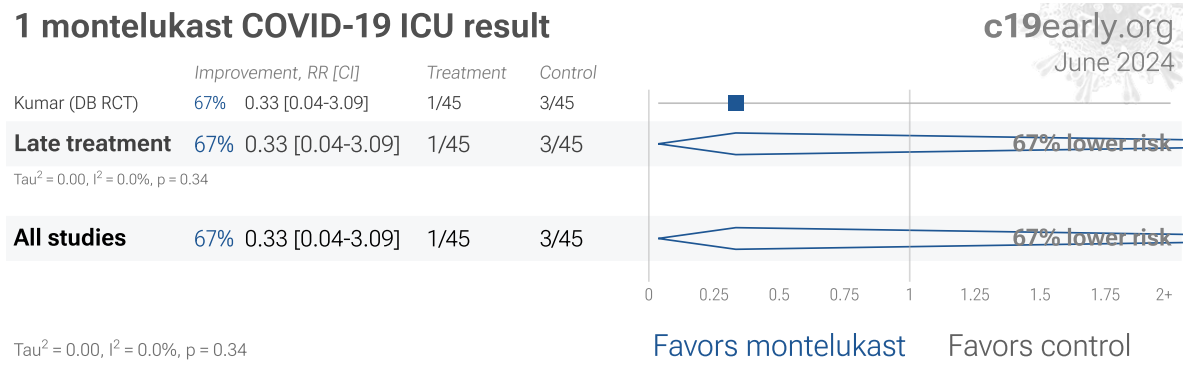


Figure 6. **Random effects meta-analysis for ICU admission.**

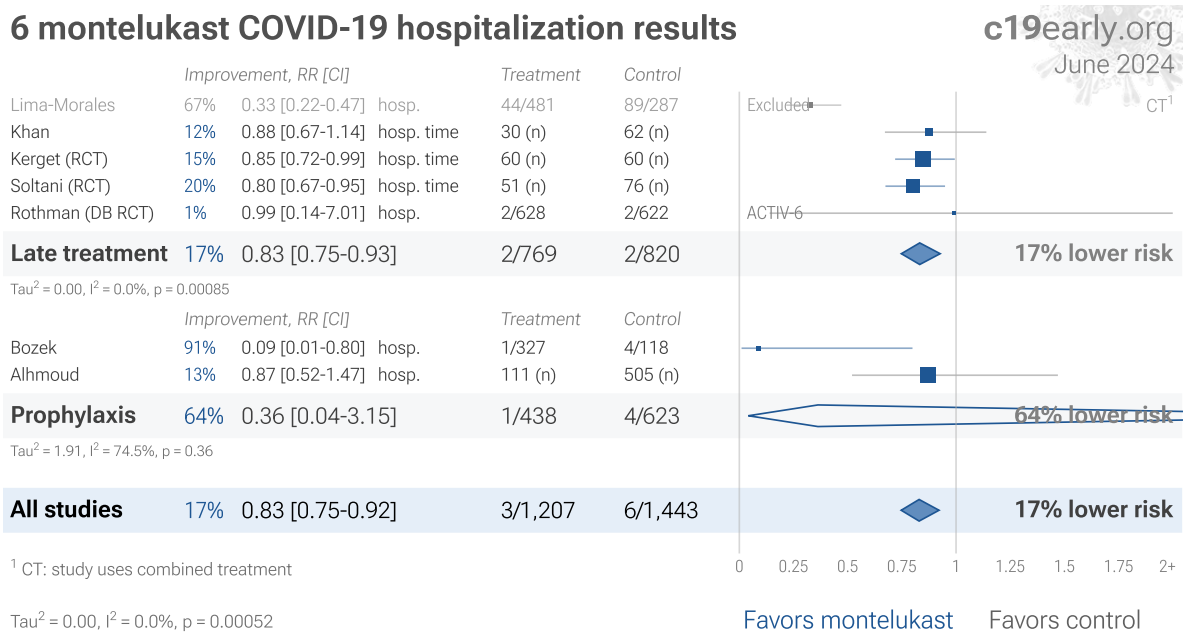


Figure 7. Random effects meta-analysis for hospitalization.

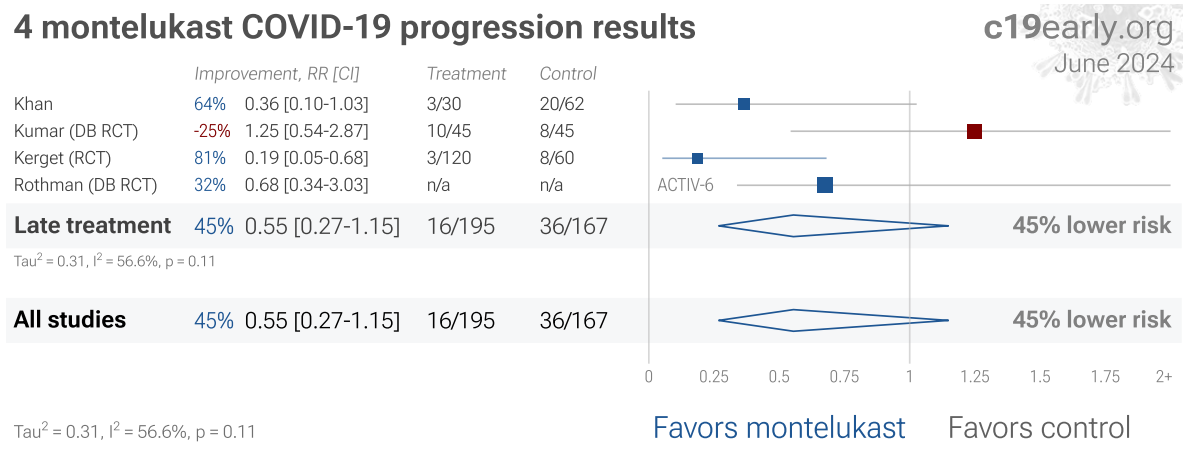


Figure 8. Random effects meta-analysis for progression.

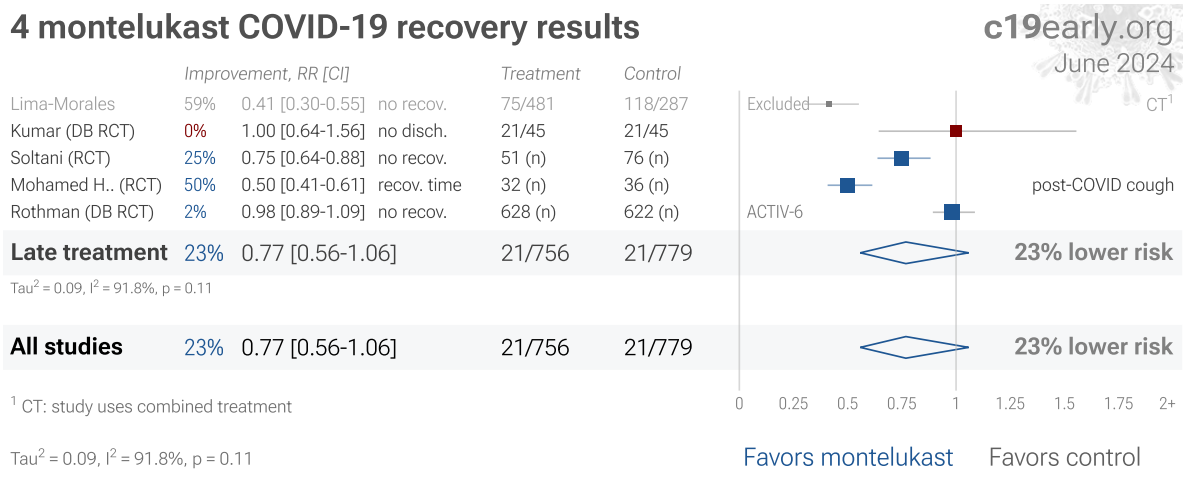


Figure 9. Random effects meta-analysis for recovery.

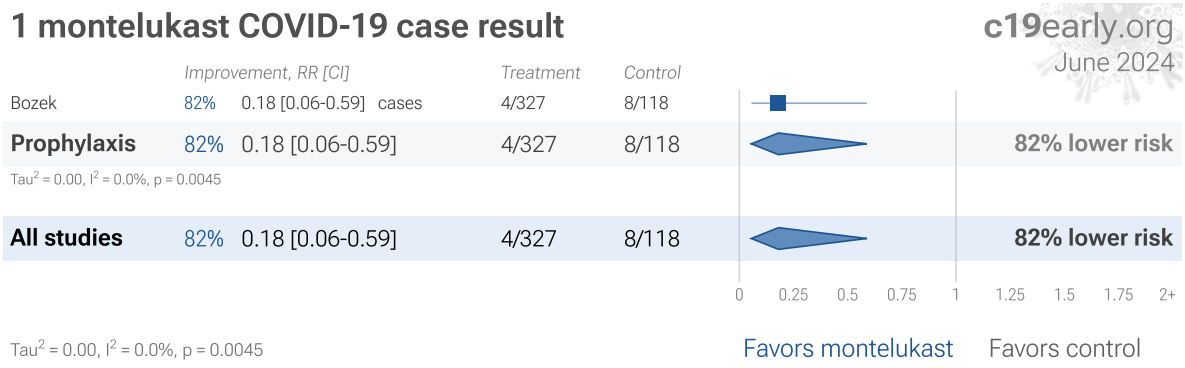


Figure 10. Random effects meta-analysis for cases.

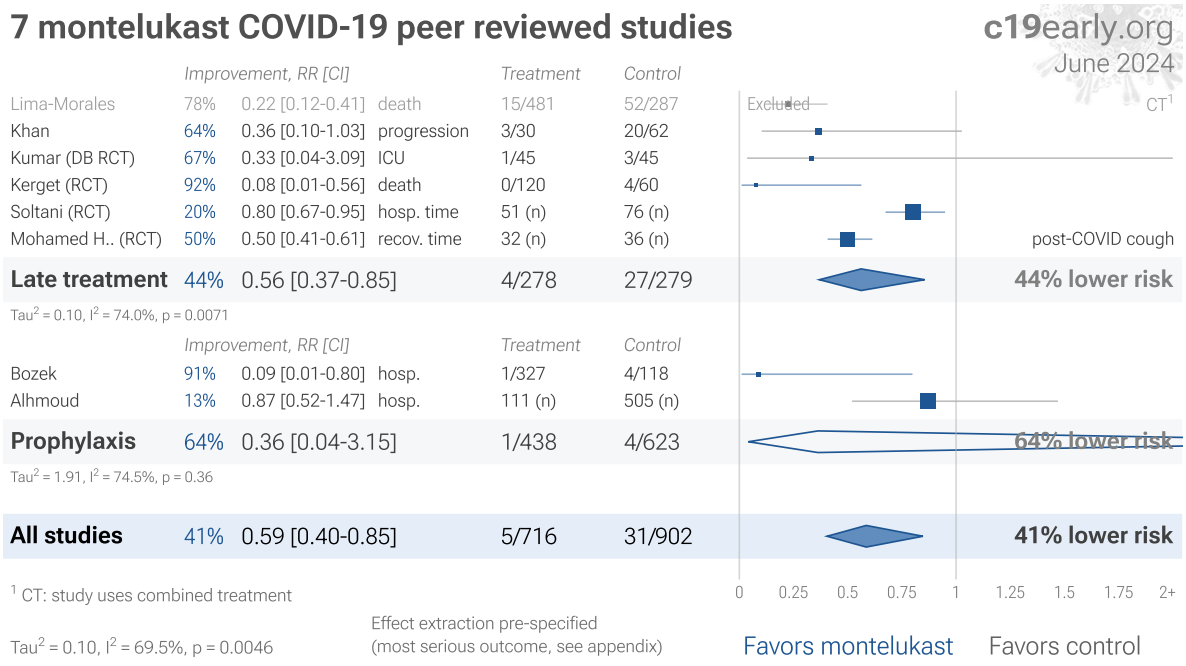


Figure 11. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 12 shows a comparison of results for RCTs and non-RCT studies. Figure 13, 14, and 15 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

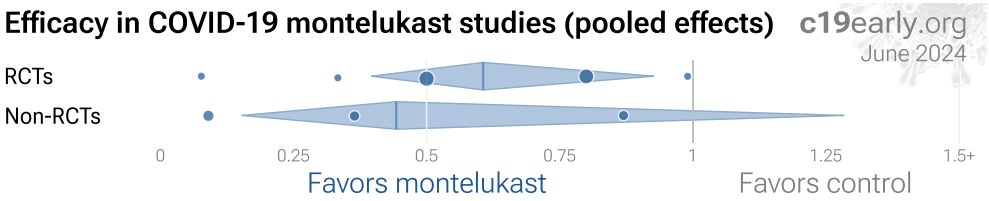


Figure 12. Results for RCTs and non-RCT studies.

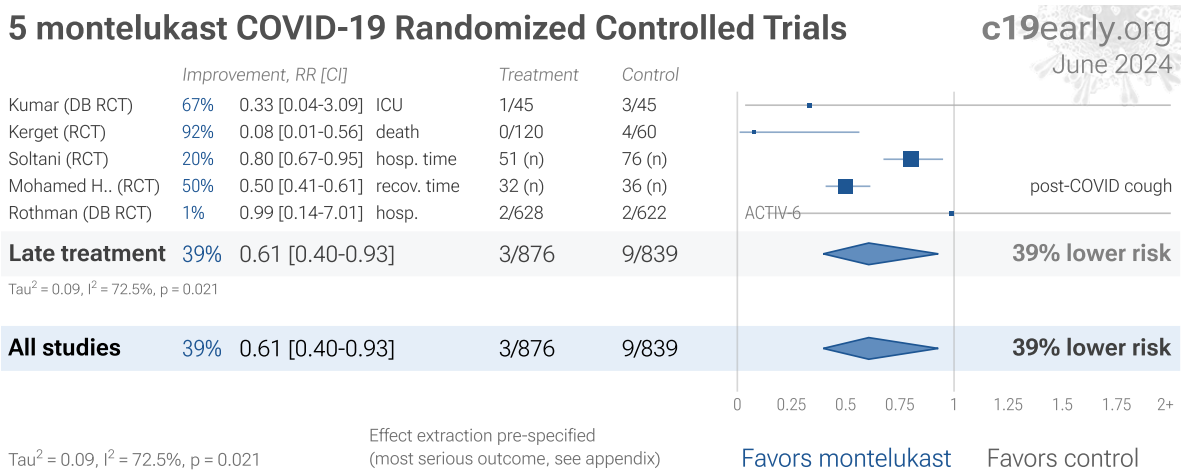


Figure 13. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious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

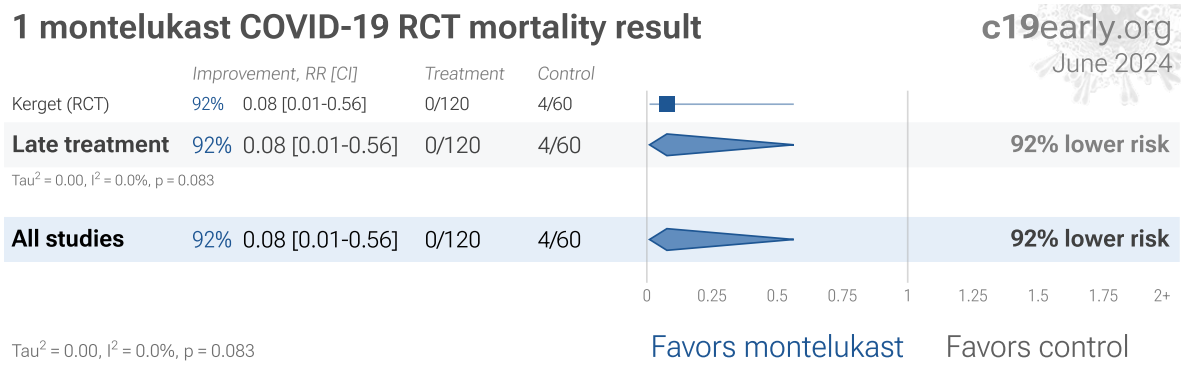


Figure 14. Random effects meta-analysis for RCT mortality results.

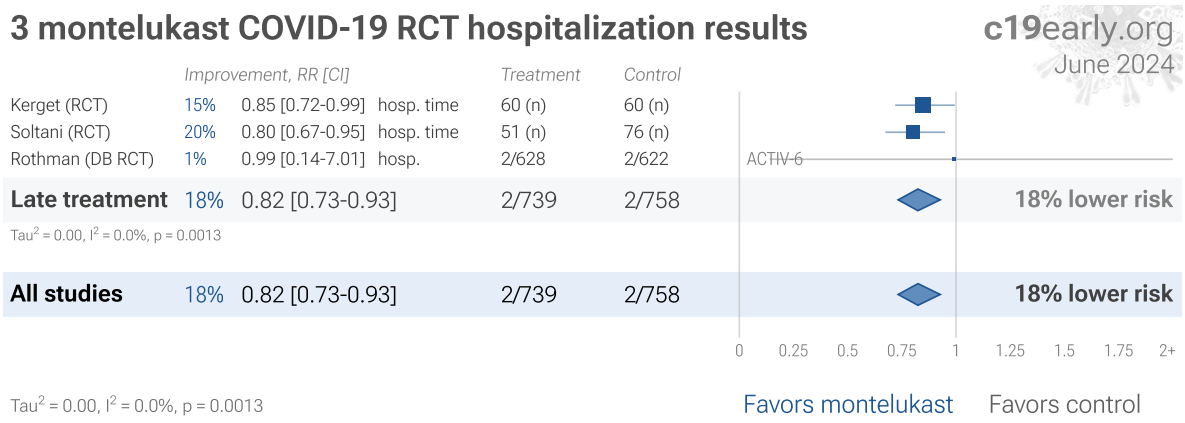


Figure 15. **Random effects meta-analysis for RCT hospitalization results.**

RCTs have many potential biases. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases[21], and analysis of double-blind RCTs has identified extreme levels of bias[22]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

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

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 72 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 montelukast 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 studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [27,28].

Using all studies identifies efficacy 7+ months faster (8+ months for low-cost treatments). Currently, 45 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 29 have been confirmed in RCTs, with a mean delay of 7.1 months. When considering only low cost treatments, 24 have been confirmed with a delay of 8.5 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

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

Unreported RCTs

2 montelukast RCTs have not reported results [1,2]. The trials report report an estimated total of 664 patients. The results are delayed from 9 months to over 2 years.

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 [29,30]. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases [31]
<24 hours	-33 hours symptoms [32]
24-48 hours	-13 hours symptoms [32]
Inpatients	-2.5 hours to improvement [33]

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

Figure 16 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 72 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

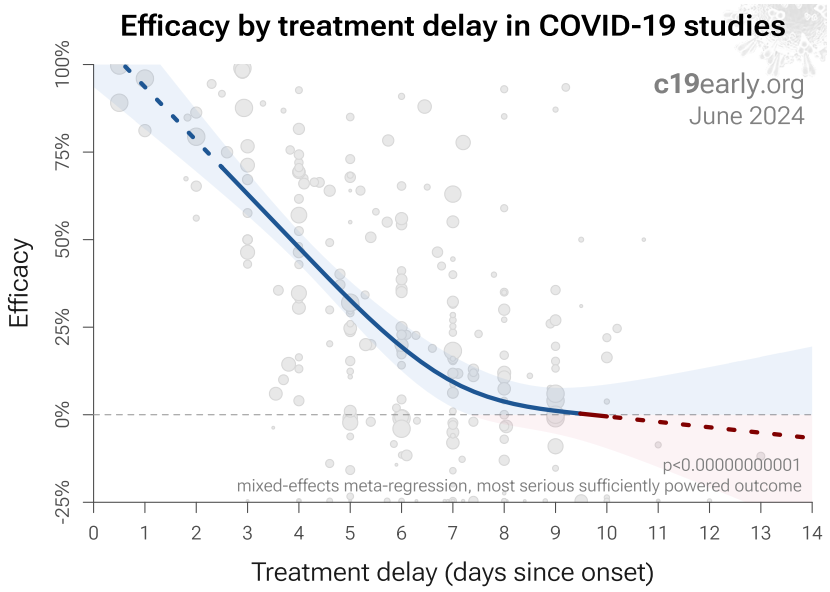


Figure 16. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 72 treatments.

Patient demographics. Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results, for example as in *López-Medina et al.*

Variants. Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants[35], for example the Gamma variant shows significantly different characteristics[36-39]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants[40,41].

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

Other treatments. The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic[42-52], therefore efficacy may depend strongly on combined treatments.

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

Effect measured. Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta analysis. The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment

is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Combining studies is required. For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results.

Specific outcome and pooled analyses. We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Using more information. Another way to view pooled analysis is that we are using more of the available information. Logically we should, and do, use additional information. For example dose-response and treatment delay-response relationships provide significant additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Ethical and practical issues limit high-risk trials. Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster collection of evidence.

Improvement across outcomes. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Validating pooled outcome analysis for COVID-19. Analysis of the the association between different outcomes across studies from all 72 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 17 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 18 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 19 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.0000014$ to $p = 0.000000005$.

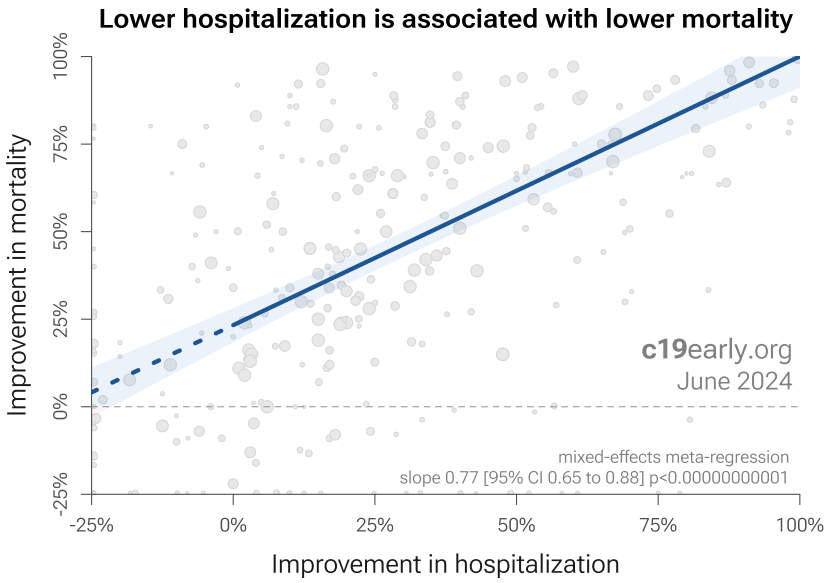


Figure 17. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

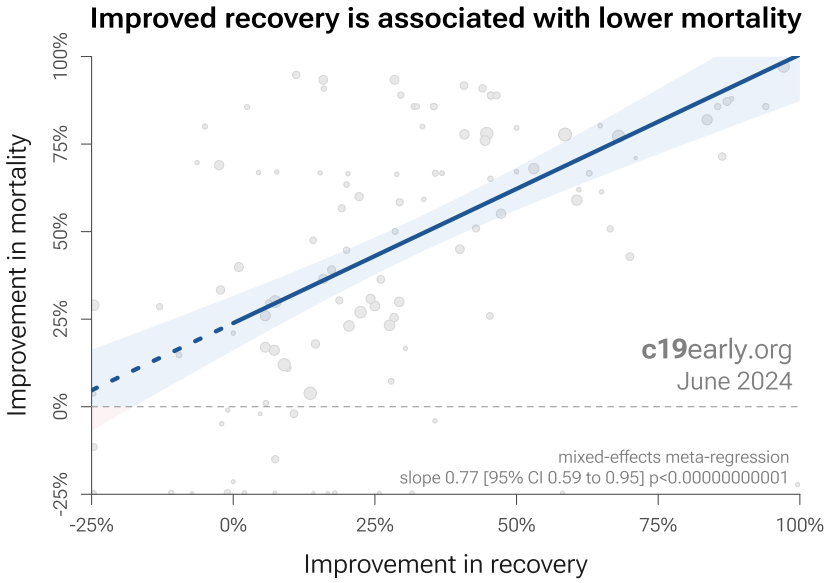


Figure 18. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

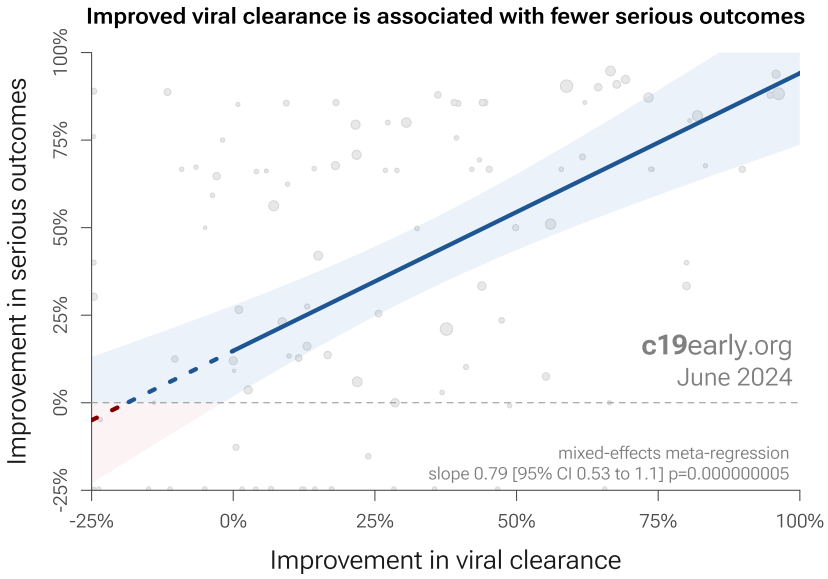


Figure 17. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (6 months for RCTs). Currently, 45 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 these have been confirmed with one or more specific outcomes, with a mean delay of 5.0 months. When restricting to RCTs only, 56% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.4 months. Figure 20 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

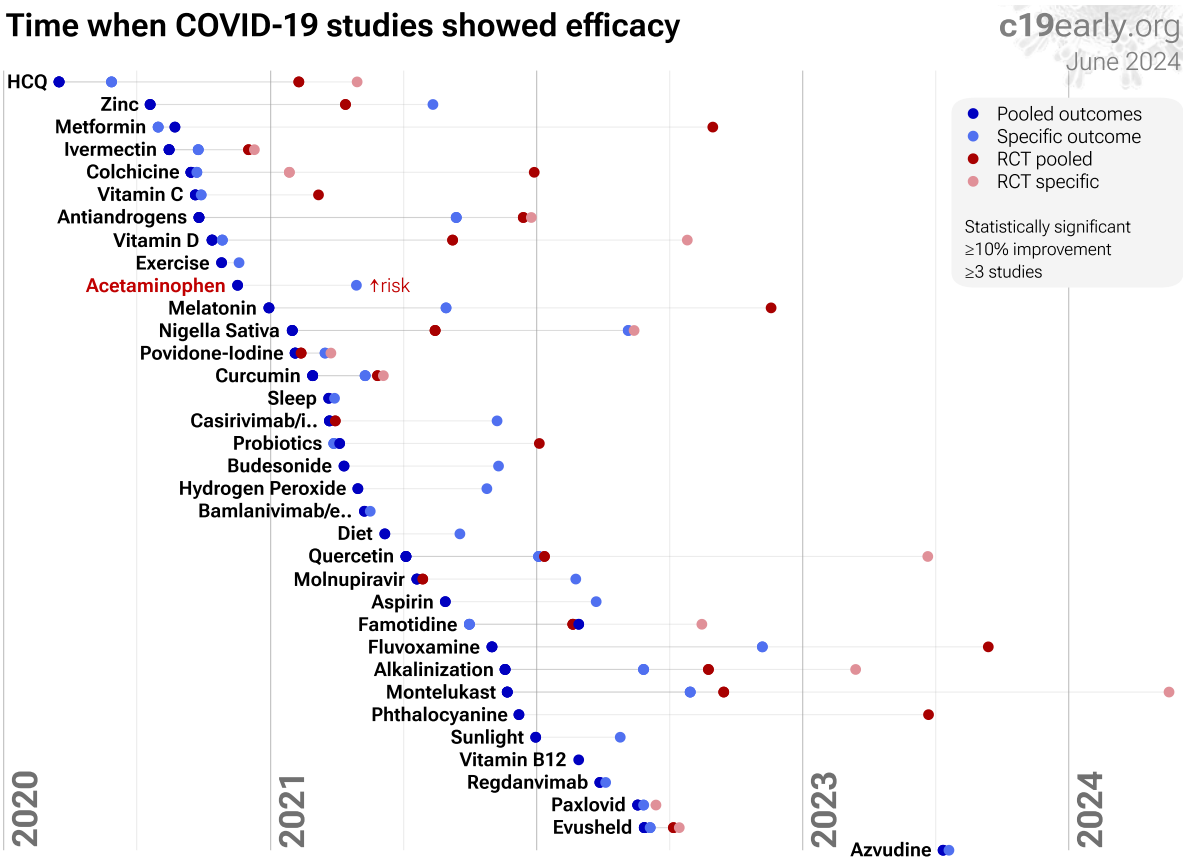


Figure 20. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations. Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary. Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Discussion

Boxed warning. Montelukast has a boxed warning for neuropsychiatric side effects[3].

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[56-59]. For montelukast, 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 21 shows a scatter plot of results for prospective and retrospective studies. The median effect size for retrospective studies is 64% improvement, compared to 50% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.

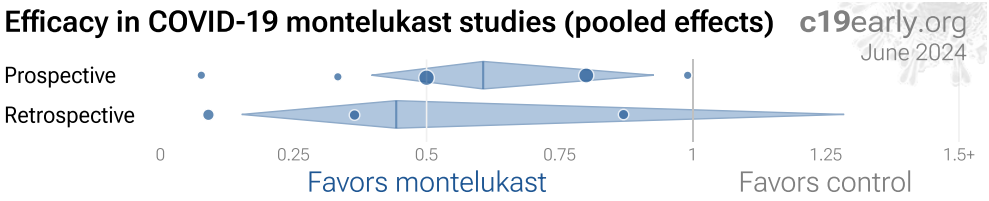


Figure 21. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 22 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 $p < 0.05$[60-67]. 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.

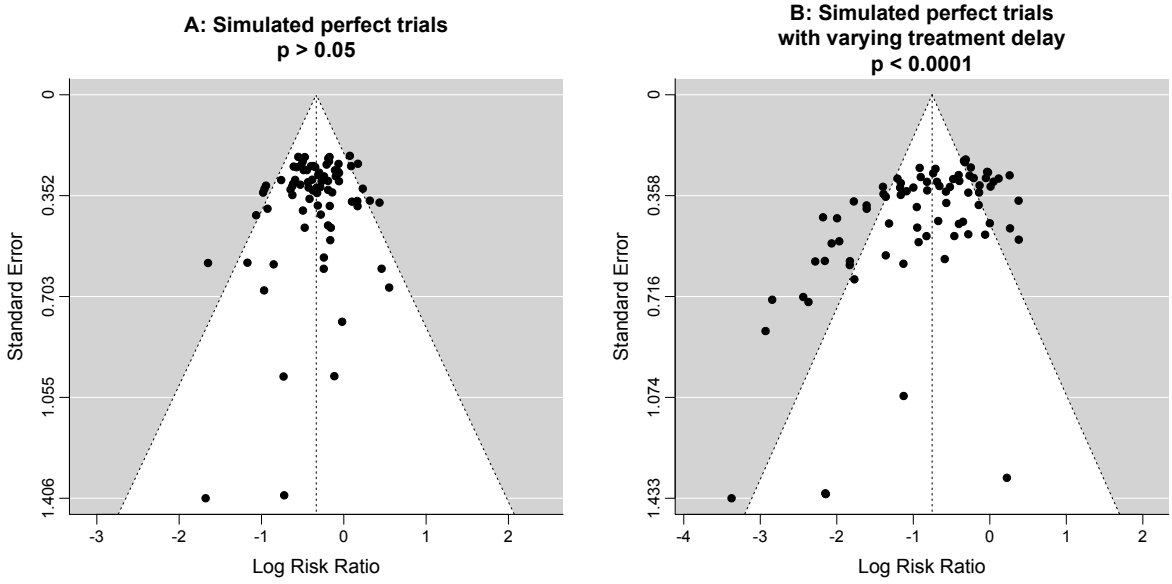


Figure 22. **Example funnel plot analysis for simulated perfect trials.**

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. Montelukast for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 montelukast 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 montelukast trials represent the optimal conditions for efficacy.

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone[42-52]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes. 1 of 8 studies combine treatments. The results of montelukast alone may differ. None of the RCTs use combined treatment.

Reviews. *Barré et al.* present a review covering montelukast for COVID-19.

Perspective

Results compared with other treatments. SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors[11-15], providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk[16], either by directly minimizing infection or replication, by supporting immune

system function, or by minimizing secondary complications. Figure 23 shows an overview of the results for montelukast in the context of multiple COVID-19 treatments, and Figure 24 shows a plot of efficacy vs. cost for COVID-19 treatments.

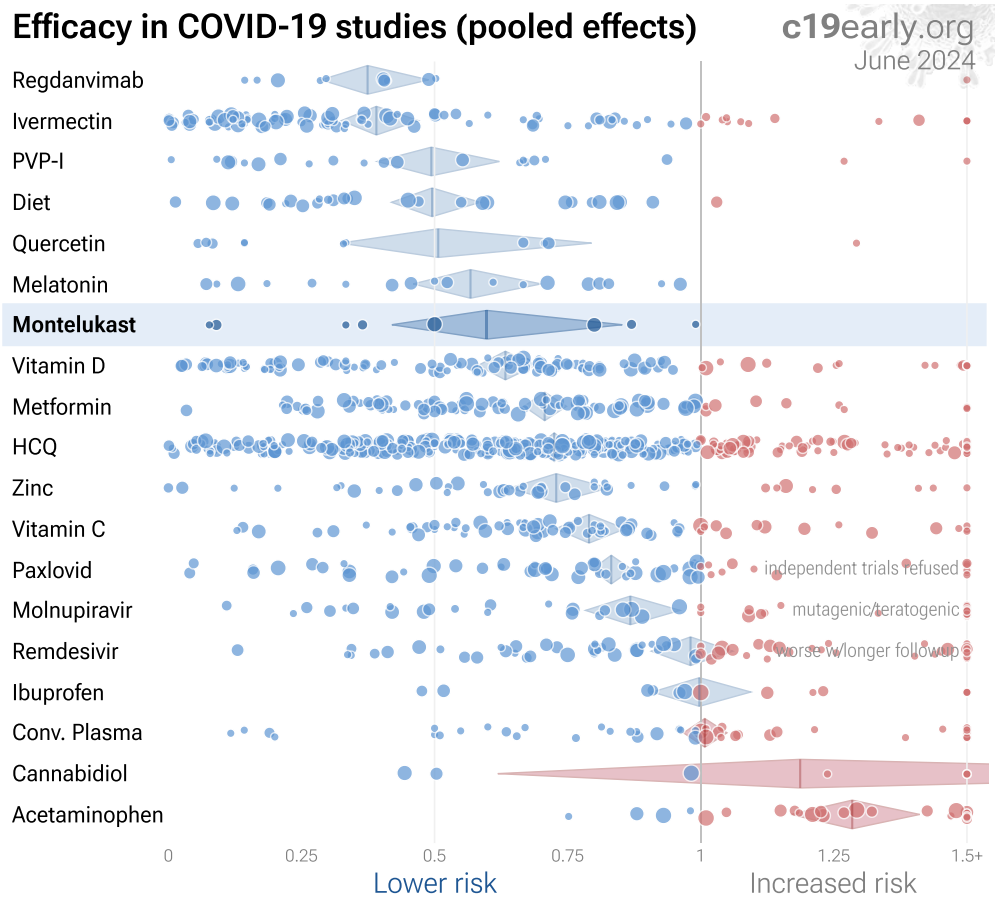


Figure 23. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy[69].

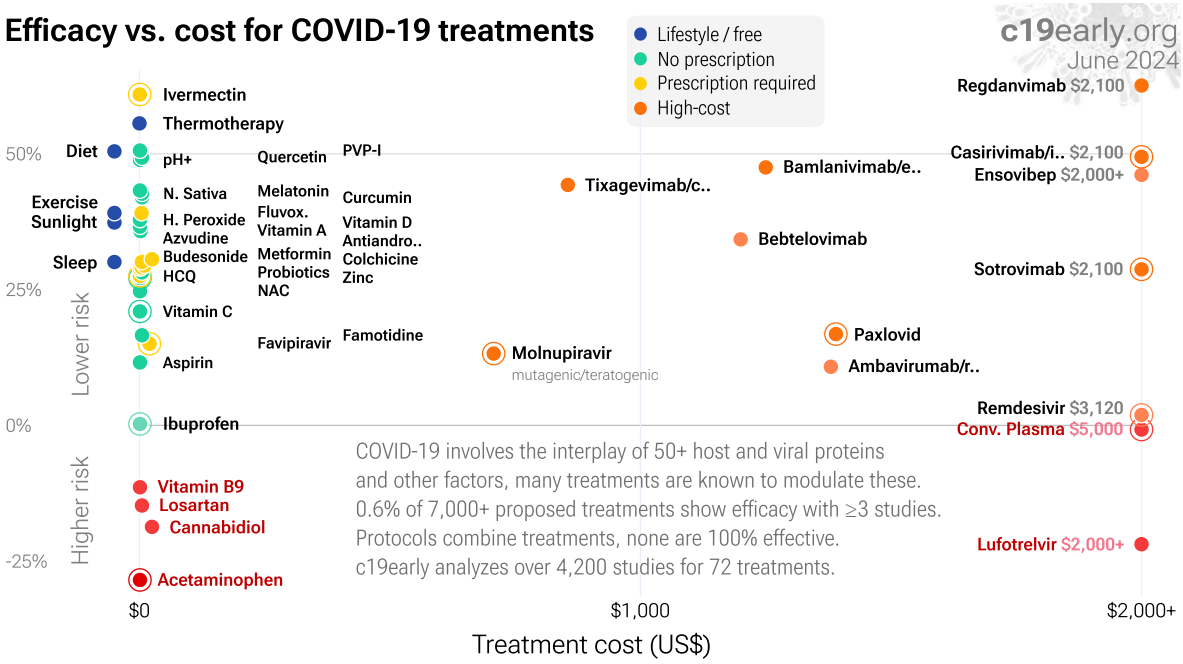


Figure 24. **Efficacy vs. cost for COVID-19 treatments.**

Conclusion

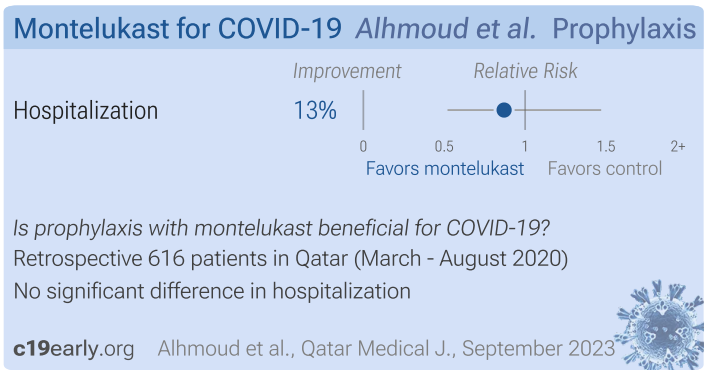
Studies to date show that montelukast is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, and cases. 4 studies from 4 independent teams in 4 countries show significant improvements. Meta analysis using the most serious outcome reported shows 40% [15-58%] lower risk. Results are similar for Randomized Controlled Trials and peer-reviewed studies.

Montelukast has a boxed warning for neuropsychiatric side effects[3].

Currently there is limited data, with only 33 control events for the most serious outcome in trials to date.

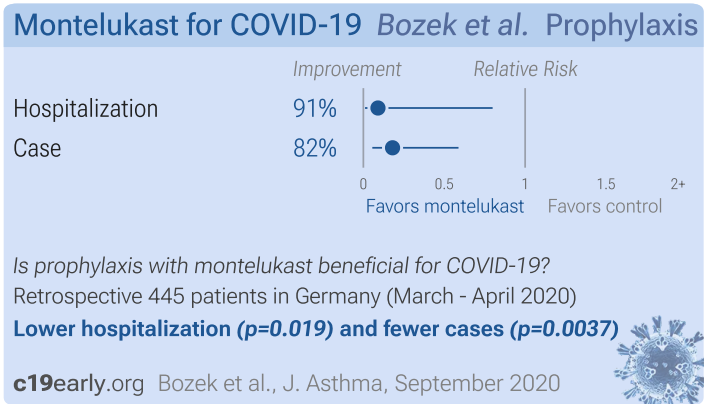
Study Notes

Alhmoud



Alhmoud: Retrospective 616 COVID-19 patients with asthma in Qatar showing no significant difference in hospitalization risk with montelukast use.

Bozek



Bozek: Retrospective 445 elderly patients with severe asthma showing reduced risk of COVID-19 infection with montelukast treatment.

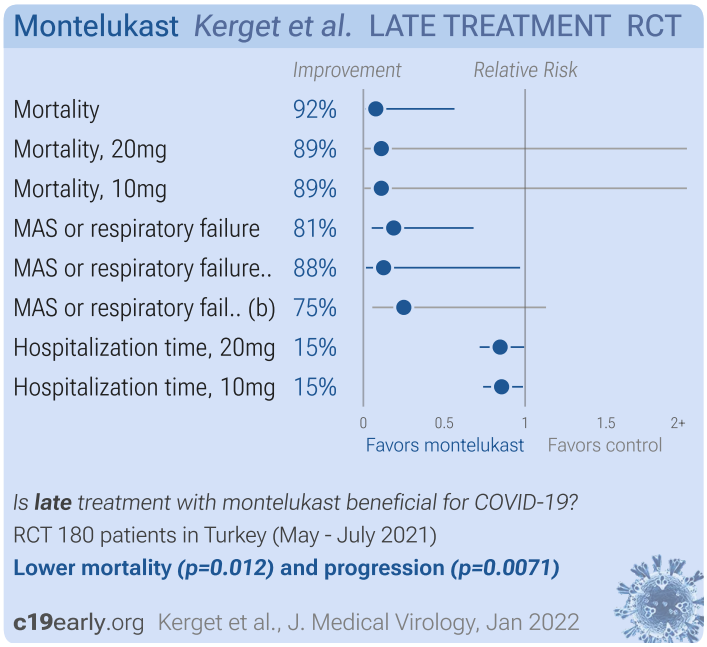
Cordero

Cordero: Estimated 284 patient montelukast late treatment RCT with results not reported over 9 months after estimated completion.

Durdagi

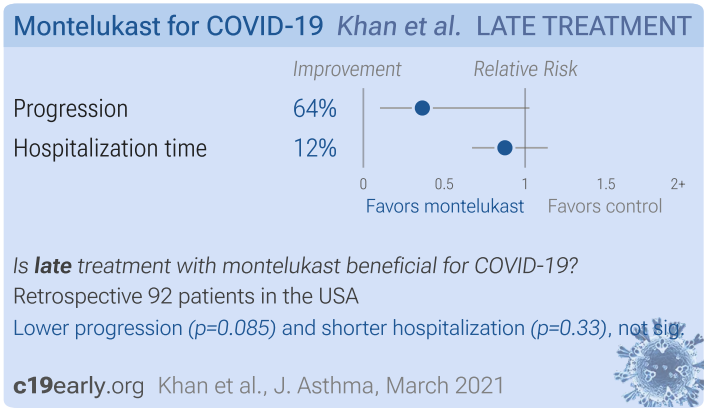
Durdagi: Estimated 380 patient montelukast early treatment RCT with results not reported over 2 years after estimated completion.

Kerget



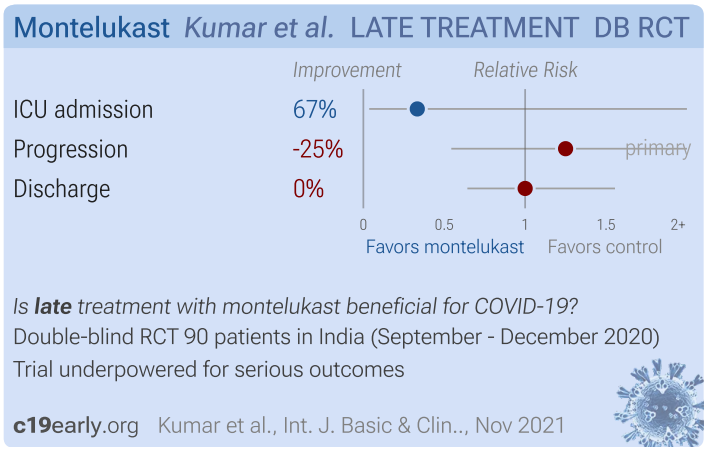
Kerget: RCT 180 hospitalized COVID-19 patients in Turkey showing faster reduction in inflammatory markers, improved pulmonary function, and lower rates of macrophage activation syndrome, respiratory failure and mortality with montelukast treatment (10mg or 20mg daily) in addition to standard care. The higher dose of 20mg daily showed greater improvement in pulmonary function compared to 10mg daily. There was no mortality in the montelukast groups compared to 6.7% mortality with standard care alone.

Khan



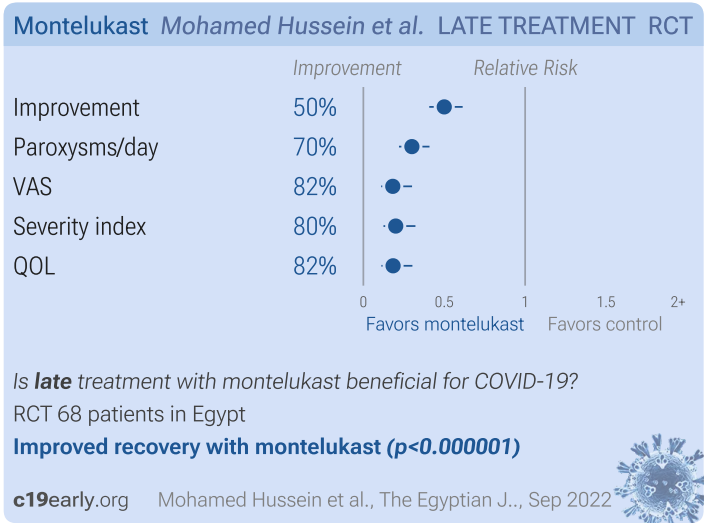
Khan: Retrospective 92 hospitalized patients showing lower clinical deterioration with montelukast treatment, without statistical significance in multivariable analysis. The treatment group was older.

Kumar



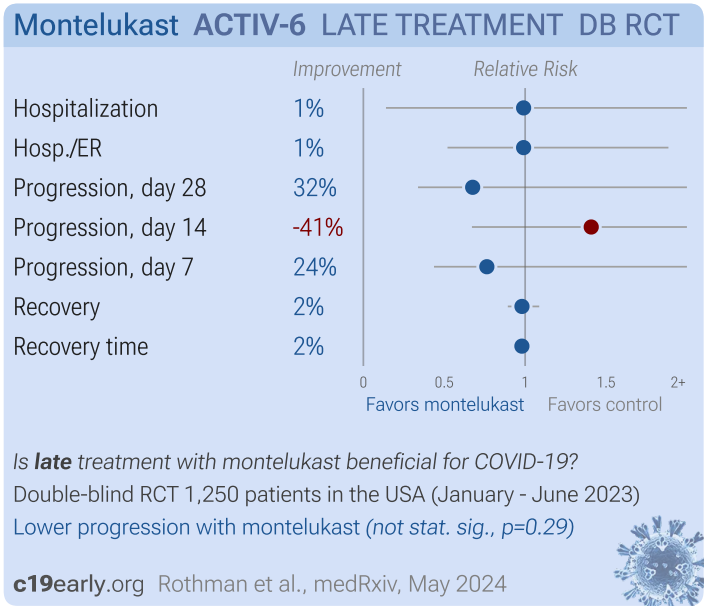
Kumar (B): RCT 90 mild to moderate COVID-19 patients showing no significant differences with montelukast treatment.

Mohamed Hussein



Mohamed Hussein: RCT 68 post-COVID-19 outpatients showing improvement in cough severity measures with montelukast treatment. The montelukast group had a greater reduction in number of cough paroxysms per day, cough severity visual analog scale, cough severity index, and improved cough quality of life scores compared to the control group. The montelukast group also had a shorter duration of cough.

Rothman



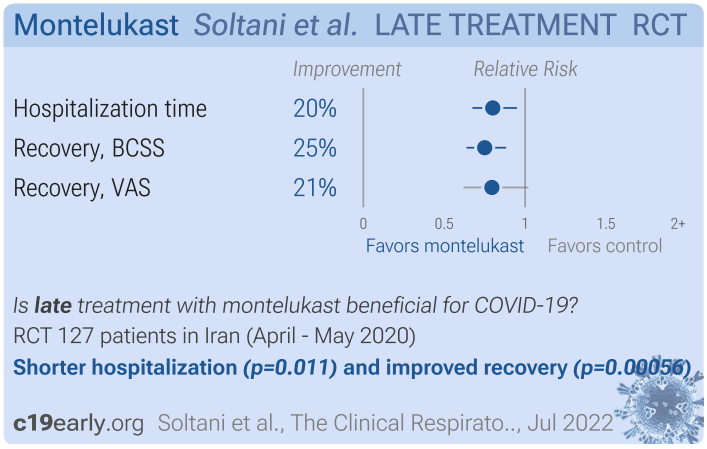
Rothman: RCT 1,250 outpatients with mild to moderate COVID-19 showing no significant difference in time to sustained recovery with montelukast treatment. There were no deaths and only 2 hospitalizations in each group.

Notably, results were better with patients that had mild COVID-19 at baseline compared to moderate/severe cases, and overall efficacy is reduced by poor results with extremely late treatment 9 days after onset, and with patients that had no symptoms at baseline.

Authors note the treatment drug was recalled and replaced from another source but do not report why the drug was recalled. Authors describe previous research testing 10mg and 20mg doses, noting that only 20mg showed improved pulmonary function testing, however authors do not indicate why they chose to test the lower dose.

It is unclear why authors report all-cause hospitalization and urgent care rather than COVID-19 specific outcomes. Given the low rate of urgent care visits and hospitalization, and the expected baseline frequency of these events independent of COVID-19, most or all of these events may be unrelated to COVID-19.

Authors note that previous research showed improvements specifically for cough, and authors collected cough data, however no results for cough are reported.



Soltani: RCT 180 hospitalized COVID-19 patients showing improved cough frequency and severity with gabapentin and gabapentin/montelukast compared to dextromethorphan, with the combination being more efficacious. The gabapentin/montelukast group had a significantly greater reduction in cough frequency (measured by the Breathlessness, Cough, and Sputum Scale) compared to the gabapentin alone group. There was no significant difference between the two groups in cough severity reduction measured by Visual Analog Scale.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are montelukast and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of montelukast for COVID-19 that report a comparison with a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to[78]. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1[81]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only

report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.3) with scipy (1.13.1), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.2), and plotly (5.22.0).

Forest plots are computed using PythonMeta [82] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective [29,30].

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

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

Durdagi, 6/1/2022, Randomized Controlled Trial, Turkey, trial NCT04718285 (history).	Estimated 380 patient RCT with results unknown and over 2 years late.

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.

Cordero, 8/31/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Spain, trial NCT04695704 (history) (E-SPERANZA).	Estimated 284 patient RCT with results unknown and over 9 months late.
Kerget, 1/4/2022, Randomized Controlled Trial, Turkey, peer-reviewed, mean age 54.6, 4 authors, study period May 2021 - July 2021, trial NCT05094596 (history).	risk of death, 92.3% lower, RR 0.08, $p = 0.01$, treatment 0 of 120 (0.0%), control 4 of 60 (6.7%), NNT 15, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of death, 88.9% lower, RR 0.11, $p = 0.12$, treatment 0 of 60 (0.0%), control 4 of 60 (6.7%), NNT 15, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), 20mg.

	risk of death, 88.9% lower, RR 0.11, $p = 0.12$, treatment 0 of 60 (0.0%), control 4 of 60 (6.7%), NNT 15, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), 10mg.
	MAS or respiratory failure, 81.2% lower, RR 0.19, $p = 0.007$, treatment 3 of 120 (2.5%), control 8 of 60 (13.3%), NNT 9.2.
	MAS or respiratory failure, 87.5% lower, RR 0.12, $p = 0.03$, treatment 1 of 60 (1.7%), control 8 of 60 (13.3%), NNT 8.6, 20mg.
	MAS or respiratory failure, 75.0% lower, RR 0.25, $p = 0.09$, treatment 2 of 60 (3.3%), control 8 of 60 (13.3%), NNT 10.0, 10mg.
	hospitalization time, 15.5% lower, relative time 0.85, $p = 0.04$, treatment mean 9.3 (±3.6) n=60, control mean 11.0 (±5.3) n=60, 20mg.
	hospitalization time, 14.5% lower, relative time 0.85, $p = 0.03$, treatment mean 9.4 (±2.1) n=60, control mean 11.0 (±5.3) n=60, 10mg.
Khan, 3/4/2021, retrospective, USA, peer-reviewed, 16 authors.	**risk of progression, 63.5% lower, RR 0.36, $p = 0.09$**, treatment 3 of 30 (10.0%), control 20 of 62 (32.3%), NNT 4.5, adjusted per study, odds ratio converted to relative risk, multivariable.
	hospitalization time, 12.5% lower, relative time 0.88, $p = 0.33$, treatment median 7.0 IQR 6.5 n=30, control median 8.0 IQR 6.0 n=62.
Kumar (B), 11/22/2021, Double Blind Randomized Controlled Trial, placebo-controlled, India, peer-reviewed, mean age 45.0, 10 authors, study period 1 September, 2020 - 31 December, 2020.	**risk of ICU admission, 66.7% lower, RR 0.33, $p = 0.62$**, treatment 1 of 45 (2.2%), control 3 of 45 (6.7%), NNT 23.
	risk of progression, 25.0% higher, RR 1.25, $p = 0.79$, treatment 10 of 45 (22.2%), control 8 of 45 (17.8%), primary outcome.
	risk of no hospital discharge, no change, RR 1.00, $p = 1.00$, treatment 21 of 45 (46.7%), control 21 of 45 (46.7%).
Lima-Morales, 2/10/2021, prospective, Mexico, peer-reviewed, 10 authors, average treatment delay 7.2 days, this trial uses multiple treatments in the treatment arm (combined with azithromycin, montelukast, and aspirin) - results of individual treatments may vary, excluded: combined treatments may contribute more to the effect seen.	**risk of death, 77.7% lower, RR 0.22, $p < 0.001$**, treatment 15 of 481 (3.1%), control 52 of 287 (18.1%), NNT 6.7, adjusted per study, odds ratio converted to relative risk, multivariate.
	risk of mechanical ventilation, 51.9% lower, RR 0.48, $p = 0.15$, treatment 8 of 434 (1.8%), control 11 of 287 (3.8%), NNT 50.
	risk of hospitalization, 67.4% lower, RR 0.33, $p < 0.001$, treatment 44 of 481 (9.1%), control 89 of 287 (31.0%), NNT 4.6, adjusted per study, odds ratio converted to relative risk, multivariate.
	risk of no recovery, 58.6% lower, RR 0.41, $p < 0.001$, treatment 75 of 481 (15.6%), control 118 of 287 (41.1%), NNT 3.9, adjusted per study, inverted to make RR<1 favor treatment, odds

	ratio converted to relative risk, recovery at day 14 after symptoms, multivariate.
Mohamed Hussein, 9/15/2022, Randomized Controlled Trial, Egypt, peer-reviewed, mean age 43.0, 7 authors, post-COVID cough.	**improvement, 50.0% lower, relative time 0.50, $p < 0.001$**, treatment mean 5.0 (±1.4) n=32, control mean 10.0 (±1.5) n=36.
	paroxysms/day, 70.0% lower, relative time 0.30, $p < 0.001$, treatment mean 3.0 (±1.2) n=32, control mean 10.0 (±4.1) n=36.
	VAS, 81.8% lower, relative time 0.18, $p < 0.001$, treatment mean 12.0 (±6.0) n=32, control mean 66.0 (±12.0) n=36.
	severity index, 80.0% lower, relative time 0.20, $p < 0.001$, treatment mean 4.0 (±1.1) n=32, control mean 20.0 (±5.0) n=36.
	QOL, 81.6% lower, relative time 0.18, $p < 0.001$, treatment mean 18.0 (±2.5) n=32, control mean 98.0 (±2.0) n=36.
Rothman, 5/18/2024, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, median age 53.0, 32 authors, study period 27 January, 2023 - 23 June, 2023, trial NCT04885530 (history) (ACTIV-6).	**risk of hospitalization, 1.0% lower, RR 0.99, $p = 1.00$**, treatment 2 of 628 (0.3%), control 2 of 622 (0.3%), NNT 32551.
	hosp./ER, 1.0% lower, RR 0.99, $p = 1.00$, treatment 18 of 628 (2.9%), control 18 of 622 (2.9%), NNT 3617.
	risk of progression, 32.4% lower, OR 0.68, $p = 0.29$, inverted to make OR<1 favor treatment, clinical progression, day 28, RR approximated with OR.
	risk of progression, 40.8% higher, OR 1.41, $p = 0.82$, inverted to make OR<1 favor treatment, clinical progression, day 14, RR approximated with OR.
	risk of progression, 23.7% lower, OR 0.76, $p = 0.27$, inverted to make OR<1 favor treatment, clinical progression, day 7, RR approximated with OR.
	risk of no recovery, 2.0% lower, HR 0.98, $p = 0.71$, treatment 628, control 622, inverted to make HR<1 favor treatment.
	recovery time, 2.0% lower, relative time 0.98, $p = 0.07$, treatment mean 11.77 (±2.49) n=628, control mean 12.01 (±2.16) n=622.
Soltani, 7/31/2022, Randomized Controlled Trial, Iran, peer-reviewed, mean age 56.8, 6 authors, study period April 2020 - May 2020.	**hospitalization time, 20.0% lower, relative time 0.80, $p = 0.01$**, treatment median 8.0 IQR 3.0 n=51, control median 10.0 IQR 7.0 n=76.
	risk of no recovery, 25.0% lower, RR 0.75, $p < 0.001$, treatment mean 1.96 (±0.69) n=51, control mean 1.47 (±0.81) n=76, relative BCSS improvement, GPT/MTL vs. GPT.
	risk of no recovery, 20.6% lower, RR 0.79, $p = 0.07$, treatment mean 1.8 (±1.11) n=51, control mean 1.43 (±1.13) n=76, relative VAS improvement, GPT/MTL vs. GPT.

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.

Alhmoud, 9/23/2023, retrospective, Qatar, peer-reviewed, median age 44.0, 10 authors, study period 10 March, 2020 - 10 August, 2020.	risk of hospitalization, 13.0% lower, OR 0.87, $p = 0.61$, treatment 111, control 505, adjusted per study, multivariable, RR approximated with OR.
Bozek, 9/17/2020, retrospective, Germany, peer-reviewed, 2 authors, study period March 2020 - April 2020.	risk of hospitalization, 91.0% lower, RR 0.09, $p = 0.02$, treatment 1 of 327 (0.3%), control 4 of 118 (3.4%), NNT 32.
	risk of case, 82.0% lower, RR 0.18, $p = 0.004$, treatment 4 of 327 (1.2%), control 8 of 118 (6.8%), NNT 18.

Supplementary Data

Supplementary Data

Footnotes

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

References

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