Ursodeoxycholic acid for COVID-19: real-time meta analysis of 12 studies

@CovidAnalysis, April 2024, Version 11
https://c19early.org/udcameta.html

Abstract

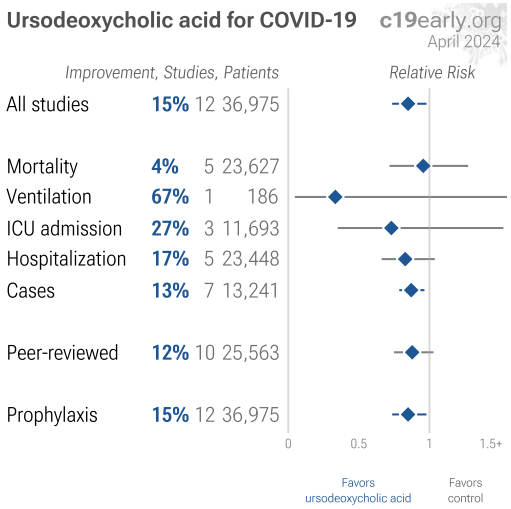
Statistically significant lower risk is seen for cases. 6 studies from 6 independent teams in 3 countries show statistically significant improvements.

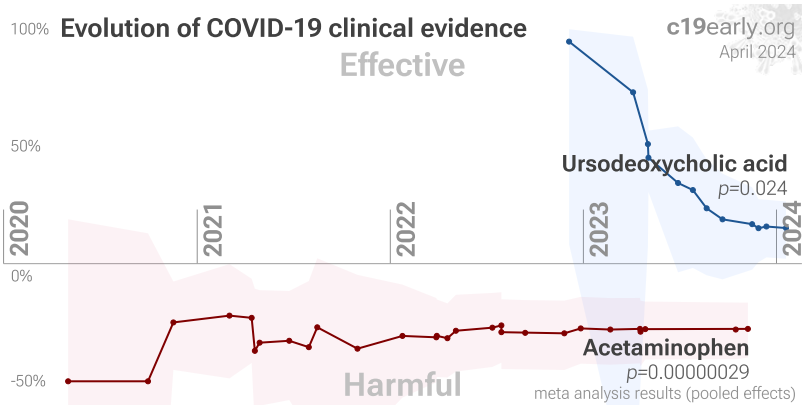
Meta analysis using the most serious outcome reported shows 15% [2-26%] lower risk. Results are similar for peer-reviewed studies.

Results are robust — in exclusion sensitivity analysis 5 of 12 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

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 are significantly more effective.

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

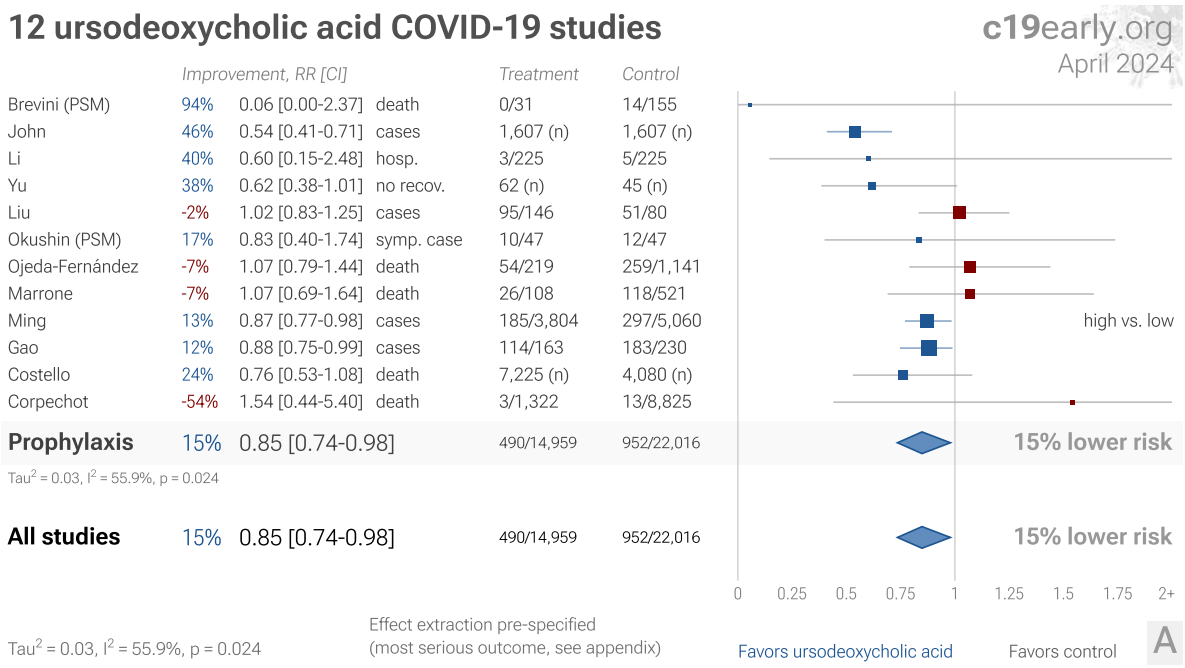




HIGHLIGHTS

UDCA reduces risk for COVID-19 with very high confidence for cases, high confidence for pooled analysis, and low confidence for hospitalization and recovery.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 69 treatments, outcome specific analyses and combined evidence from all studies.



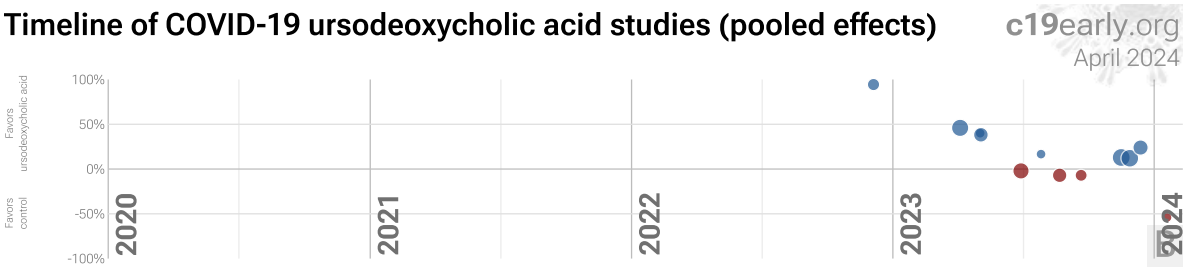


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the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

Introduction

Immediate treatment recommended. SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological issues *Duloquin, Hampshire, Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors *Note A, Malone, Murigneux, Lv, Lui, Niarakis*, 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 *c19early.org*, 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 ursodeoxycholic acid for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, individual outcomes, and peer-reviewed studies.

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.

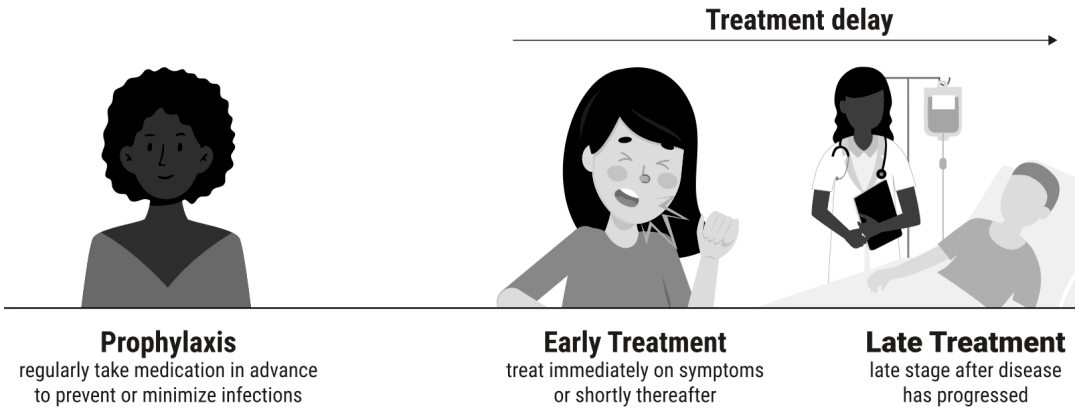


Figure 2. Treatment stages.

Preclinical Research

2 *In Vitro* studies support the efficacy of ursodeoxycholic acid *Brevini, Ming*.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results for all studies, for peer-reviewed studies, and for specific outcomes. Figure 3, 4, 5, 6, 7, 8, 9, and 10 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, recovery, cases, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**15%** [2-26%] *	12	36,975	170
Peer-reviewed studies	**12%** [-3-25%]	10	25,563	143
Mortality	**4%** [-27-28%]	5	23,627	122
ICU admission	27% [-52-65%]	3	11,693	96
Hospitalization	**17%** [-4-34%]	5	23,448	117
Cases	**13%** [4-21%] **	7	13,241	48

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

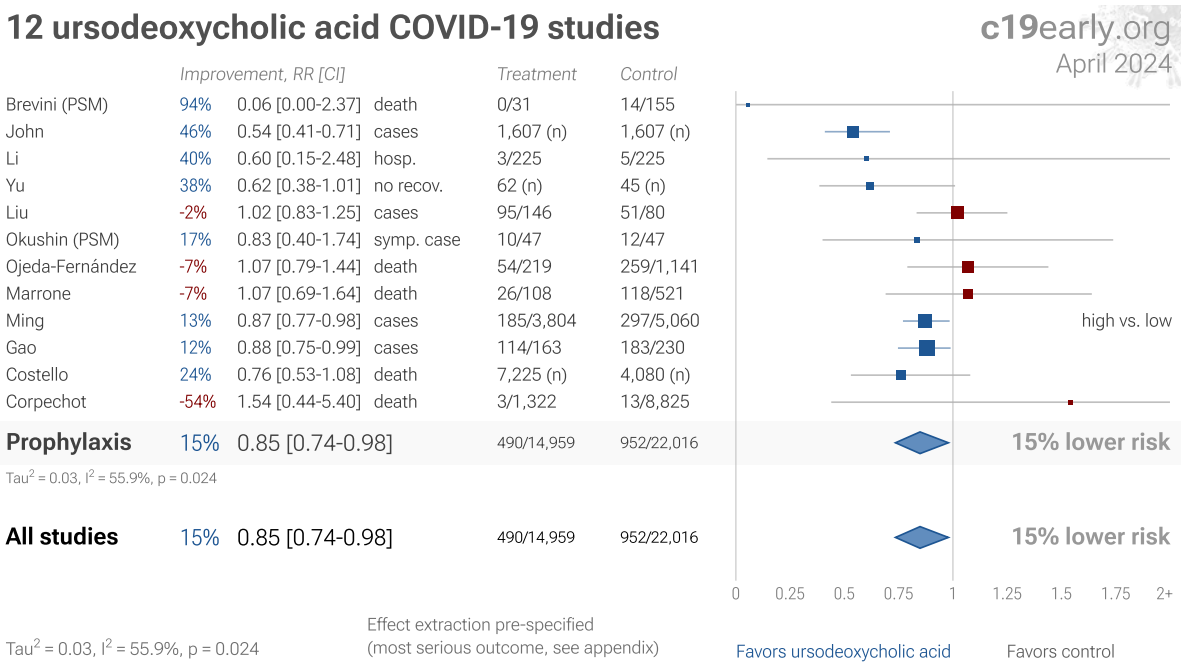


Figure 3. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

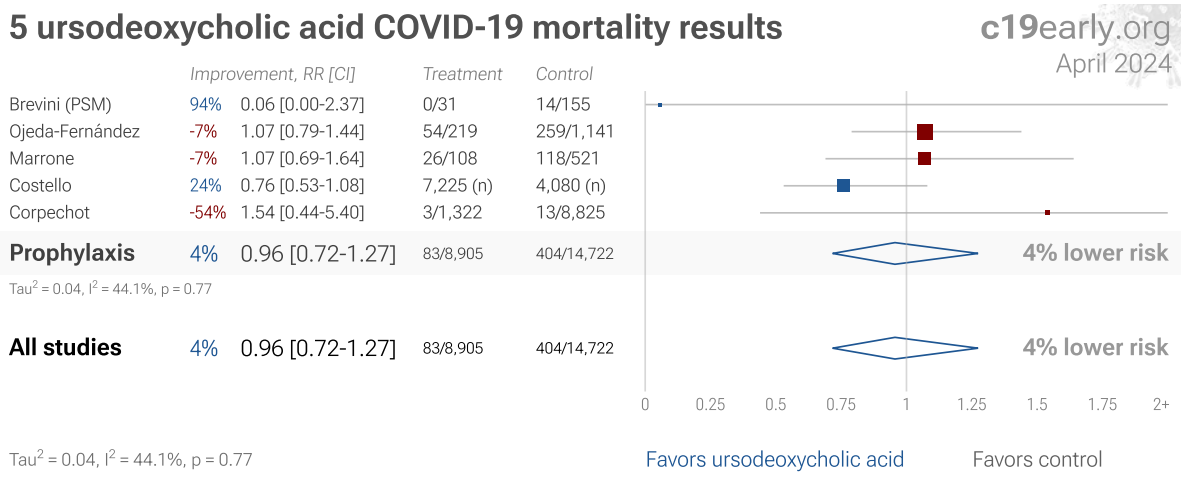


Figure 4. **Random effects meta-analysis for mortality results.**

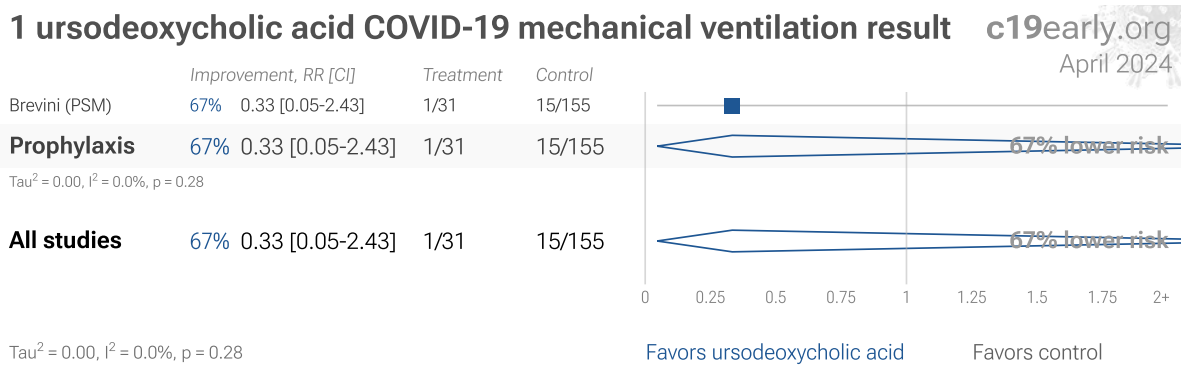


Figure 5. **Random effects meta-analysis for ventilation.**

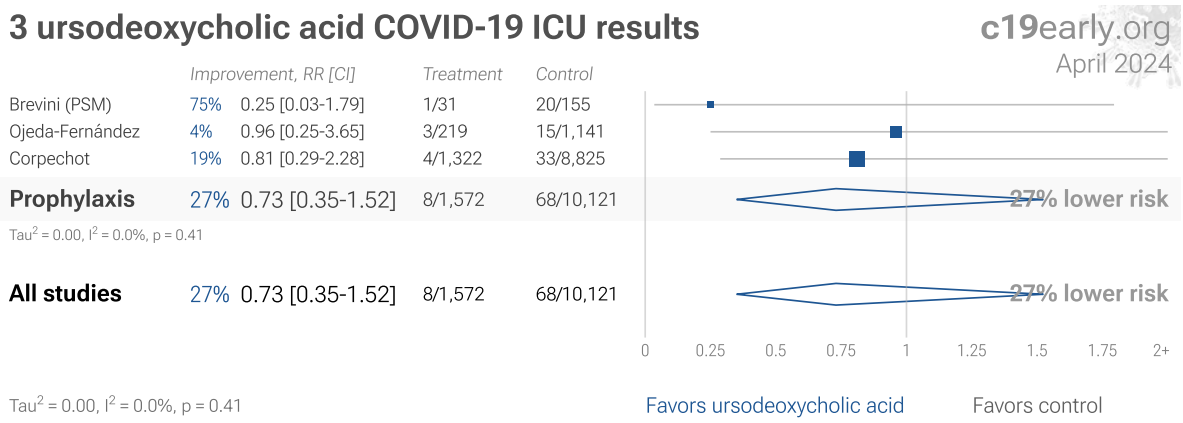


Figure 6. Random effects meta-analysis for ICU admission.

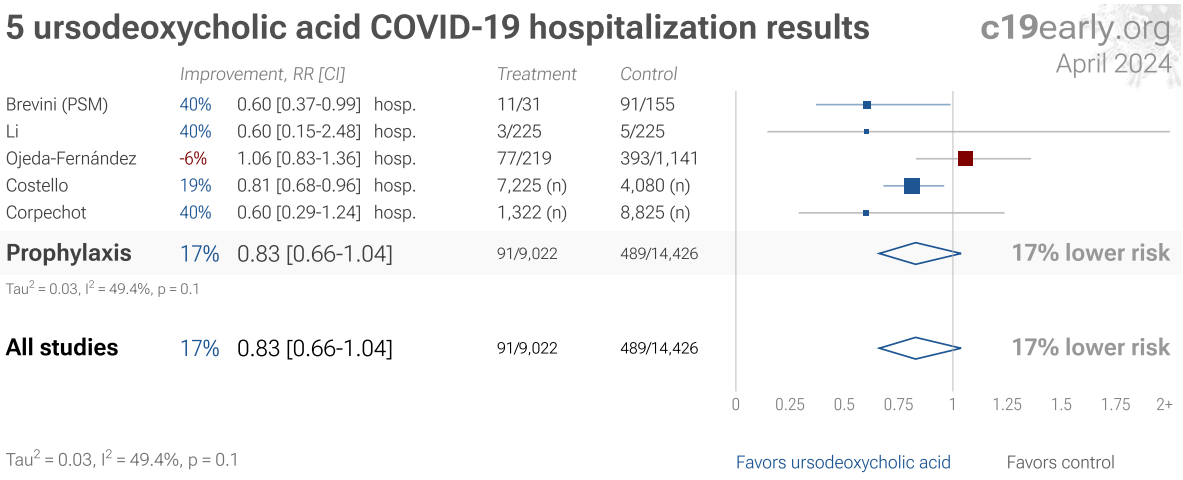


Figure 7. Random effects meta-analysis for hospitalization.

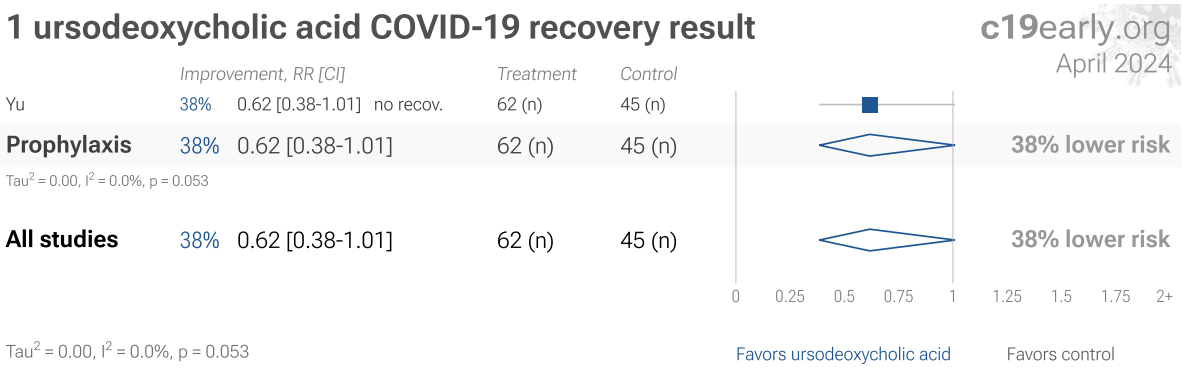


Figure 8. Random effects meta-analysis for recovery.

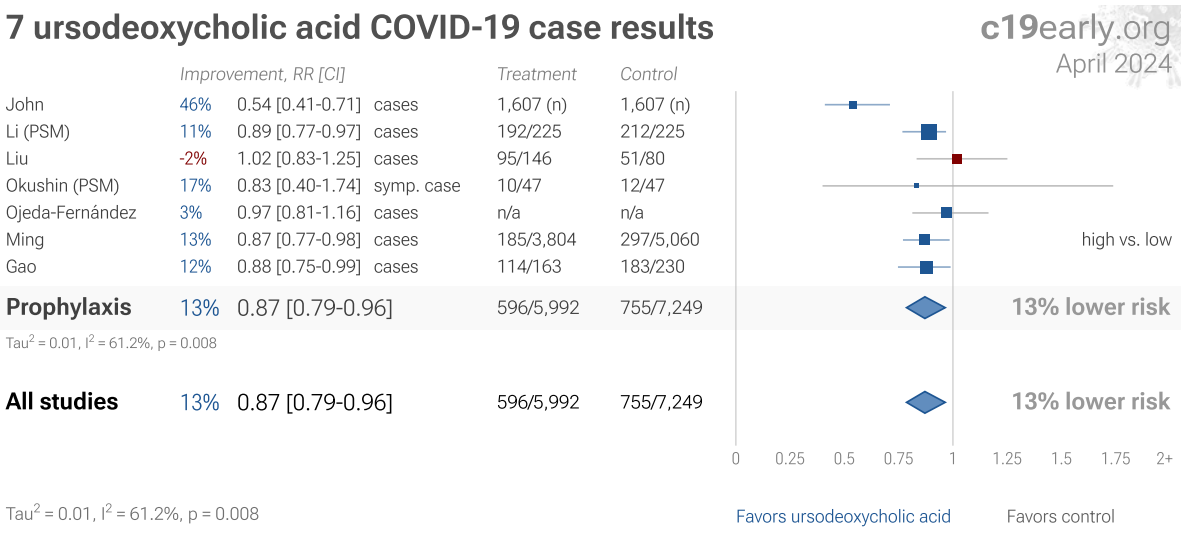


Figure 9. **Random effects meta-analysis for cases.**

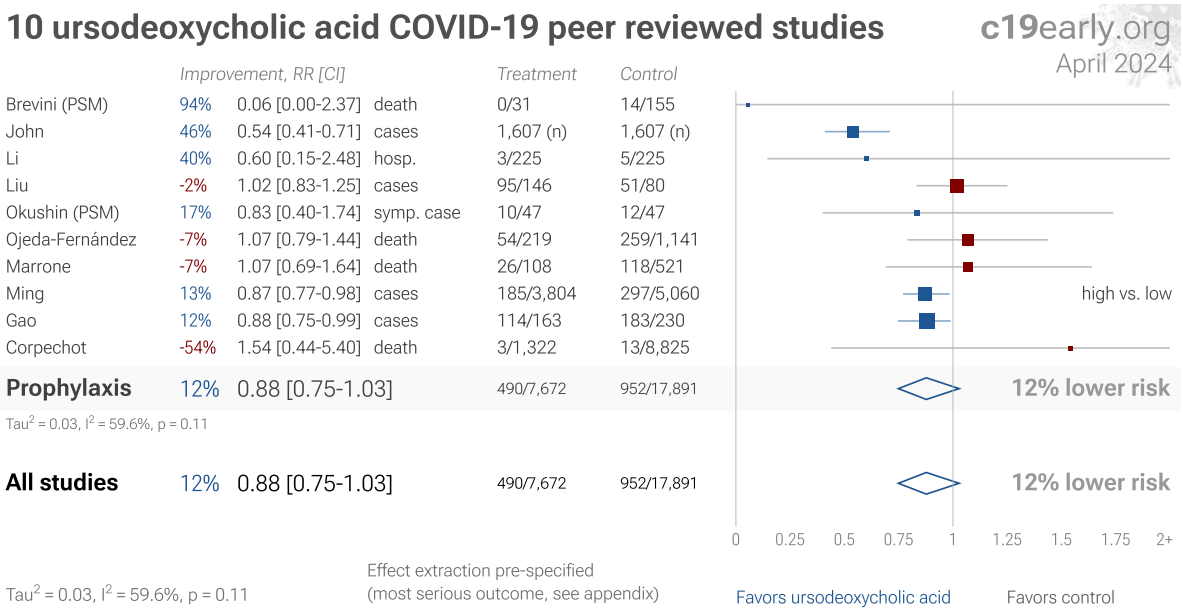


Figure 10. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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.

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 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 *Ikematsu*
<24 hours	-33 hours symptoms *Hayden*
24-48 hours	-13 hours symptoms *Hayden*
Inpatients	-2.5 hours to improvement *Kumar*

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

Figure 11 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 69 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

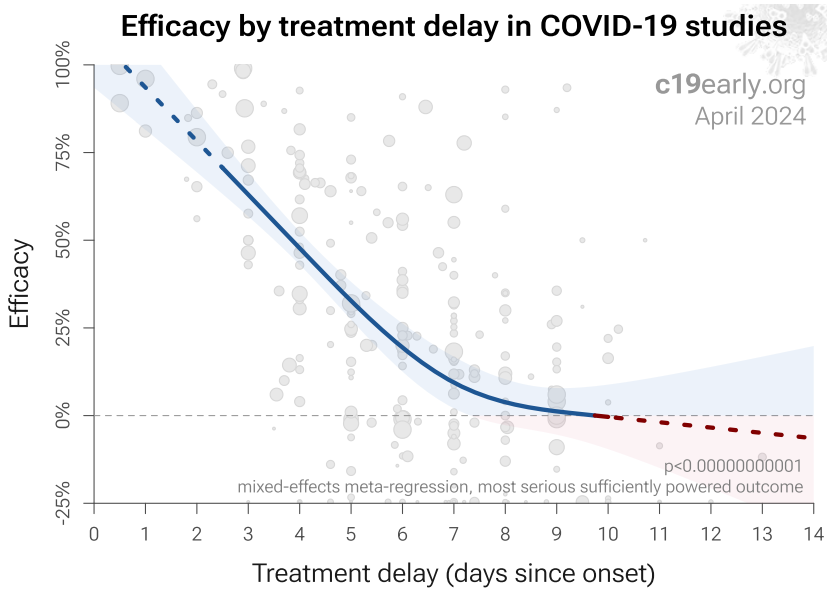


Figure 11. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 69 treatments.

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 *Korves*, 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 degree to which TMPRSS2 contributes to viral entry can differ across variants *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 supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*, 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 69 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 12 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 13 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 14 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 $p = 0.0000045$ to $p = 0.0000000067$.

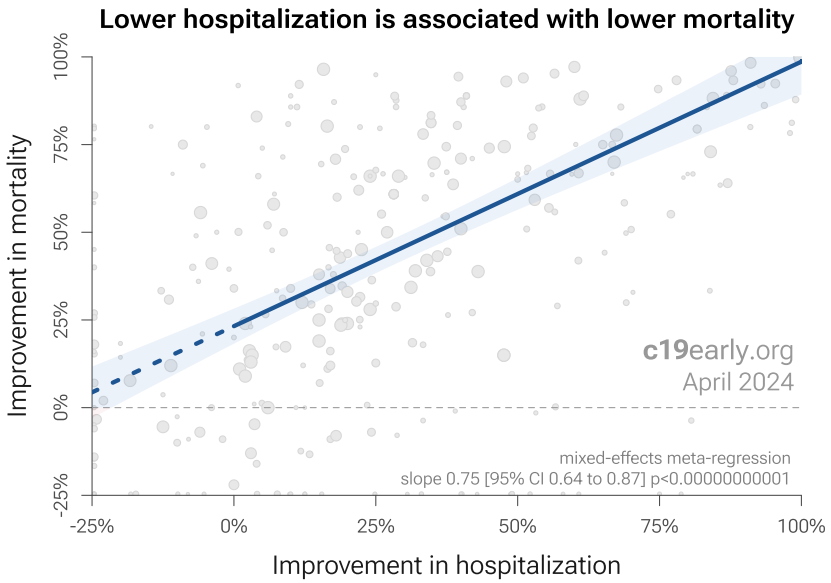


Figure 12. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

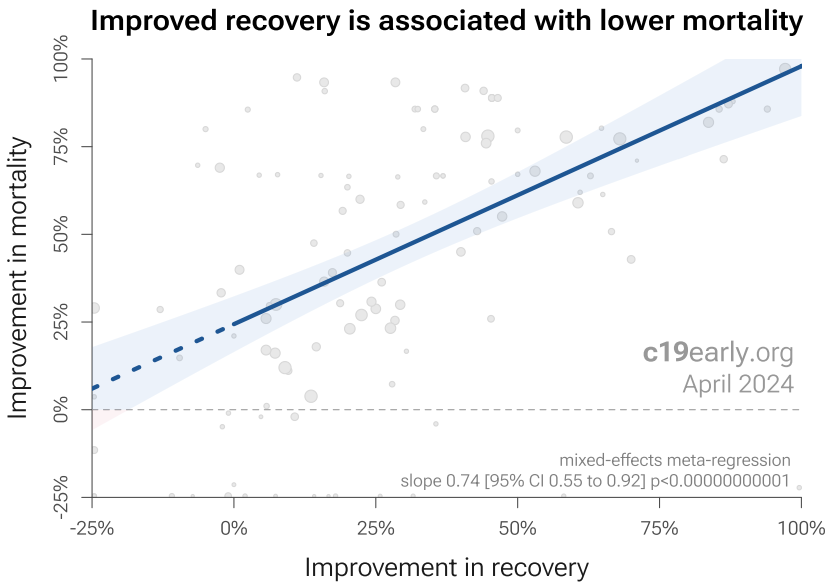


Figure 13. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

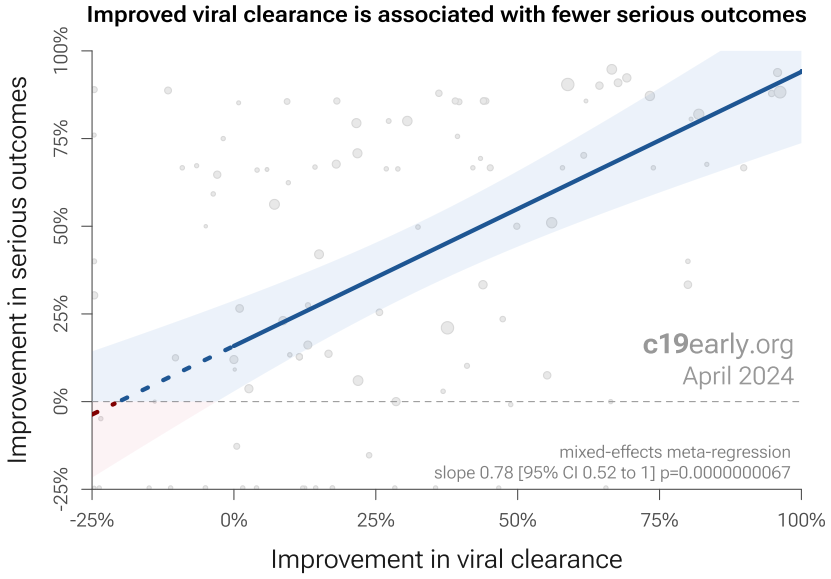


Figure 12. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

Pooled outcomes identify efficacy 4 months faster (6 months for RCTs). Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 85% of these have been confirmed with one or more specific outcomes, with a mean delay of 3.7 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 5.8 months. Figure 15 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

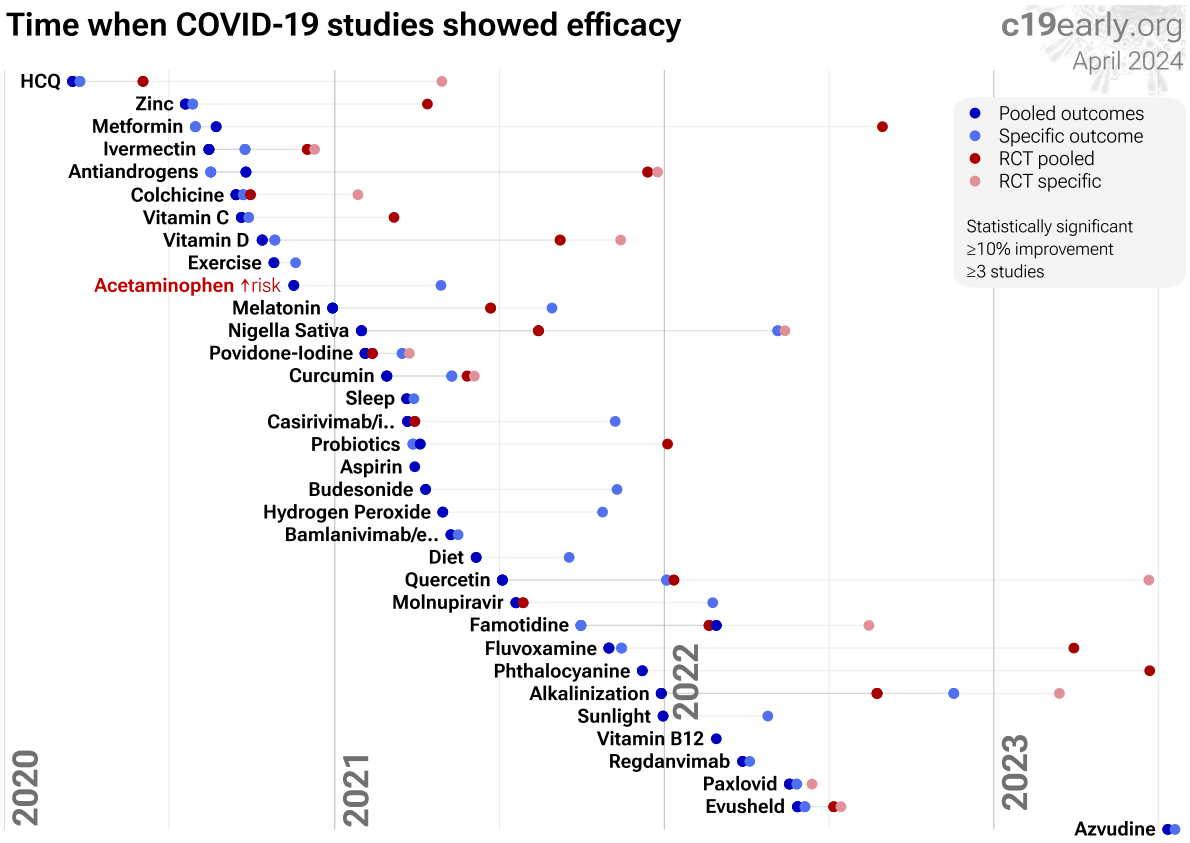


Figure 15. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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

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

Discussion

Publication bias. Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguesso, twitter.com*. For ursodeoxycholic acid, 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 16 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical

variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

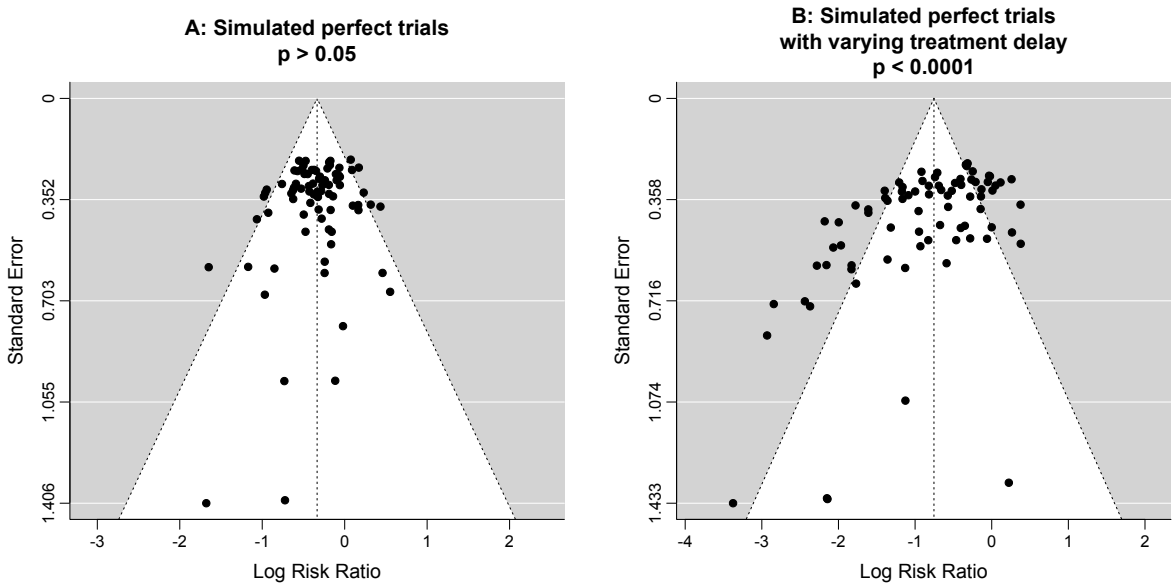


Figure 16. **Example funnel plot analysis for simulated perfect trials.**

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. UDCA for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 ursodeoxycholic acid 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 ursodeoxycholic acid 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 *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

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

No treatment 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.

Reviews. Multiple reviews cover ursodeoxycholic acid for COVID-19, presenting additional background on mechanisms and related results, including *Fiorucci, Huang*.

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 *Lui, Lv, Malone, Murigneux, Niarakis*, providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk *c19early.org*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 17 shows an overview of the results for ursodeoxycholic acid in the context of multiple COVID-19 treatments, and Figure 18 shows a plot of efficacy vs. cost for COVID-19 treatments.

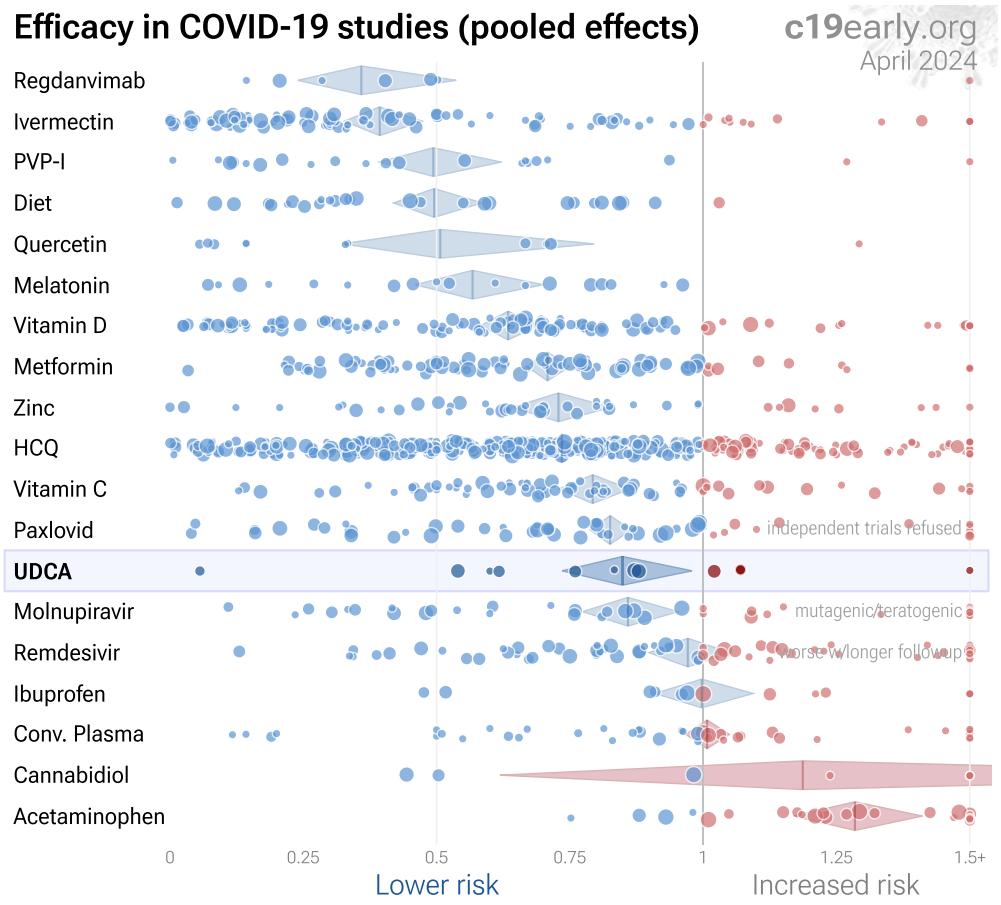


Figure 17. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,400 proposed treatments show efficacy *c19early.org (B)*.

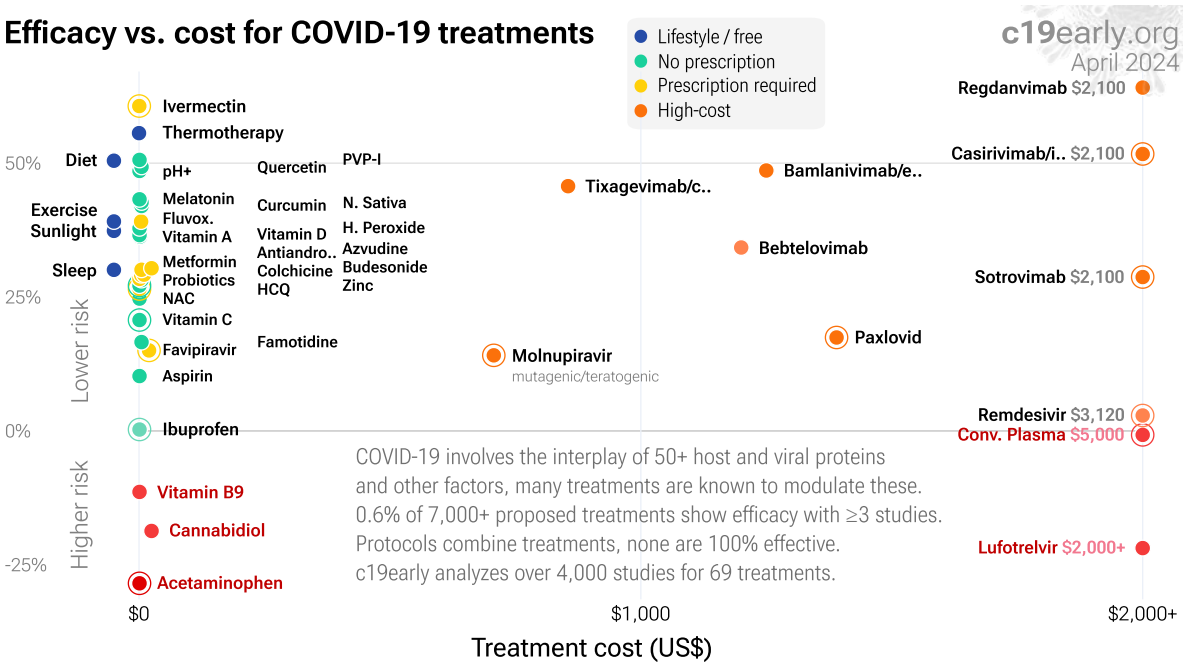


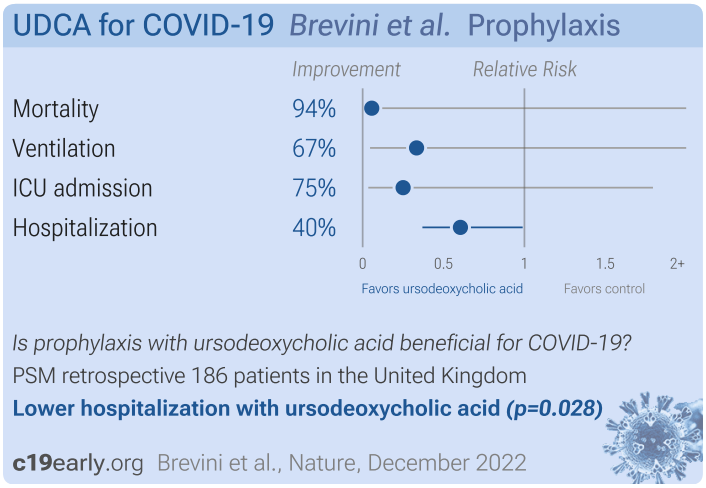
Figure 18. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Statistically significant lower risk is seen for cases. 6 studies from 6 independent teams in 3 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 15% [2-26%] lower risk. Results are similar for peer-reviewed studies. Results are robust — in exclusion sensitivity analysis 5 of 12 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Study Notes

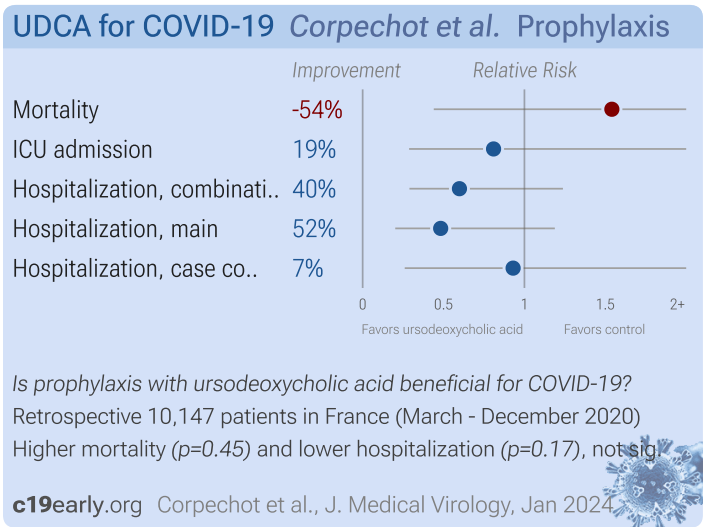
Brevini



Brevini: Retrospective study from two registries of 1,096 COVID-19 patients with chronic liver disease, including 31 treated with ursodeoxycholic acid (UDCA). Propensity score matching was used to compare outcomes between UDCA-treated and untreated patients. The analysis found that UDCA treatment was associated with reduced hospitalization, ICU admission, ventilation, and death from COVID-19. The authors suggest that UDCA may decrease susceptibility to SARS-CoV-2 infection by downregulating the host receptor ACE2 through inhibition of the farnesoid X receptor.

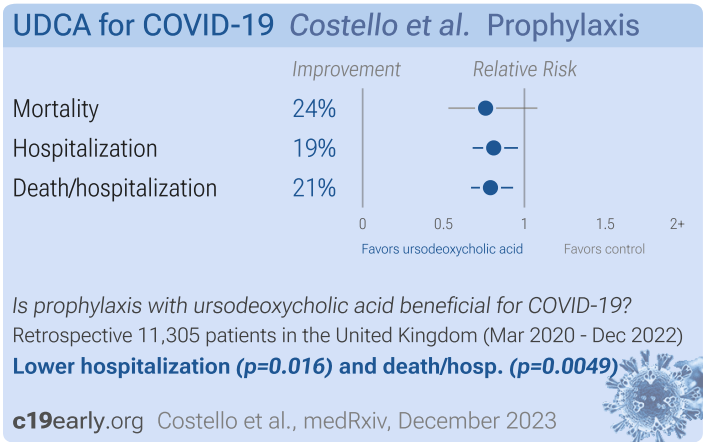
Authors also show that UDCA-mediated downregulation of ACE2 reduces susceptibility to SARS-CoV-2 infection in vitro, in vivo and in human lungs and livers perfused ex situ; and that UDCA reduces the expression of ACE2 in the nasal epithelium in humans.

Corpechot



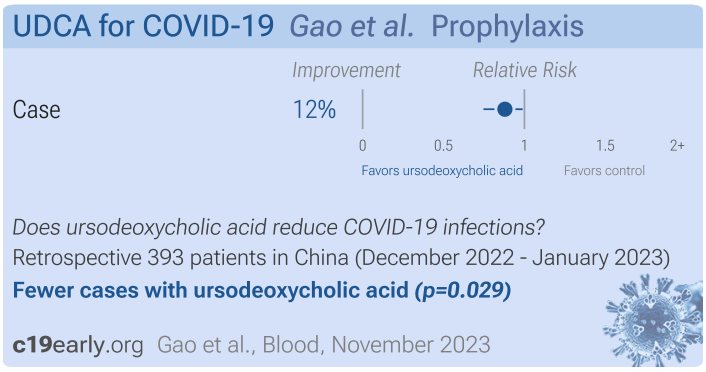
Corpechot: Retrospective cohort study of 10,147 chronic liver disease patients in France, with 1,322 exposed to ursodeoxycholic acid (UDCA), showing lower risk of hospitalization for COVID-19 with UDCA exposure, without statistical significance (adjusted OR 0.48, 95% CI 0.20-1.19). A case-control analysis of 88 hospitalized patients and 840 matched controls showed no significant difference, and there was no significant difference for ICU admission and mortality. The study is underpowered due to the low number of COVID-19 hospitalizations.

Costello



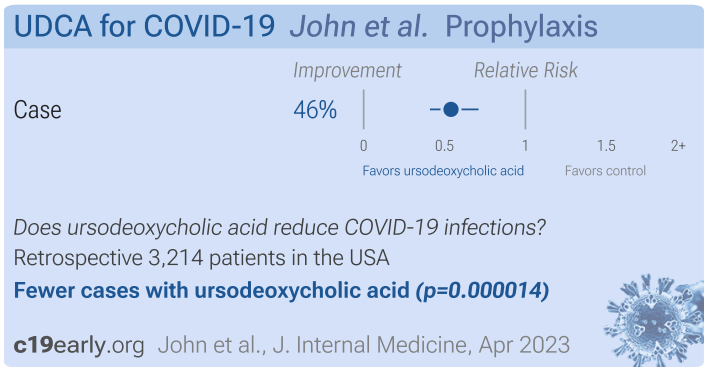
Costello: OpenSAFELY retrospective 11,320 primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) patients showing lower risk of COVID-19 hospitalization or death with ursodeoxycholic acid (UDCA) treatment.

Gao



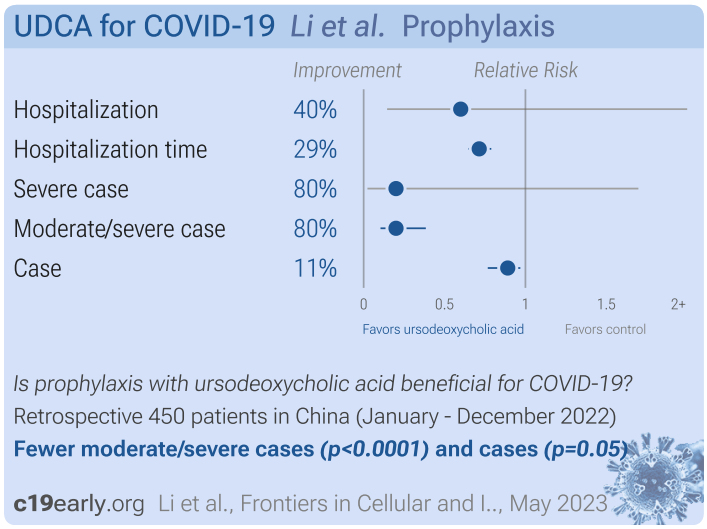
Gao: Retrospective 393 hospitalized patients with hematologic disorders in China, showing lower risk of COVID-19 with UDCA use.

John



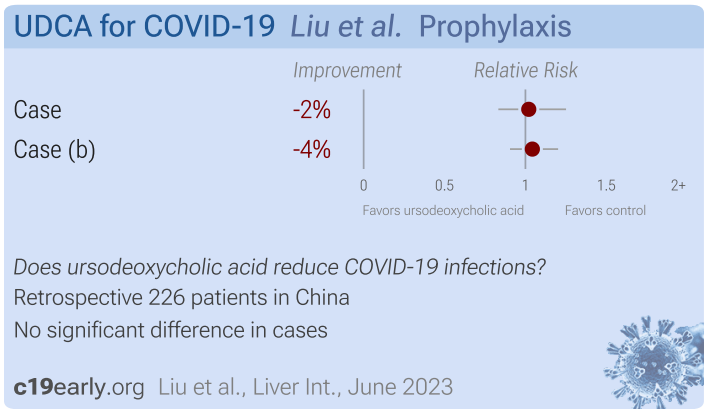
John: Retrospective 3,214 veterans with cirrhosis comparing 1,607 participants taking ursodeoxycholic acid (UDCA) to 1,607 propensity score matched controls not taking UDCA. UDCA use was associated with significantly lower odds of SARS-CoV-2 infection (aOR 0.54), symptomatic COVID-19 (aOR 0.54), moderate or worse COVID-19 (aOR 0.51), and severe/critical COVID-19 (aOR 0.48). While retrospective, the results suggest UDCA may reduce COVID-19 susceptibility and severity in patients with cirrhosis through downregulation of ACE2 receptors.

Li



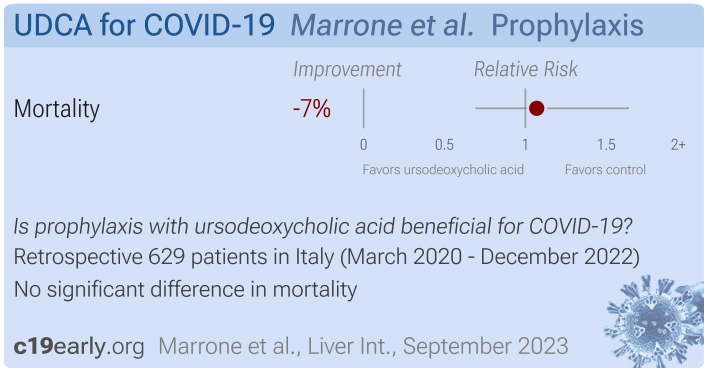
Li: Retrospective propensity score matched cohort study of 225 chronic liver disease patients on UDCA therapy matched to 225 controls without UDCA in China. UDCA use was associated with lower COVID-19 infection rate (85% vs 94%), lower maximum temperature, less severe symptoms, shorter recovery time (5 vs 7 days median), and lower risk of infection on regression (OR 0.32). The results rely on patient self-report rather than lab confirmed COVID-19 diagnosis.

Liu



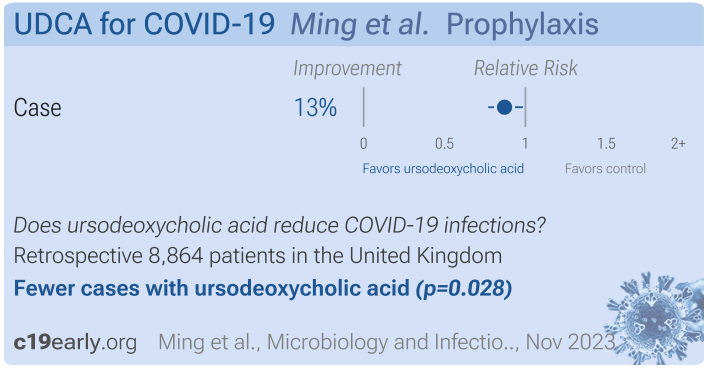
Liu: Retrospective 280 Chinese families with children previously seen in a liver clinic assessing whether ursodeoxycholic acid (UDCA) reduced SARS-CoV-2 infection risk. Among infected families, the study found no significant difference in confirmed or suspected SARS-CoV-2 infections between children taking UDCA (80.9%) and those not taking it (77.6%) (p=0.843).

Marrone



Marrone: PSM retrospective 629 hospitalized COVID-19 patients showing no significant difference in survival between 108 patients taking UDCA prior to infection compared to 521 matched controls not taking the drug. The lack of observed benefit in this retrospective inpatient cohort does not preclude potential protective effects of UDCA against infection or illness severe enough to require hospitalization.

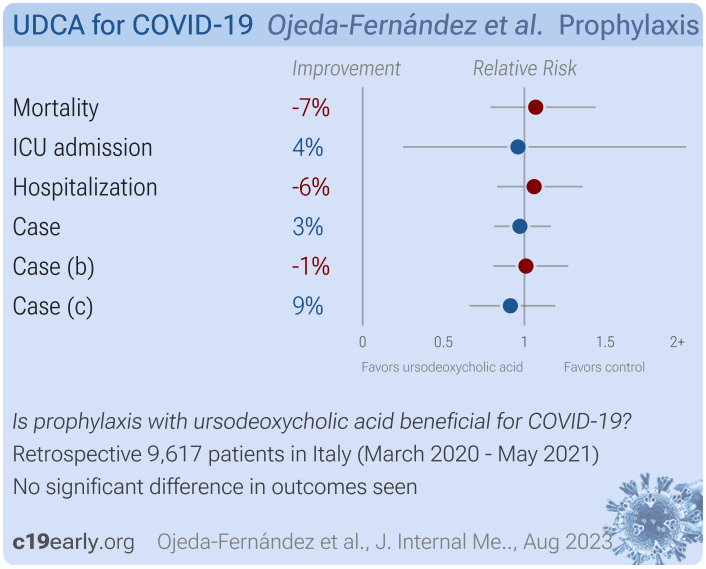
Ming



Ming: Retrospective 8,964 primary care patients prescribed ursodeoxycholic acid (UDCA) in the UK. Higher categorized UDCA adherence (≥80%) was associated with lower COVID-19 incidence (OR 0.86), whereas adherence as a continuous variable was not significant. However, adherence was measured indirectly via prescription records

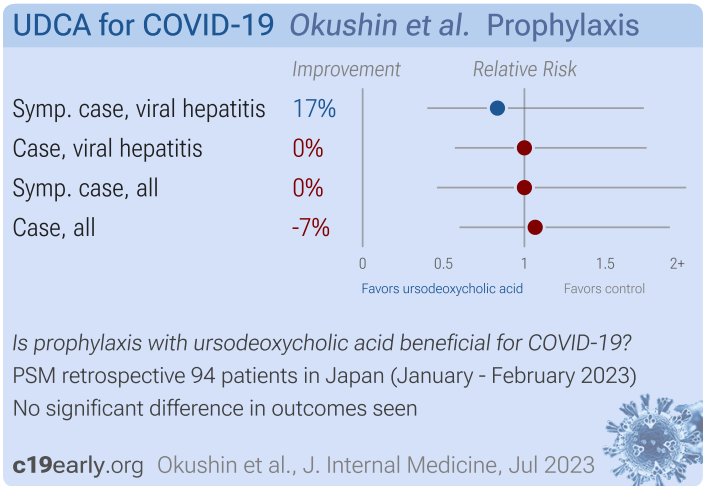
which may not reflect actual usage. Additionally, more adherent patients may differ systematically on unmeasured confounders (e.g., health behaviors) that influence COVID-19 risk.

Ojeda-Fernández

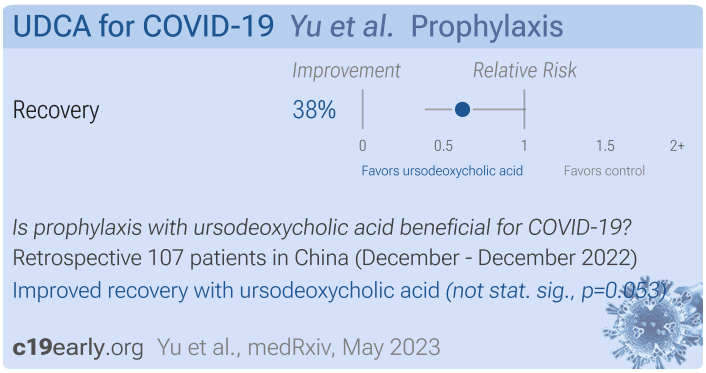


Ojeda-Fernández: Retrospective cohort study of 9,617 patients with liver disease in Italy, divided into UDCA users and non-users. UDCA exposure was not associated with reduced SARS-CoV-2 infection or improved COVID-19 outcomes including death, hospitalization, and ICU admission in this unvaccinated cohort. The large sample size provides power, but administrative data limitations include lack of important confounders like BMI and hypertension.

Okushin



Okushin: Retrospective 94 outpatients attending a university hospital gastroenterology clinic in Japan showing no significant difference in SARS-CoV-2 infection rates between ursodeoxycholic acid (UDCA)-treated patients and control groups without UDCA treatment. However, UDCA-treated patients tended to have higher rates of subclinical infection based on serology, suggesting UDCA may reduce COVID-19 severity.



Yu: Retrospective 115 COVID-19 patients hospitalized during an Omicron outbreak in China, of which 65 received ursodeoxycholic acid (UDCA) treatment and 50 received standard care. It found that UDCA was associated with faster body temperature recovery, with a hazard ratio of 1.62 (95% CI 0.99-2.60, p=0.053) compared to standard care after adjusting for covariates. Patients receiving higher UDCA doses (≥300mg daily) had significantly faster recovery than the standard care group, with a hazard ratio of 1.82 (95% CI 1.07-3.10, p=0.028). To further analyze the exposure-response relationship, the authors developed an AI model called VirtualBody that accurately predicted individualized UDCA pharmacokinetic profiles. Additional analysis using VirtualBody-generated data found UDCA AUC, indicating total exposure over time, had a stronger correlation with clinical outcome than cumulative dose. Overall, the study suggests UDCA may shorten recovery time from COVID-19, especially at higher doses, warranting further investigation.

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 ursodeoxycholic acid 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 ursodeoxycholic acid for COVID-19 that report a comparison with a control group are included in the main analysis. This is a living analysis and is updated regularly.

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

of the correction factors equal to 1 [Sweeting]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.20.0).

Forest plots are computed using PythonMeta [Deng] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.1.2) using the metafor (3.0-2) and rms (6.2-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

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

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

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

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.

Brevini, 12/5/2022, retrospective, United Kingdom, peer-reviewed, 80 authors.	risk of death, 94.4% lower, RR 0.06, *p* = 0.13, treatment 0 of 31 (0.0%), control 14 of 155 (9.0%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching.
	risk of mechanical ventilation, 66.7% lower, RR 0.33, *p* = 0.48, treatment 1 of 31 (3.2%), control 15 of 155 (9.7%), NNT 16, propensity score matching.
	risk of ICU admission, 75.0% lower, RR 0.25, *p* = 0.21, treatment 1 of 31 (3.2%), control 20 of 155 (12.9%), NNT 10, propensity score matching.
	risk of hospitalization, 39.6% lower, RR 0.60, *p* = 0.03, treatment 11 of 31 (35.5%), control 91 of 155 (58.7%), NNT 4.3, propensity score matching.
Corpechot, 1/19/2024, retrospective, France, peer-reviewed, 5 authors, study period 1 March, 2020 - 31 December, 2020.	risk of death, 54.0% higher, RR 1.54, *p* = 0.45, treatment 3 of 1,322 (0.2%), control 13 of 8,825 (0.1%).
	risk of ICU admission, 19.1% lower, RR 0.81, *p* = 1.00, treatment 4 of 1,322 (0.3%), control 33 of 8,825 (0.4%), NNT 1401.

	risk of hospitalization, 40.2% lower, RR 0.60, p = 0.17, treatment 1,322, control 8,825, combination of cohort and case control analyses.
	risk of hospitalization, 51.8% lower, RR 0.48, p = 0.11, treatment 6 of 1,322 (0.5%), control 80 of 8,825 (0.9%), NNT 221, adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of hospitalization, 7.0% lower, OR 0.93, p = 0.92, treatment 7 of 88 (8.0%) cases, 58 of 840 (6.9%) controls, adjusted per study, case control OR.
Costello, 12/13/2023, retrospective, United Kingdom, preprint, 16 authors, study period 1 March, 2020 - 31 December, 2022.	**risk of death, 24.0% lower, HR 0.76, p = 0.13**, treatment 7,225, control 4,080.
	risk of hospitalization, 19.0% lower, HR 0.81, p = 0.02, treatment 7,225, control 4,080.
	risk of death/hospitalization, 21.0% lower, HR 0.79, p = 0.005, treatment 7,225, control 4,080.
Gao, 11/28/2023, retrospective, China, peer-reviewed, 5 authors, study period December 2022 - January 2023.	**risk of case, 12.1% lower, RR 0.88, p = 0.03**, treatment 114 of 163 (69.9%), control 183 of 230 (79.6%), NNT 10, odds ratio converted to relative risk.
John, 4/5/2023, retrospective, USA, peer-reviewed, 15 authors.	**risk of case, 46.0% lower, OR 0.54, p < 0.001**, treatment 1,607, control 1,607, RR approximated with OR.
Li, 5/3/2023, retrospective, China, peer-reviewed, mean age 53.0, 5 authors, study period January 2022 - December 2022.	**risk of hospitalization, 40.0% lower, RR 0.60, p = 0.72**, treatment 3 of 225 (1.3%), control 5 of 225 (2.2%), NNT 112.
	hospitalization time, 28.6% lower, relative time 0.71, p < 0.001, treatment median 5.0 IQR 3.0 n=225, control median 7.0 IQR 3.0 n=225.
	risk of severe case, 80.0% lower, RR 0.20, p = 0.22, treatment 1 of 225 (0.4%), control 5 of 225 (2.2%), NNT 56.
	risk of moderate/severe case, 80.0% lower, RR 0.20, p < 0.001, treatment 10 of 225 (4.4%), control 50 of 225 (22.2%), NNT 5.6.
	risk of case, 10.9% lower, RR 0.89, p = 0.05, treatment 192 of 225 (85.3%), control 212 of 225 (94.2%), NNT 11, odds ratio converted to relative risk, propensity score matching.
Liu, 6/29/2023, retrospective, China, peer-reviewed, survey, 2 authors.	**risk of case, 2.1% higher, RR 1.02, p = 0.88**, treatment 95 of 146 (65.1%), control 51 of 80 (63.7%), confirmed.
	risk of case, 4.3% higher, RR 1.04, p = 0.61, treatment 118 of 146 (80.8%), control 62 of 80 (77.5%), confirmed + suspected.
Marrone, 9/21/2023, retrospective, Italy, peer-reviewed, 10 authors, study period 1 March, 2020 - 31 December, 2022.	**risk of death, 7.0% higher, HR 1.07, p = 0.77**, treatment 26 of 108 (24.1%), control 118 of 521 (22.6%), adjusted per study, multivariable, Cox proportional hazards.

Ming, 11/16/2023, retrospective, United Kingdom, peer-reviewed, 3 authors, high vs. low.	risk of case, 12.9% lower, RR 0.87, $p = 0.03$, treatment 185 of 3,804 (4.9%), control 297 of 5,060 (5.9%), NNT 99, odds ratio converted to relative risk, high vs. low adherence.
Ojeda-Fernández, 8/22/2023, retrospective, Italy, peer-reviewed, 11 authors, study period 1 March, 2020 - 31 May, 2021, trial NCT05659654 (history).	risk of death, 7.0% higher, HR 1.07, $p = 0.67$, treatment 54 of 219 (24.7%), control 259 of 1,141 (22.7%), adjusted per study, multivariable, Cox proportional hazards.
	risk of ICU admission, 4.0% lower, HR 0.96, $p = 0.96$, treatment 3 of 219 (1.4%), control 15 of 1,141 (1.3%), adjusted per study, multivariable, Cox proportional hazards.
	risk of hospitalization, 6.0% higher, HR 1.06, $p = 0.66$, treatment 77 of 219 (35.2%), control 393 of 1,141 (34.4%), adjusted per study, multivariable, Cox proportional hazards.
	risk of case, 2.8% lower, OR 0.97, $p = 0.77$, wave 1 and wave 2 combined, RR approximated with OR.
	risk of case, 0.9% higher, RR 1.01, $p = 0.94$, treatment 83 of 1,687 (4.9%), control 399 of 7,930 (5.0%), NNT 896, odds ratio converted to relative risk, wave 1.
	risk of case, 8.7% lower, RR 0.91, $p = 0.56$, treatment 43 of 1,125 (3.8%), control 273 of 6,731 (4.1%), NNT 428, odds ratio converted to relative risk, wave 2.
Okushin, 7/27/2023, retrospective, Japan, peer-reviewed, 7 authors, study period 1 January, 2023 - 10 February, 2023.	risk of symptomatic case, 16.7% lower, RR 0.83, $p = 0.81$, treatment 10 of 47 (21.3%), control 12 of 47 (25.5%), NNT 24, viral hepatitis, propensity score matching.
	risk of case, no change, RR 1.00, $p = 1.00$, treatment 16 of 47 (34.0%), control 16 of 47 (34.0%), viral hepatitis, propensity score matching.
	risk of symptomatic case, no change, RR 1.00, $p = 1.00$, treatment 10 of 47 (21.3%), control 10 of 47 (21.3%), all, propensity score matching.
	risk of case, 6.7% higher, RR 1.07, $p = 1.00$, treatment 16 of 47 (34.0%), control 15 of 47 (31.9%), all, propensity score matching.
Yu, 5/4/2023, retrospective, China, preprint, 11 authors, study period 10 December, 2022 - 30 December, 2022.	risk of no recovery, 38.3% lower, HR 0.62, $p = 0.05$, treatment 62, control 45, inverted to make HR<1 favor treatment.

Supplementary Data

Supplementary Data

Footnotes

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

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