Colchicine for COVID-19: real-time meta analysis of 51 studies

@CovidAnalysis, March 2024, Version 59
https://c19early.org/ometa.html

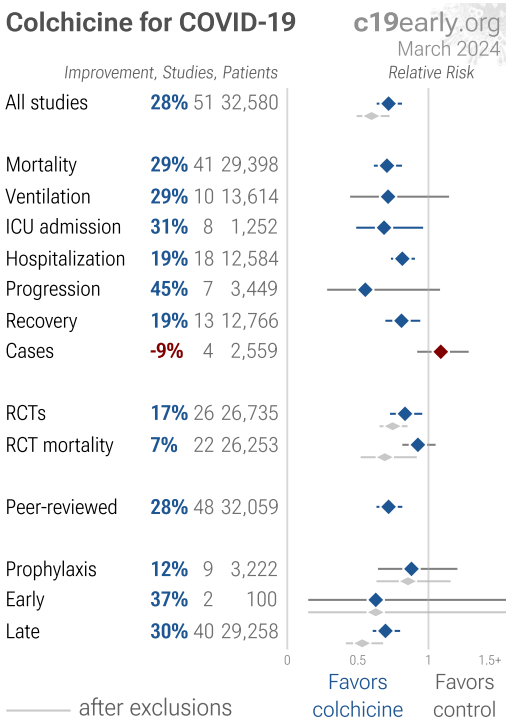
Abstract

Statistically significant lower risk is seen for mortality, ICU admission, hospitalization, and recovery. 26 studies from 26 independent teams in 15 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 28% [19-37%] lower risk. Results are similar for higher quality and peer-reviewed studies and worse for Randomized Controlled Trials. Clinical outcomes suggest benefit while viral and case outcomes do not, consistent with an intervention that aids the immune system or recovery but may have limited antiviral effects.

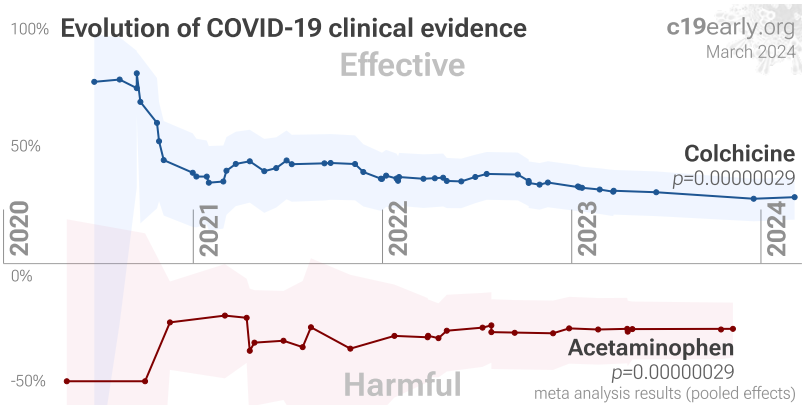
Results are robust — in exclusion sensitivity analysis 21 of 51 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

RCT results are less favorable, however they are dominated by the very late stage RECOVERY RCT which is not generalizable to earlier usage.



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 more effective.

All data to reproduce this paper and sources are in the appendix. Other meta analyses show significant improvements with colchicine for mortality *Danjuma, Elshafei, Elshiwy, Golpour, Lien, Rai, Salah, Zein*, oxygen therapy *Elshiwy*, hospitalization *Kow*, and severity *Yasmin*.



HIGHLIGHTS

Colchicine reduces risk for COVID-19 with very high confidence for mortality, hospitalization, recovery, and in pooled analysis, high confidence for ICU admission, low confidence for progression, and very low confidence for ventilation.

Colchicine was the 6th treatment shown effective with ≥3 clinical studies in September 2020, now with p = 0.00000029 from 51 studies.

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

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

51 colchicine COVID-19 studies

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March 2024

	Improvement	RR [CI]		Treatment	Control
Hunt	68%	0.32 [0.15-0.67]	death		
Hassan (RCT)	-40%	1.40 [0.48-4.12]	hosp.	7/50	5/50
Early treatment	37%	0.63 [0.15-2.65]		7/50	5/50
$Tau^2 = 0.88$, $I^2 = 81.1\%$, $p = 0.54$					
	Improvement	RR [CI]		Treatment	Control
Deftereos (RCT)	77%	0.23 [0.03-1.97]	death	1/55	4/50
Lopes (DB RCT)	80%	0.20 [0.01-4.03]	death	0/36	2/36
Brunetti (PSM)	73%	0.27 [0.08-0.89]	death	3/33	11/33
Scarsi	85%	0.15 [0.06-0.37]	death	122 (n)	140 (n)
Salehzadeh (RCT)	23%	0.77 [0.66-0.90]	hosp. time	50 (n)	50 (n)
Pinzón	35%	0.65 [0.34-1.21]	death	14/145	23/156
Sandhu	42%	0.58 [0.40-0.85]	death	16/34	63/78
Rodriguez-Nava	6%	0.94 [0.61-1.47]	death	16/52	85/261
Mahale	-7%	1.07 [0.59-1.96]	death	11/39	25/95
Valerio Pas.. (ICU)	23%	0.77 [0.31-1.94]	death	5/35	12/30
Tardif (DB RCT)	44%	0.56 [0.19-1.67]	death	5/2,235	9/2,253
Mareev	80%	0.20 [0.01-4.01]	death	0/21	2/22
García-Posada	57%	0.43 [0.16-0.84]	death	48/99	59/110
Manenti (PSW)	76%	0.24 [0.09-0.67]	death	71 (n)	70 (n)
Mostafaie (RCT)	83%	0.17 [0.02-1.34]	death	1/60	6/60
Recovery C.. (RCT)	-1%	1.01 [0.93-1.10]	death	1,173/5,610	1,190/5,730
Hueda-Zavaleta	54%	0.46 [0.23-0.91]	death	10/50	109/301
Kevorkian	96%	0.04 [0.01-0.21]	progression	28 (n)	40 (n)
Gaitán-Dua.. (RCT)	22%	0.78 [0.44-1.36]	death	22/153	28/161
Pascual-Fi.. (RCT)	80%	0.20 [0.01-4.03]	death	0/52	2/51
Dorward (RCT)	70%	0.30 [0.01-7.37]	death	0/156	1/120
Absalón-.. (DB RCT)	29%	0.71 [0.21-2.40]	death	4/56	6/60
Diaz (RCT)	12%	0.88 [0.70-1.12]	death	131/640	142/639
Alsultan (RCT)	36%	0.64 [0.20-2.07]	death	3/14	7/21
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Pourdowlat (RCT)	73%	0.27 [0.11-0.71]	hosp.	5/102	18/100
Gorial (RCT)	67%	0.33 [0.04-3.14]	death	1/80	3/80
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Sunil Naik (RCT)	-169%	2.69 [0.11-64.6]	death	1/62	0/43
Shah (RCT)	-75%	1.75 [0.53-5.83]	death	7/125	4/125
Villamañán	42%	0.58 [0.33-0.96]	death	19/111	32/111
Mehrizi	-13%	1.13 [1.08-1.19]	death	population-based cohort	
Vaziri (RCT)	81%	0.19 [0.04-0.88]	death	2/108	7/71
Late treatment	30%	0.70 [0.61-0.80]		1,814/14,289	2,165/14,969
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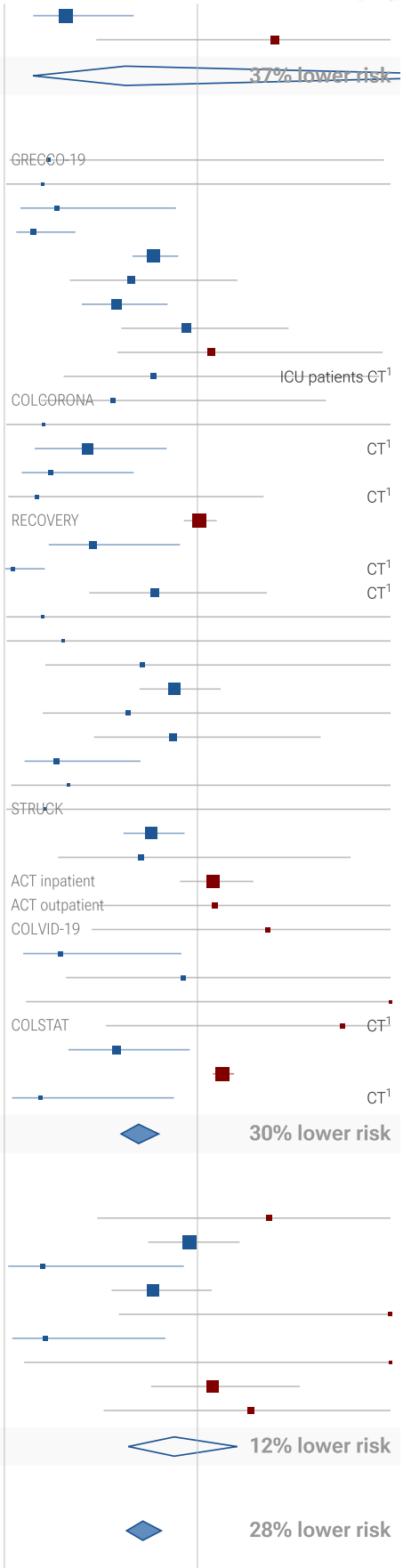
Topless	23%	0.77 [0.56-1.07]	death	population-based cohort	
Oztas	-406%	5.06 [0.59-43.2]	hosp.	5/635	1/643
Avanoglu Guler	79%	0.21 [0.04-0.83]	oxygen	6/66	3/7
Correa-Rodríguez	-150%	2.50 [0.10-60.6]	oxygen	1/163	0/81
Sáenz-Aldea	-8%	1.08 [0.76-1.53]	hosp.	case control	
Chevalier	-28%	1.28 [0.51-2.35]	death	5/21	111/569
Prophylaxis	12%	0.88 [0.64-1.21]		147/1,501	200/1,721
$Tau^2 = 0.09$, $I^2 = 53.4\%$, $p = 0.43$					
All studies	28%	0.72 [0.63-0.81]		1,968/15,840	2,370/16,740



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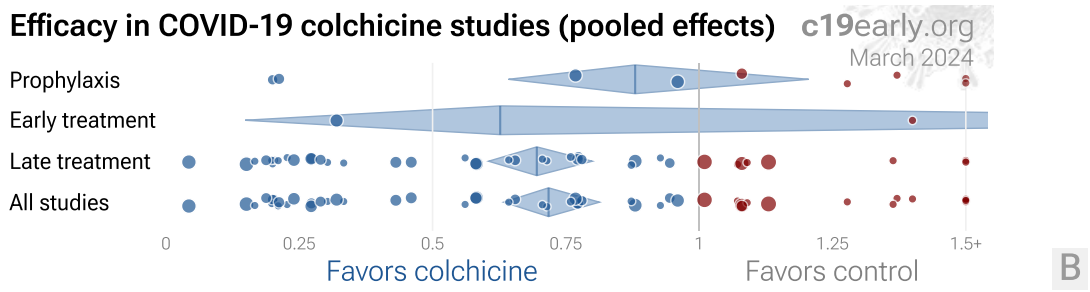

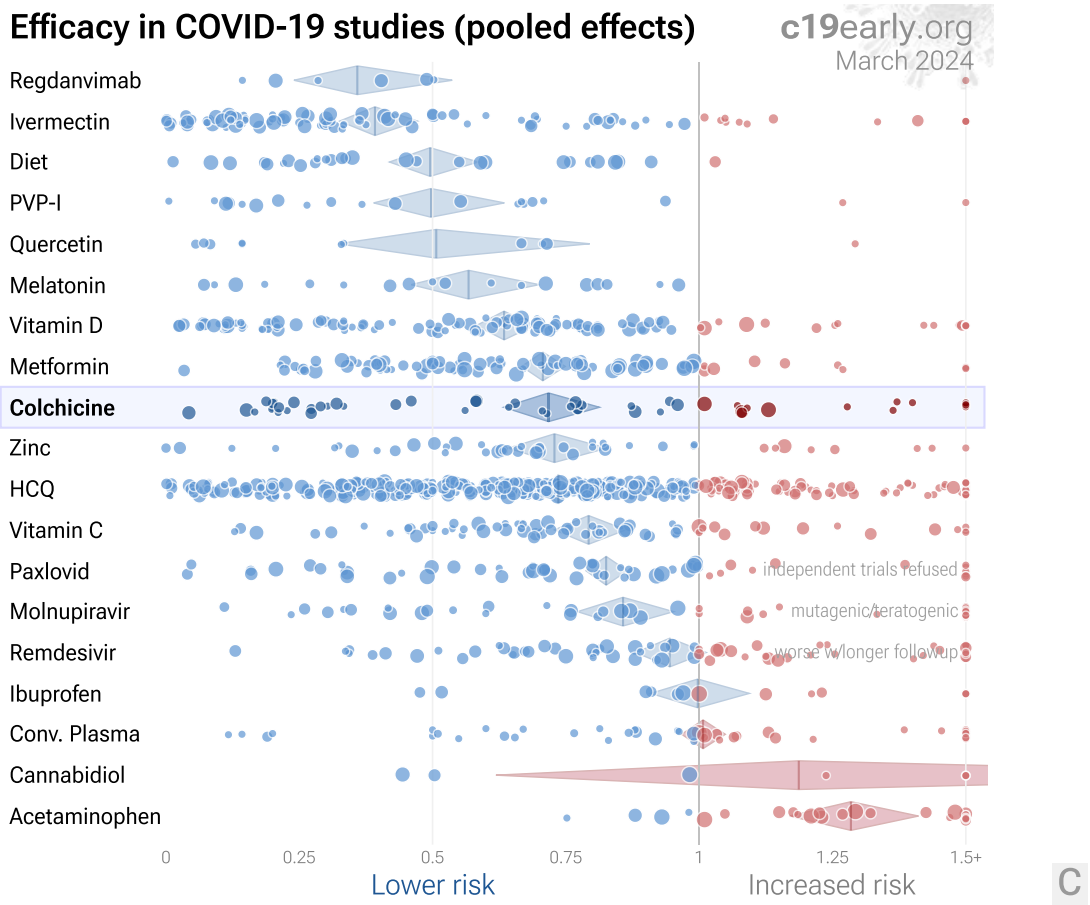

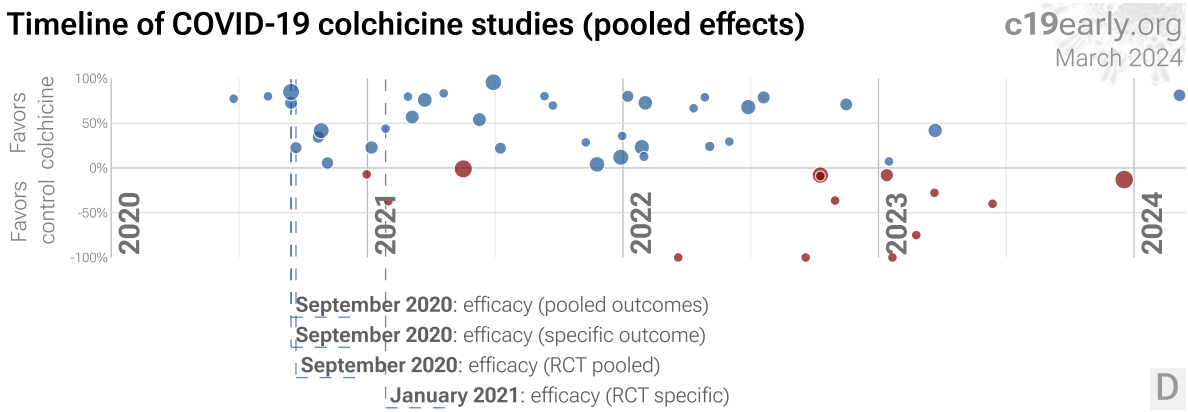

Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,960 proposed treatments show efficacy *c19early.org*. **D. Timeline of results in colchicine**

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 specific outcomes in RCTs was delayed by 4.2 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 issues *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 6,000 compounds may reduce COVID-19 risk *c19early.org (B)*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

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

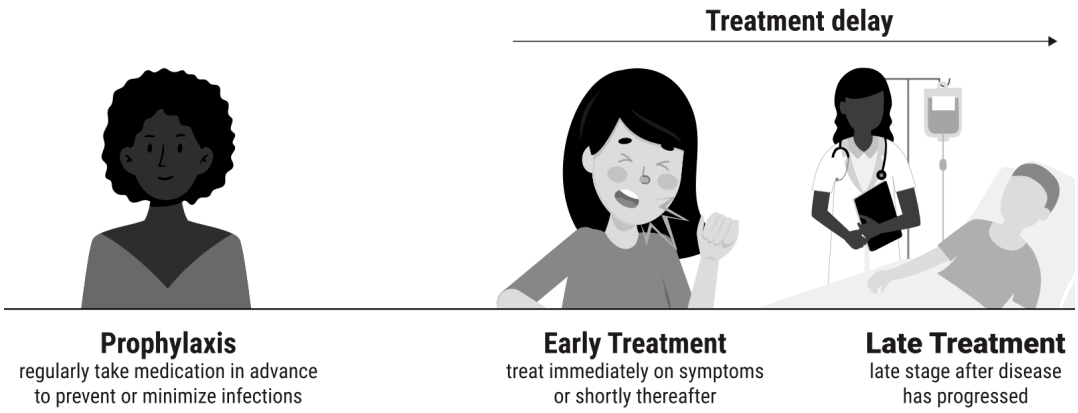

Figure 2. Treatment stages.

Mechanisms of Action

Table 1 shows potential mechanisms of action for the treatment of COVID-19 using colchicine.

Antiviral effects	Direct antiviral activity via inhibiting microtubule polymerization and viral entry.
Immunomodulatory effects	Potential prevention of an overactive immune response via modulation of immune cell functions, such as neutrophil chemotaxis, adhesion, and activation.
Anti-inflammatory effects	Reduction in inflammation and severity of cytokine storm via inibition of inflammasome activation and the release of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α.
Prevention of microvascular thrombosis	Reduction in the risk of clot formation via antithrombotic properties, such as inhibiting platelet aggregation.
Cardioprotective effects	Mitigation of myocardial injury via reduced myocardial inflammation and oxidative stress, and inhibition of NLRP3 inflammasomes.

Table 1. **Colchicine mechanisms of action.**

Results

Table 2 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, with different exclusions, and for specific outcomes. Table 3 shows results by treatment stage. Figure 3, 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, ventilation, ICU admission, hospitalization, progression, recovery, cases, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	28% [19-37%] ****	51	32,580	905
After exclusions	**40%** [28-51%] ****	41	14,780	647
Peer-reviewed studies	28% [19-37%] ****	48	32,059	889
Randomized Controlled Trials	**17%** [4-27%] **	26	26,735	587
RCTs after exclusions	25% [15-35%] ****	20	10,996	385
Mortality	29% [19-39%] ****	41	29,398	808
Ventilation	29% [-15-56%]	10	13,614	260
ICU admission	31% [4-51%] *	8	1,252	166
Hospitalization	**19%** [10-27%] ***	18	12,584	298
Recovery	**19%** [6-31%] **	13	12,766	175
Cases	-9% [-29-8%]	4	2,559	42
RCT mortality	**7%** [-5-19%]	22	26,253	557
RCT hospitalization	20% [10-30%] ***	11	9,470	205

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

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	37% [-165-85%]	30% [20-39%] ****	12% [-21-36%]
After exclusions	37% [-165-85%]	47% [32-59%] ****	14% [-16-37%]
Peer-reviewed studies	68% [33-85%] **	30% [19-39%] ****	12% [-21-36%]
Randomized Controlled Trials	-40% [-312-52%]	17% [5-28%] **	
RCTs after exclusions	-40% [-312-52%]	26% [16-35%] ****	
Mortality	68% [33-85%] **	28% [17-38%] ****	18% [-46-54%]
Ventilation		29% [-15-56%]	
ICU admission		31% [4-51%] *	
Hospitalization	-40% [-312-52%]	22% [13-29%] ****	-10% [-45-16%]
Recovery	4% [-37-32%]	22% [7-34%] **	7% [-70-49%]
Cases			-9% [-29-8%]
RCT mortality		7% [-5-19%]	
RCT hospitalization	-40% [-312-52%]	21% [10-30%] ***	

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

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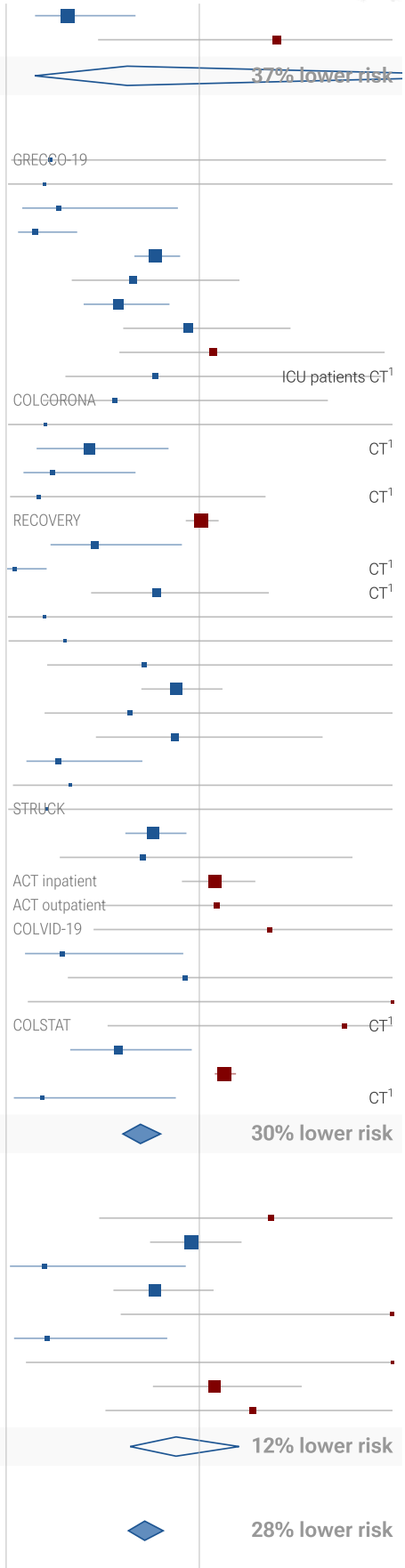

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Effect extraction pre-specified
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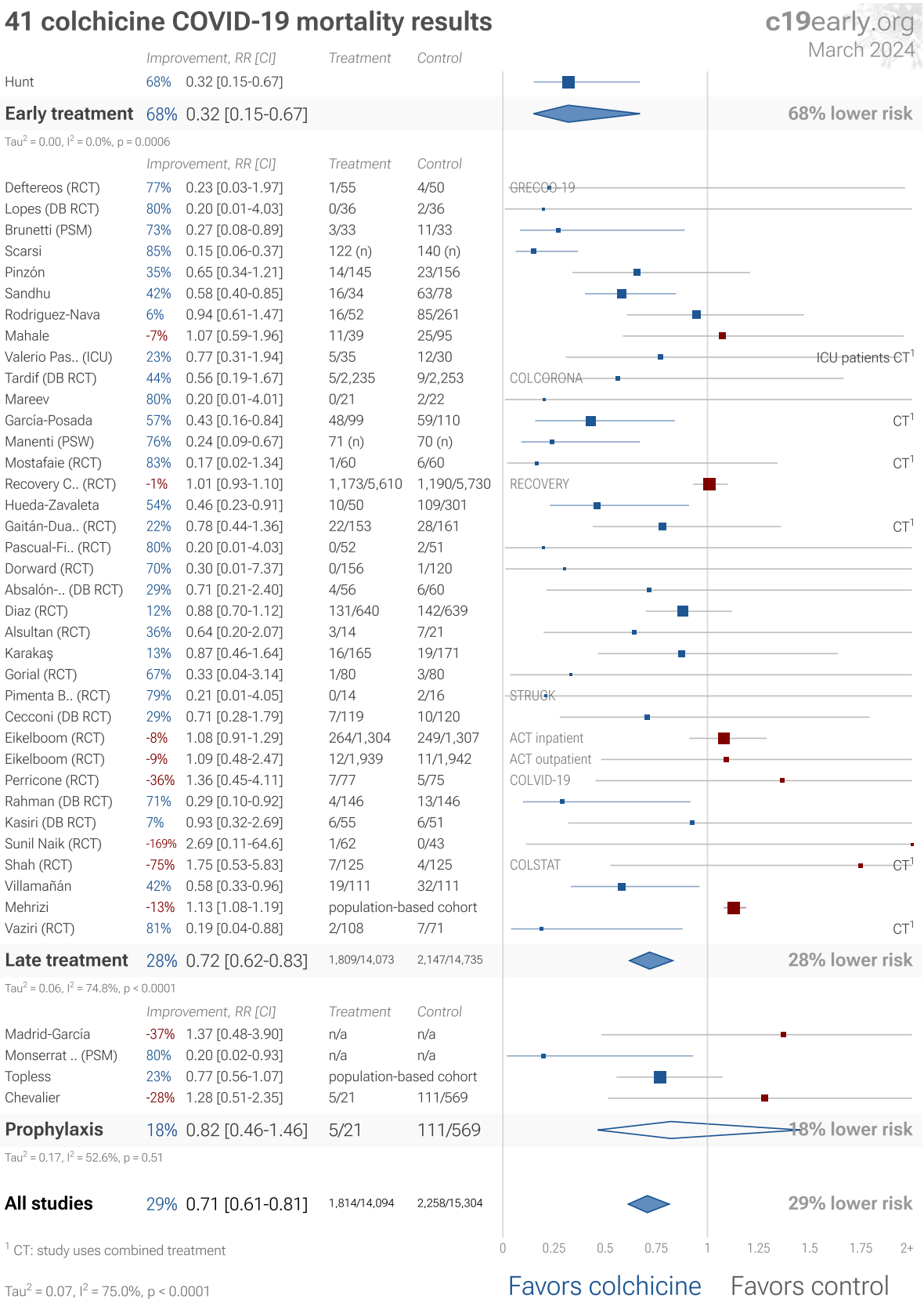


Figure 4. **Random effects meta-analysis for mortality results.**

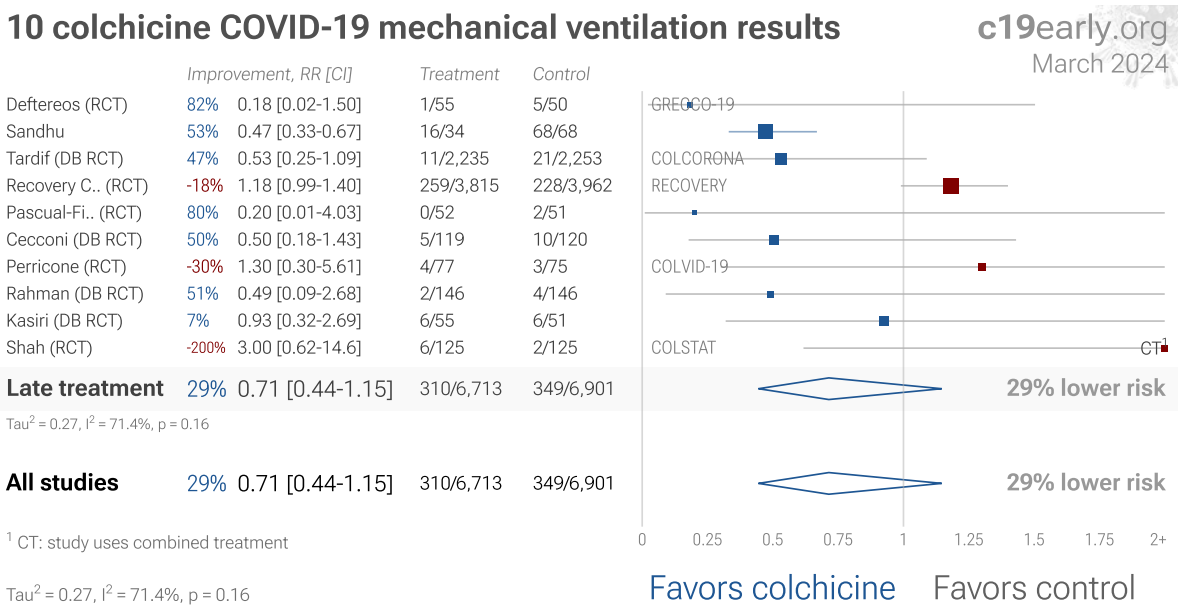


Figure 5. Random effects meta-analysis for ventilation.

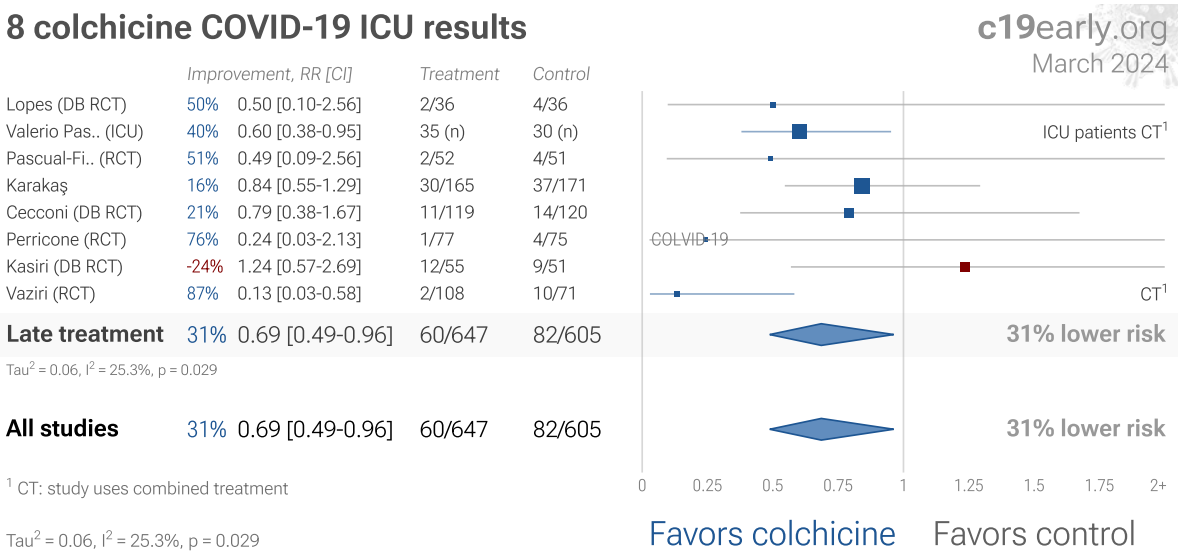


Figure 6. Random effects meta-analysis for ICU admission.

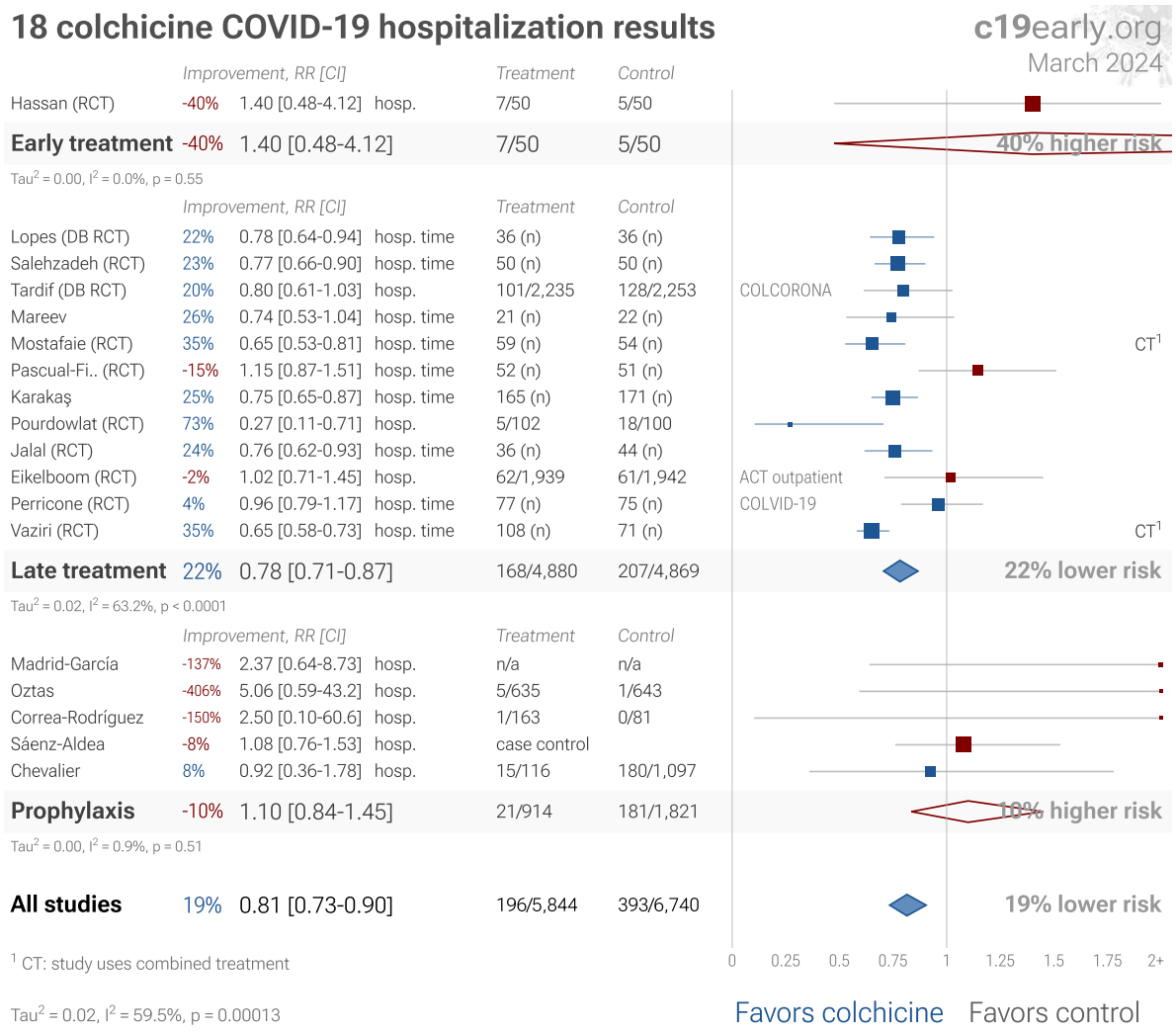


Figure 7. Random effects meta-analysis for hospitalization.

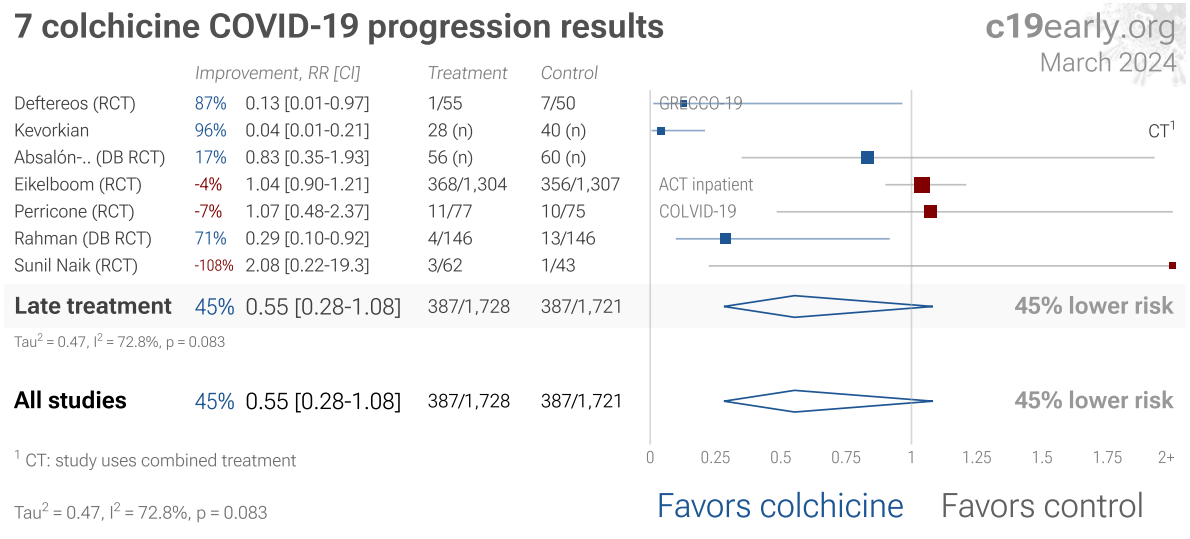


Figure 8. Random effects meta-analysis for progression.

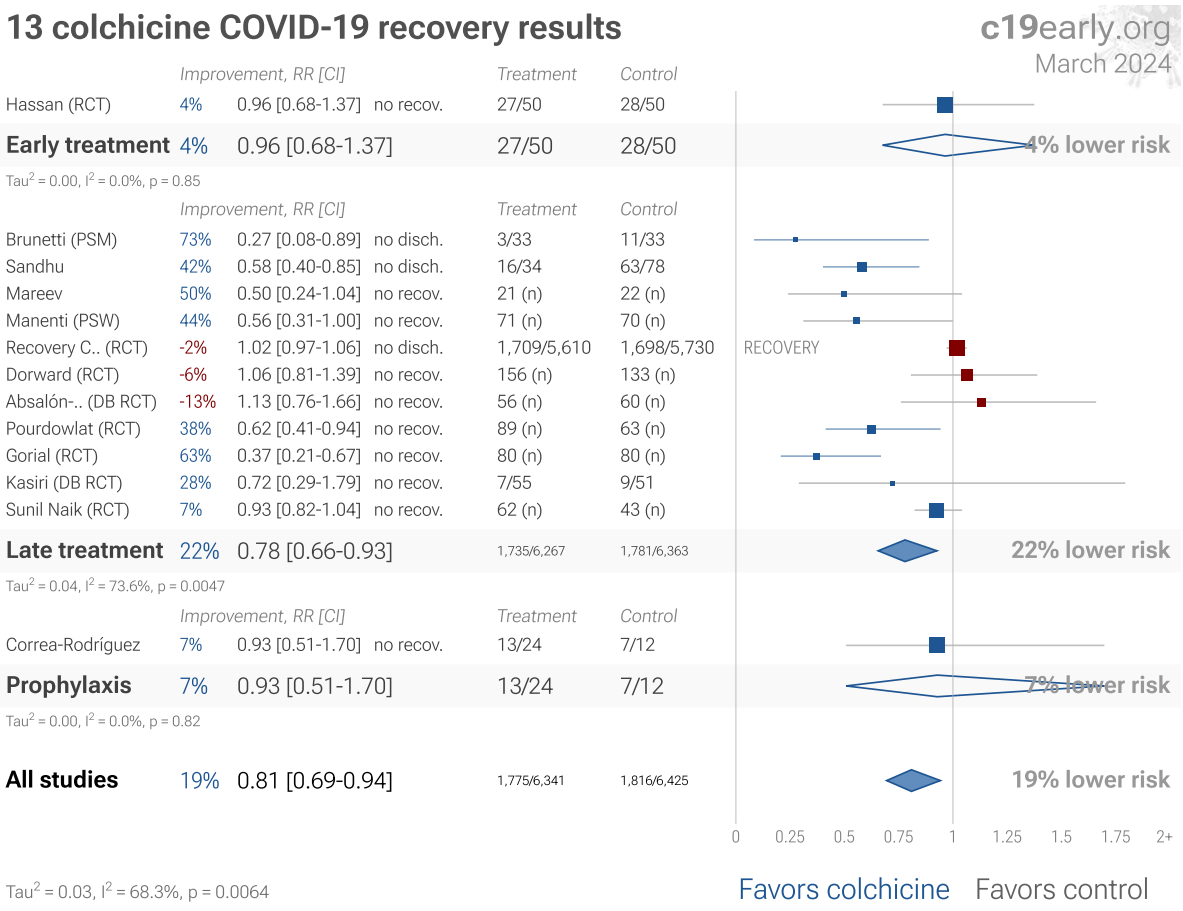


Figure 9. Random effects meta-analysis for recovery.

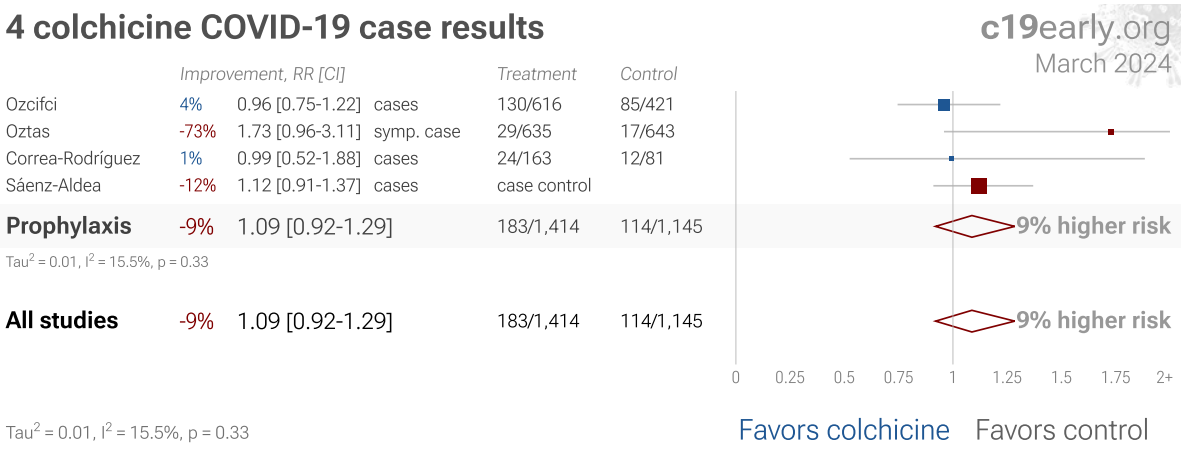


Figure 10. Random effects meta-analysis for cases.

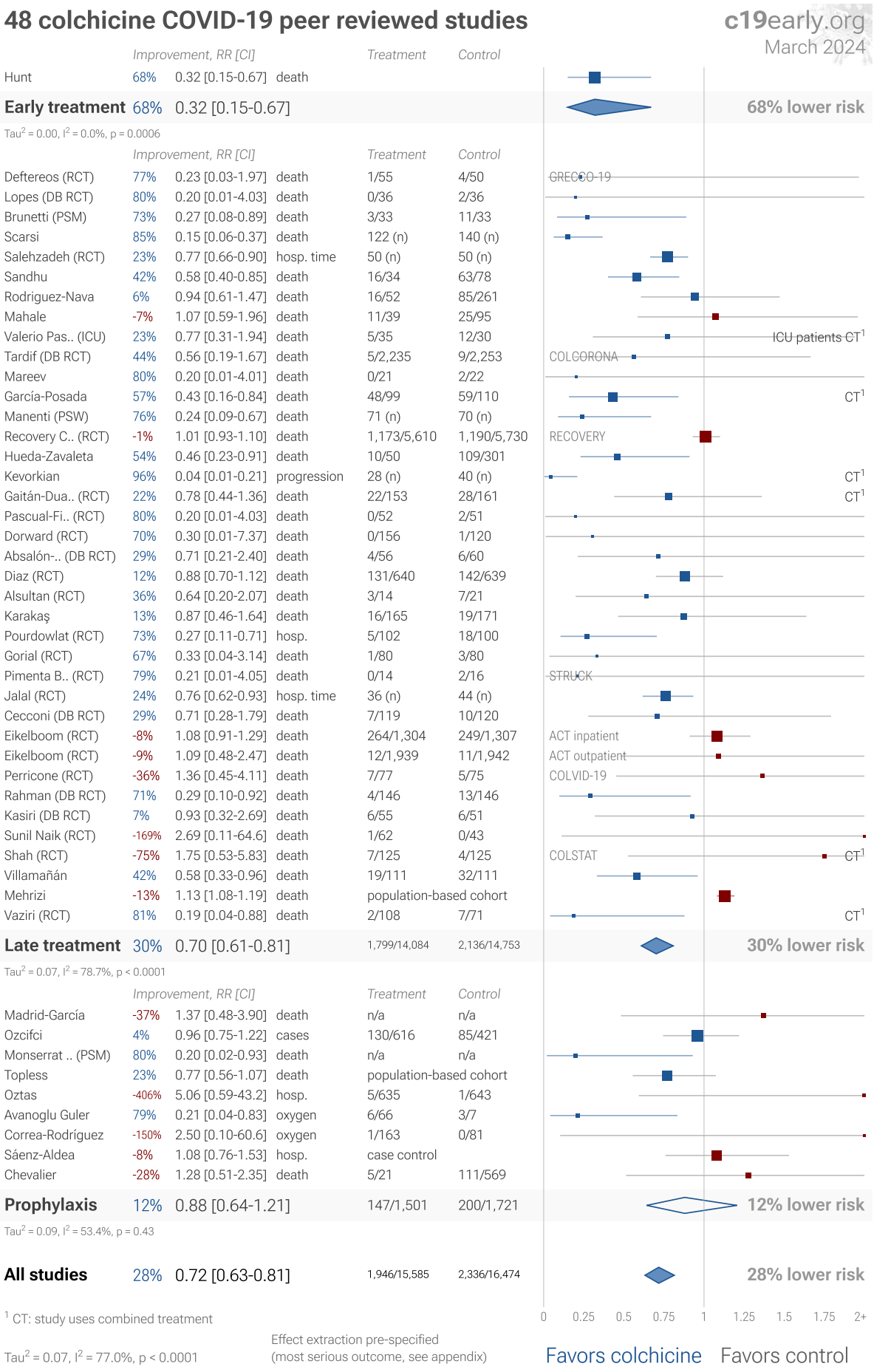


Figure 11. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant

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, 15, 16, and 17 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCTs after exclusions, RCT mortality results, RCT mortality results after exclusions, and RCT hospitalization results. RCT results are included in Table 2 and Table 3.

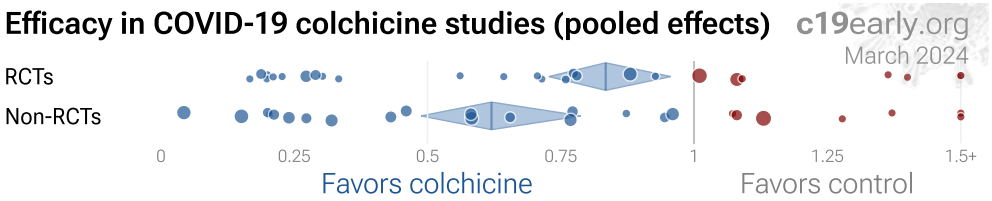


Figure 12. Results for RCTs and non-RCT studies.

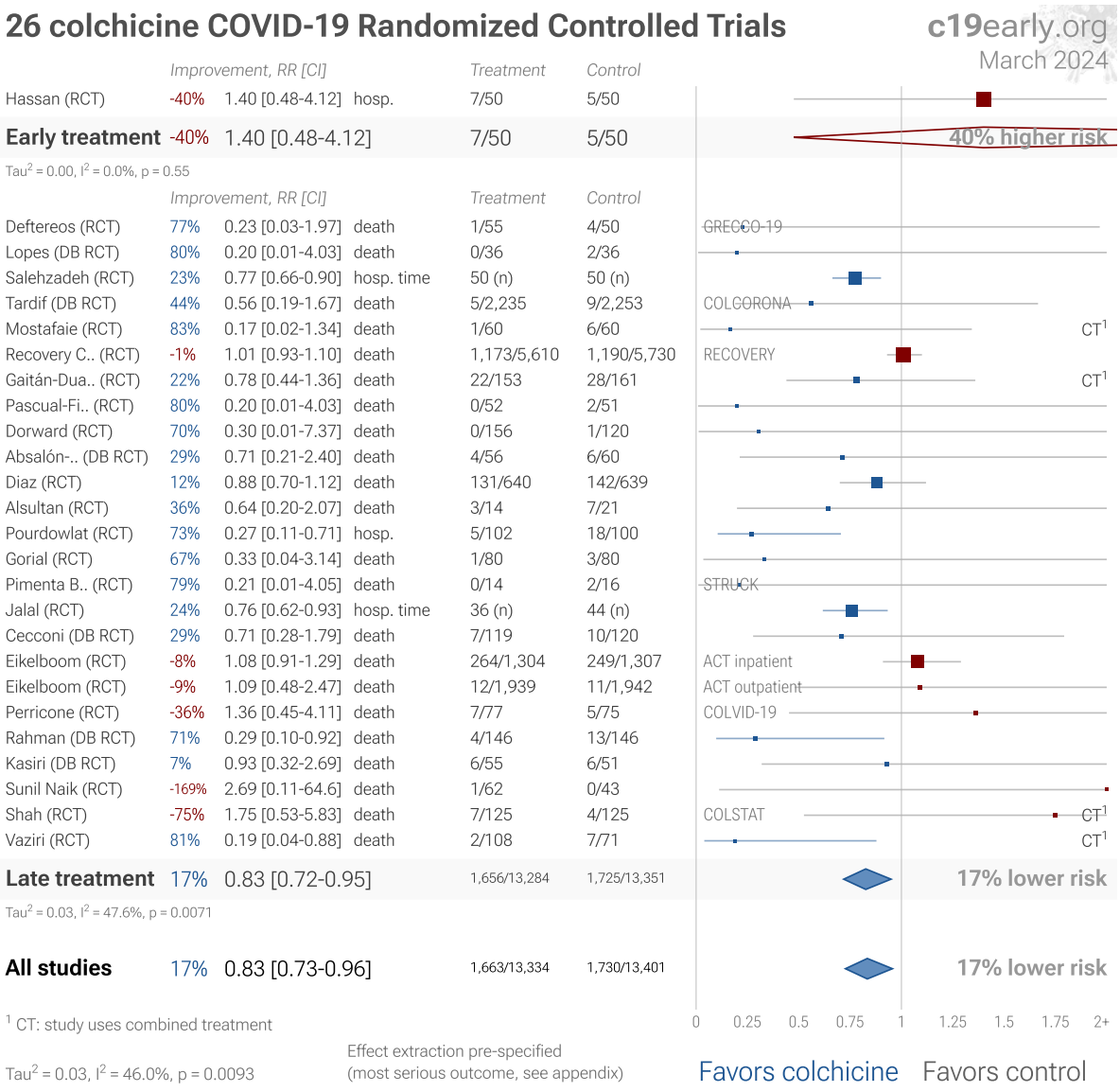


Figure 13. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

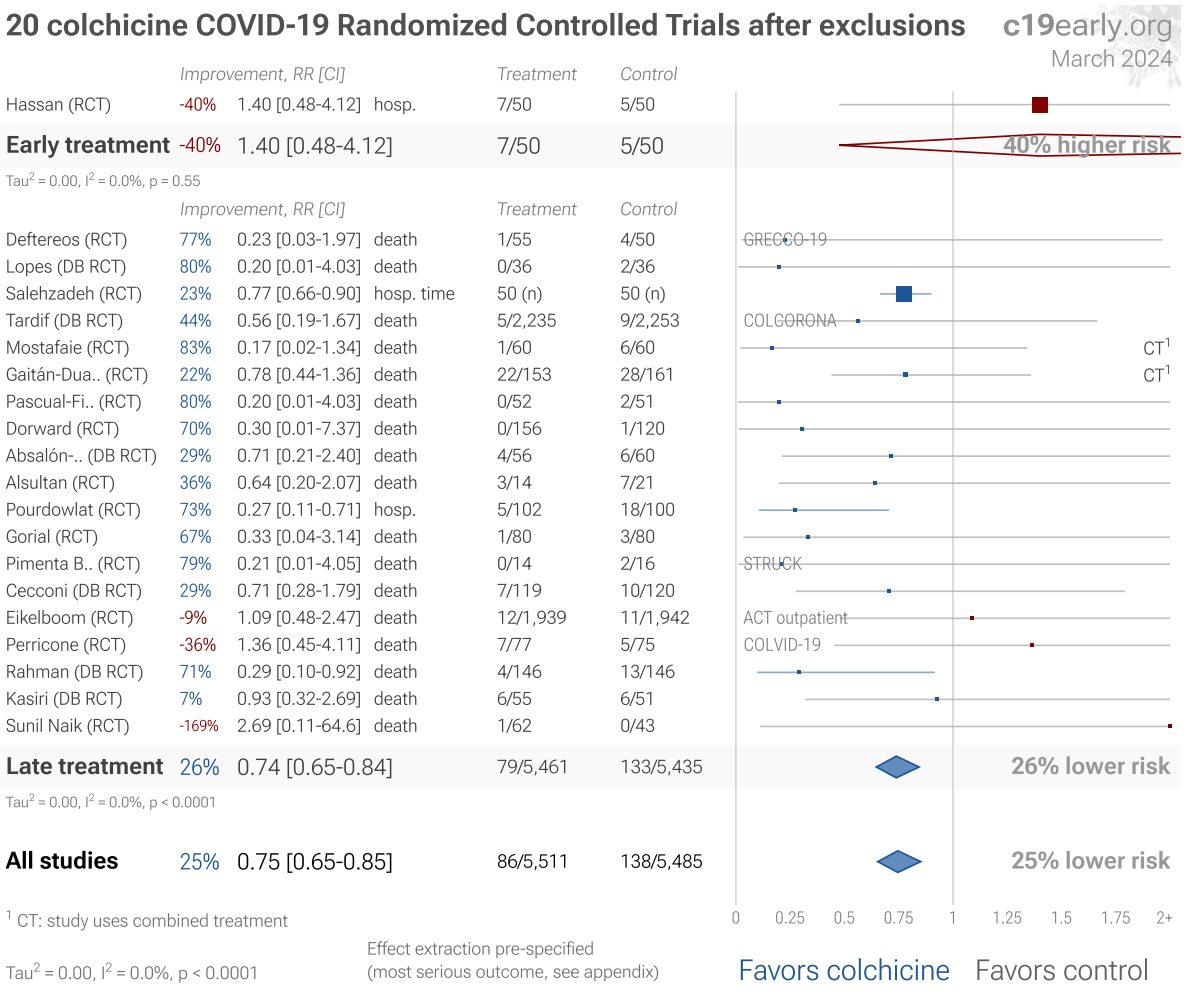


Figure 14. **Random effects meta-analysis for RCTs after exclusions.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

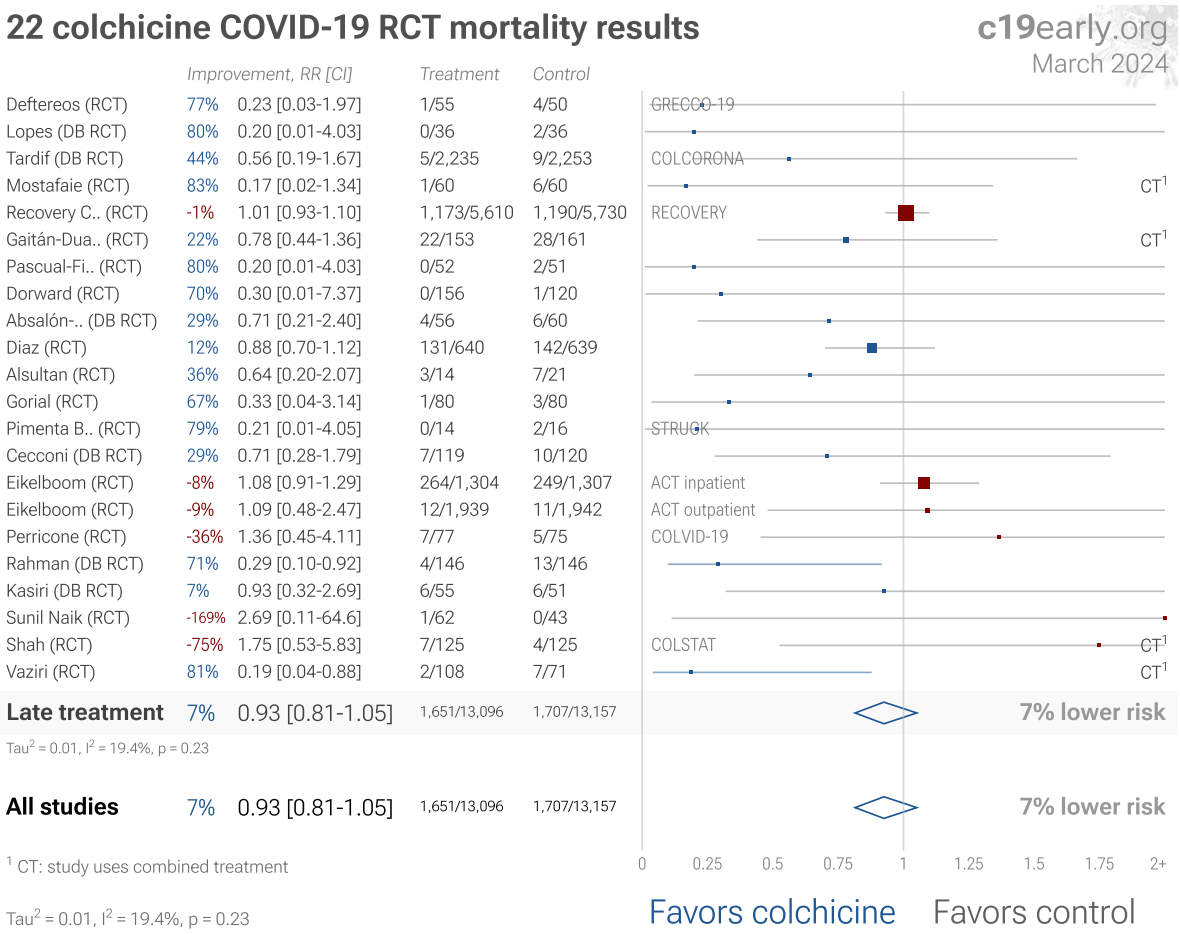


Figure 15. Random effects meta-analysis for RCT mortality results.

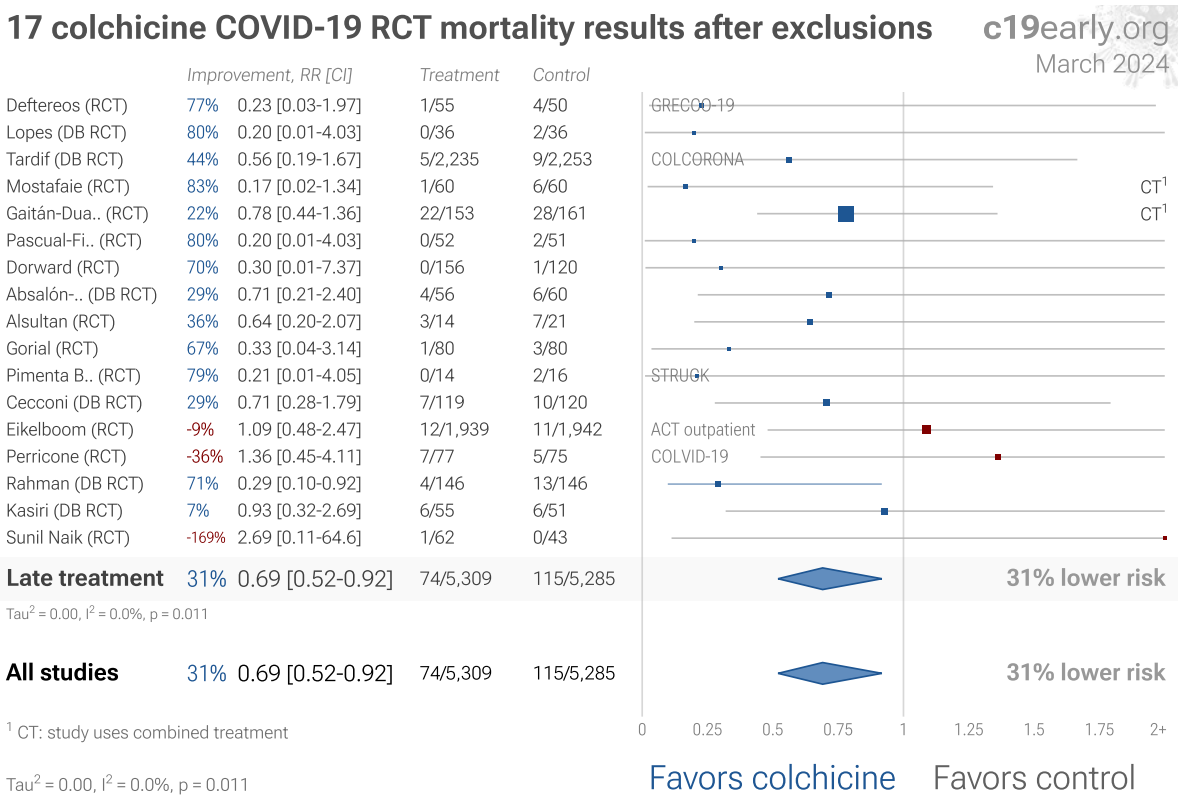


Figure 16. Random effects meta-analysis for RCT mortality results after exclusions.

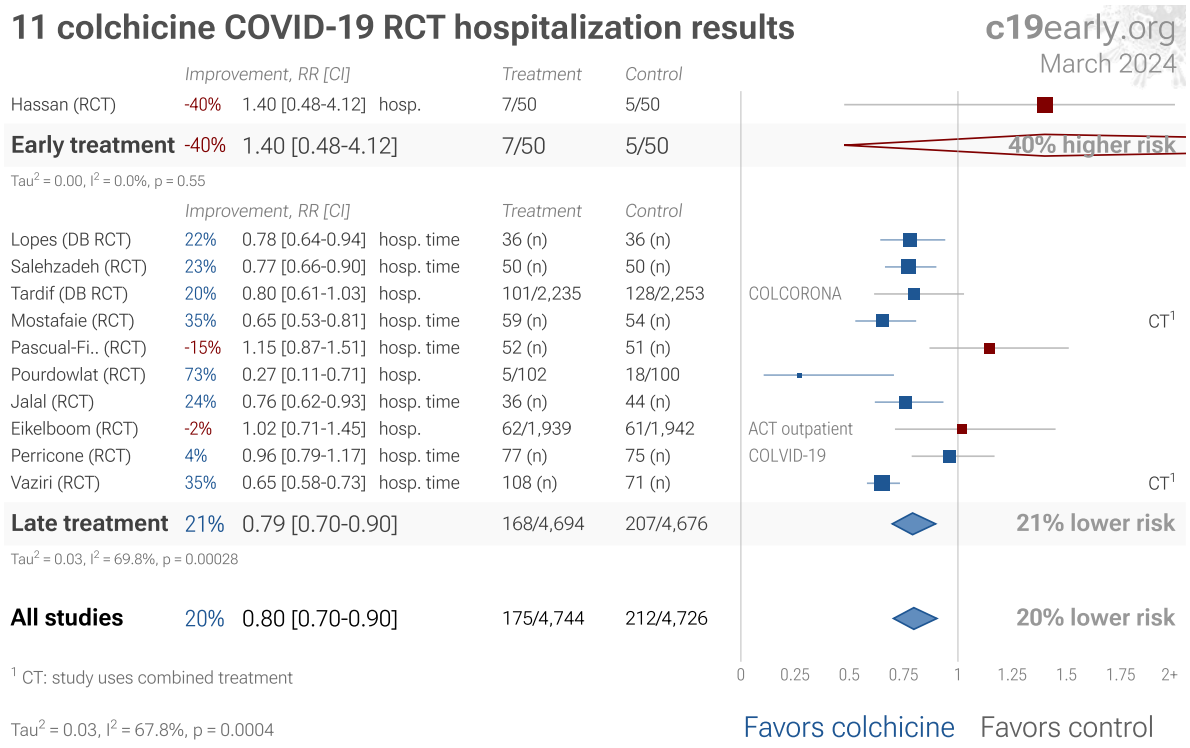


Figure 17. **Random effects meta-analysis for RCT hospitalization results.**

RCTs have many potential biases. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases *Jadad*, and analysis of double-blind RCTs has identified extreme levels of bias *Gøtzsche*. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, 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 66 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

RCT bias for widely available treatments. RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for colchicine are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT trials can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias 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 *Deaton, Nichol*.

Using all studies identifies efficacy 6+ months faster (7+ months for low-cost treatments). Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

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

Exclusions

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

The studies excluded are as below. Figure 18 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Diaz, very late stage, oxygen saturation <90% at baseline; very late stage, >80% on oxygen/ventilation at baseline.

Eikelboom, very late stage, oxygen saturation <90% at baseline.

Jalal, minimal details provided.

Karakaş, excessive unadjusted differences between groups.

Mahale, unadjusted results with no group details.

Oztas, excessive unadjusted differences between groups.

Recovery Collaborative Group, very late stage, 9 days since symptoms started, 32% baseline ventilation.

Rodriguez-Nava, substantial unadjusted confounding by indication likely; excessive unadjusted differences between groups; unadjusted results with no group details.

Shah, very late stage, >50% on oxygen/ventilation at baseline.

Vaziri, randomization resulted in significant baseline differences that were not adjusted for.

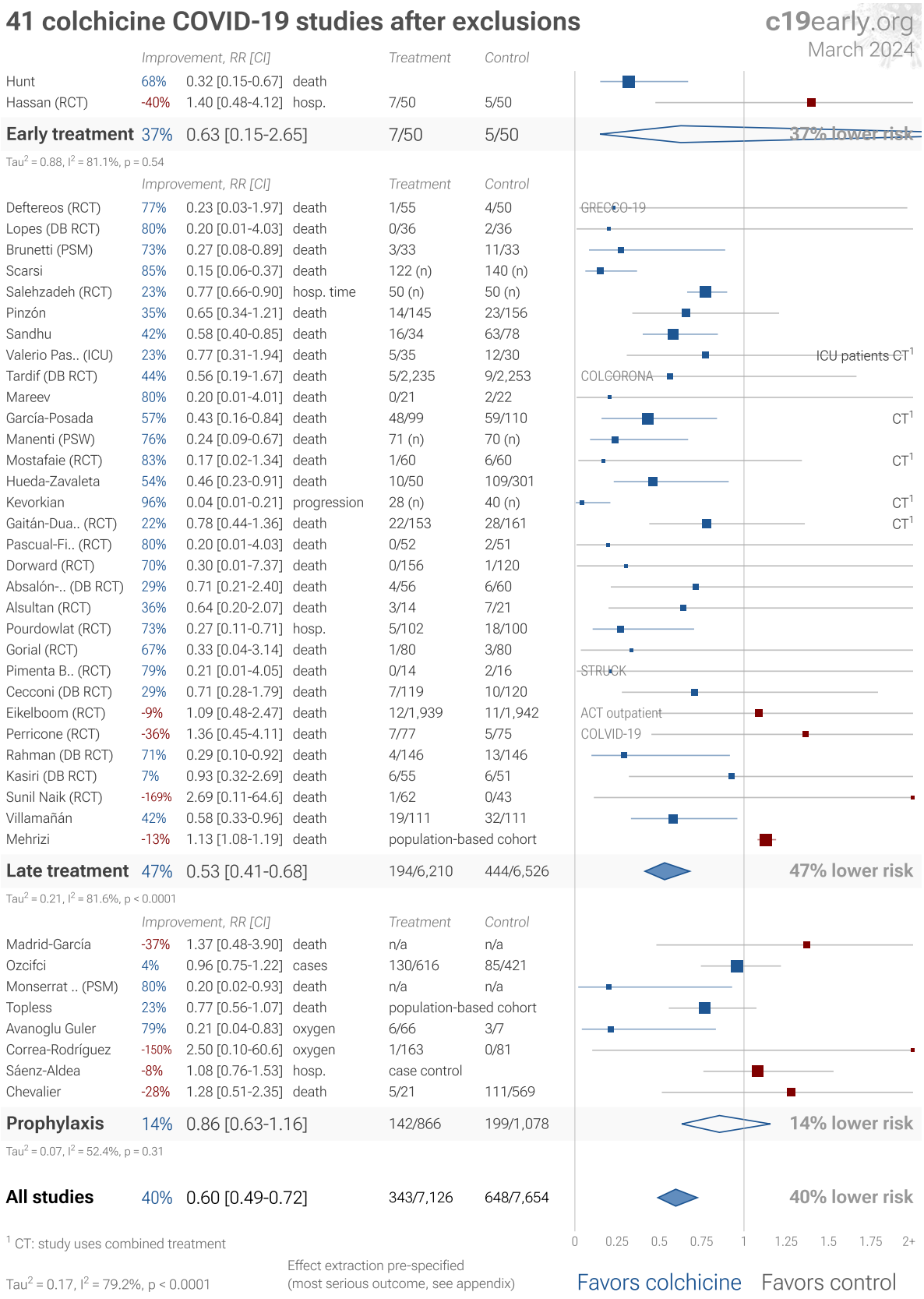


Figure 18. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours *McLean, Treanor*. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu 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 4. **Studies of baloxavir for influenza show that early treatment is more effective.**

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

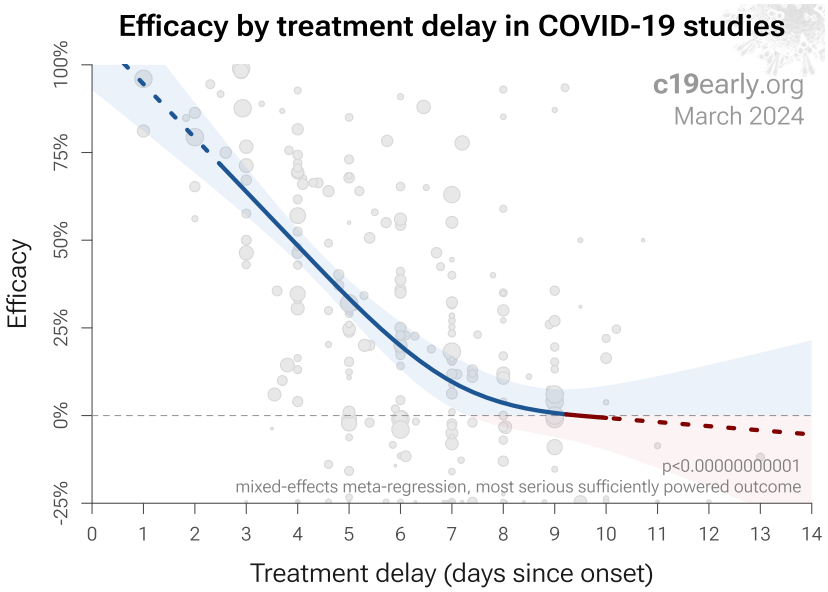


Figure 19. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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

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

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

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

Other treatments. The use of other treatments may significantly affect outcomes, including supplements, other medications, or other kinds of treatment 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.

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 20. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

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

Pooled outcomes identify efficacy 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 treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.7 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

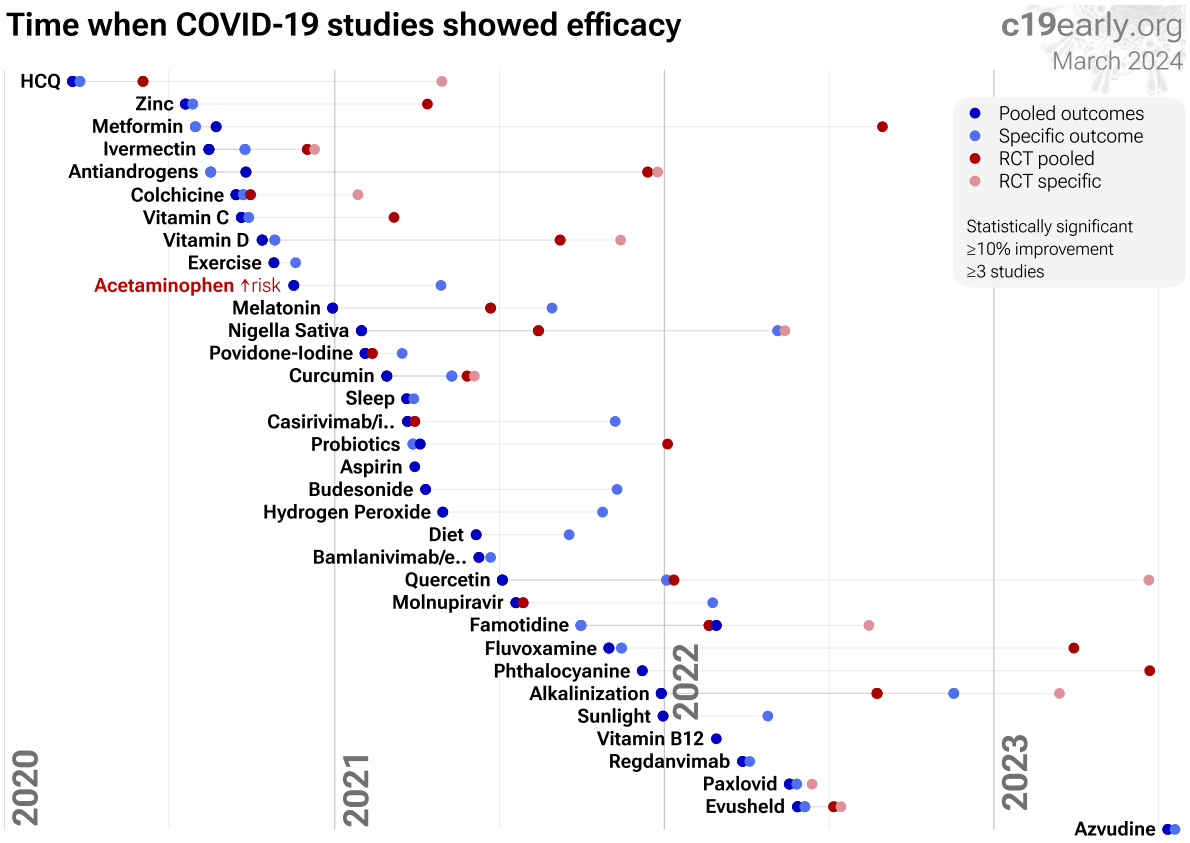


Figure 20. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting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

Meta analysis. The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

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

Discussion

Publication bias. Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguesso*.

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. 57% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 46% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 35% improvement, compared to 29% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.

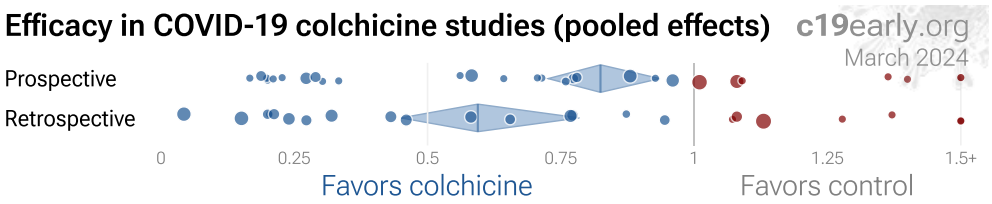


Figure 21. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 $p < 0.05$ *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.

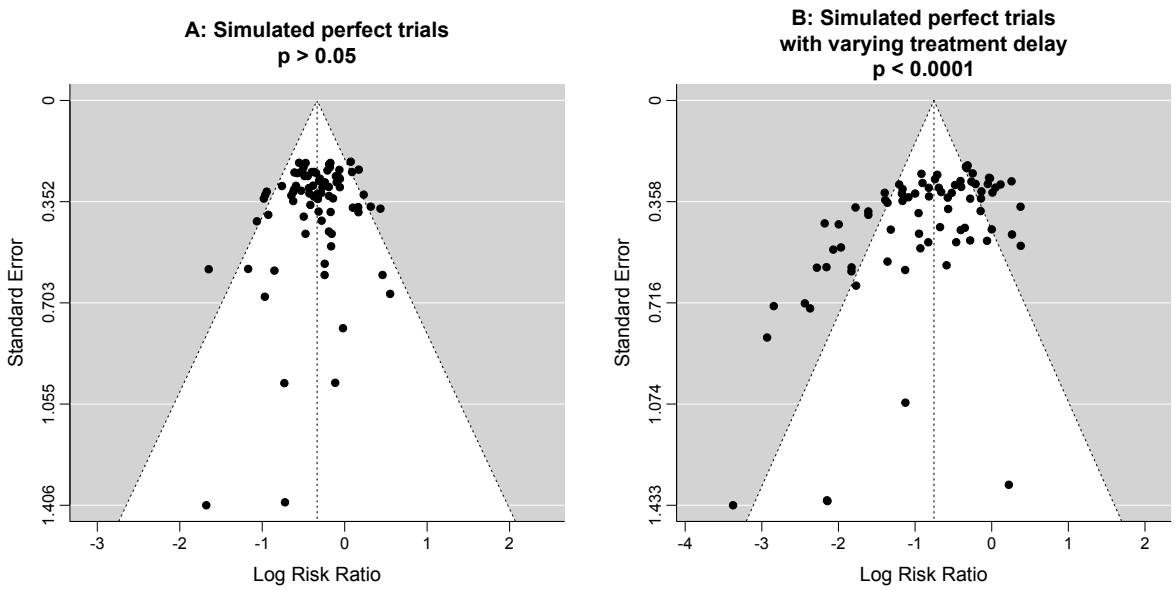


Figure 22. Example funnel plot analysis for simulated perfect trials.

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

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain

treatments.

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

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

Notes. 7 of 51 studies combine treatments. The results of colchicine alone may differ. 4 of 26 RCTs use combined treatment. Other meta analyses show significant improvements with colchicine for mortality *Danjuma, Elshafei, Elshiwy, Golpour, Lien, Rai, Salah, Zein*, oxygen therapy *Elshiwy*, hospitalization *Kow*, and severity *Yasmin*.

Conclusion

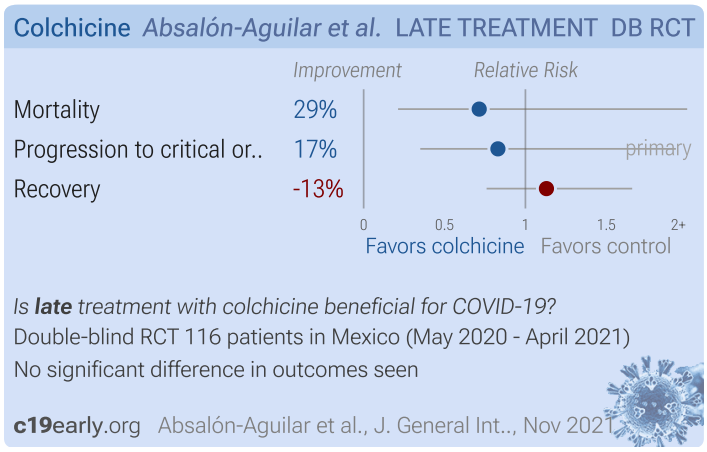
Colchicine is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, ICU admission, hospitalization, and recovery. 26 studies from 26 independent teams in 15 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 28% [19-37%] lower risk. Results are similar for higher quality and peer-reviewed studies and worse for Randomized Controlled Trials. Clinical outcomes suggest benefit while viral and case outcomes do not, consistent with an intervention that aids the immune system or recovery but may have limited antiviral effects. Results are robust — in exclusion sensitivity analysis 21 of 51 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

RCT results are less favorable, however they are dominated by the very late stage RECOVERY RCT which is not generalizable to earlier usage.

Other meta analyses show significant improvements with colchicine for mortality *Danjuma, Elshafei, Elshiwy, Golpour, Lien, Rai, Salah, Zein*, oxygen therapy *Elshiwy*, hospitalization *Kow*, and severity *Yasmin*.

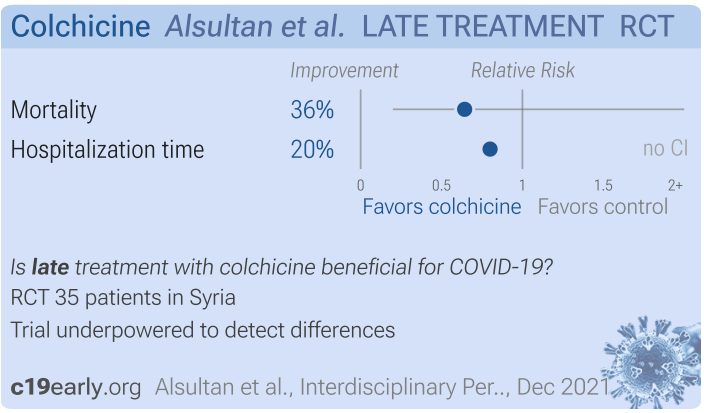
Study Notes

Absalón-Aguilar



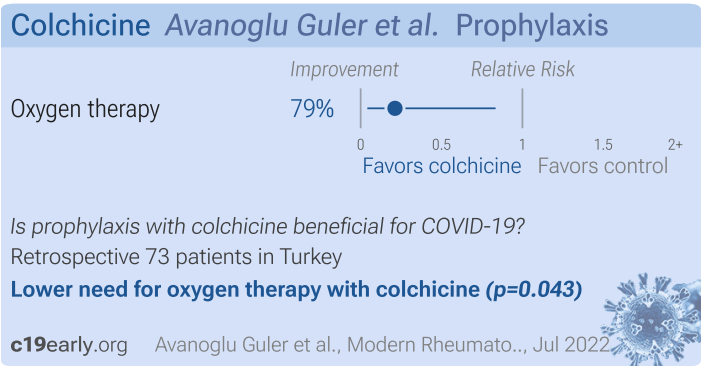
Absalón-Aguilar: Very late stage RCT with 56 colchicine and 60 control patients in Mexico, showing no significant differences.

Alsultan



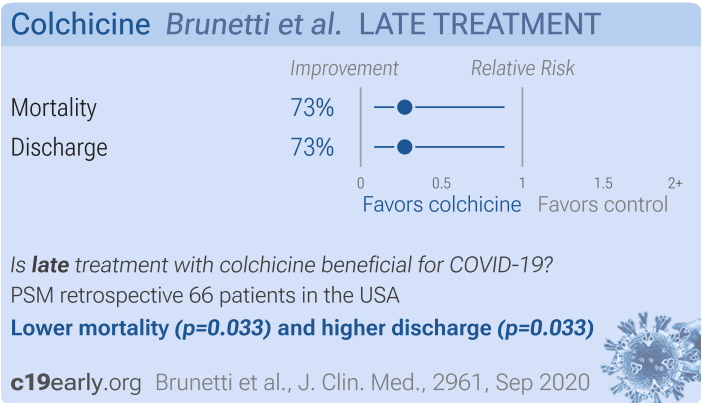
Alsultan: Small RCT 49 severe condition hospitalized patients in Syria, showing lower mortality with colchicine and shorter hospitalization time with both colchicine and budesonide (all of these were not statistically significant).

Avanoglu Guler



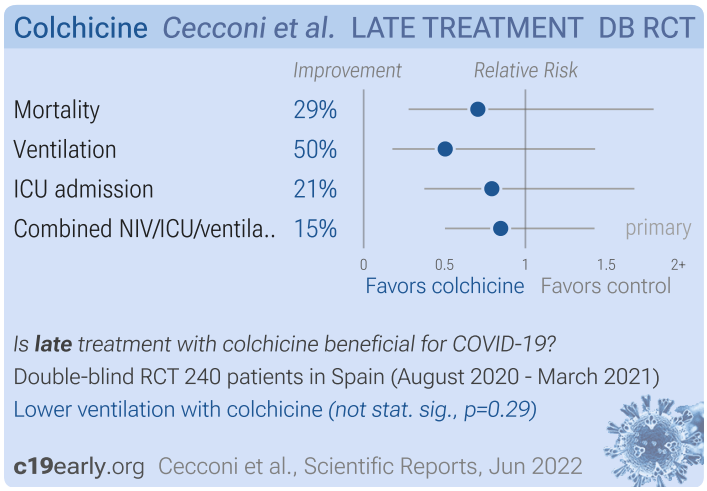
Avanoglu Guler: Retrospective 73 familial Mediterranean fever patients with COVID-19 in Turkey, showing significantly higher risk of hospitalization for respiratory support with non-adherence to colchicine treatment before the infection.

Brunetti



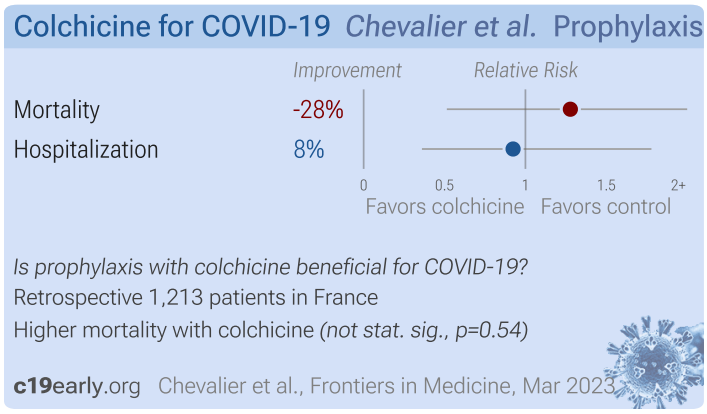
Brunetti: PSM matched analysis from consecutive hospitalized patients, with 33 colchicine and 33 control matched patients, showing lower mortality with treatment.

Cecconi



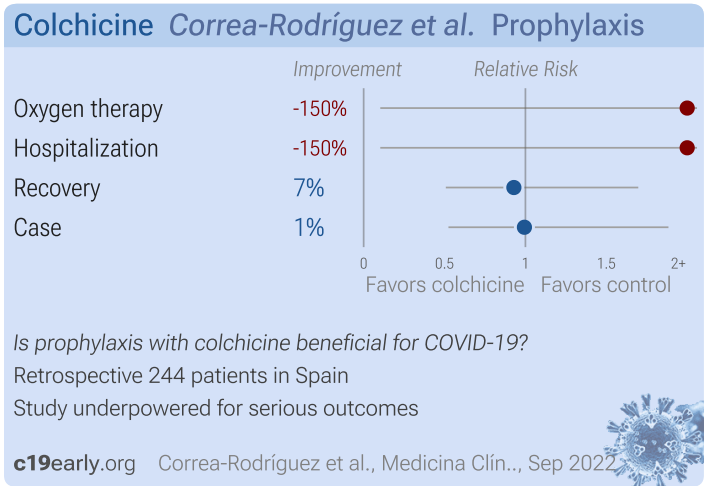
Cecconi: RCT 240 hospitalized patients with COVID-19 pneumonia, mean 9 days from the onset of symptoms, showing no significant differences with colchicine treatment. EudraCT 2020-001841-38.

Chevalier



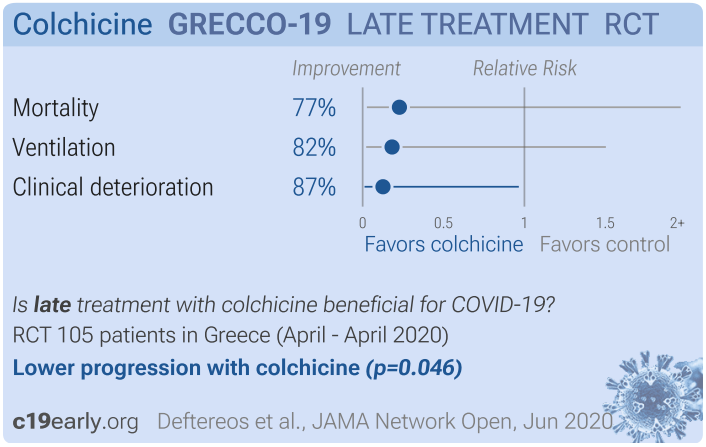
Chevalier: Retrospective 1,213 rheumatic disease patients in France, showing no significant difference with colchicine use in univariate analysis.

Correa-Rodríguez



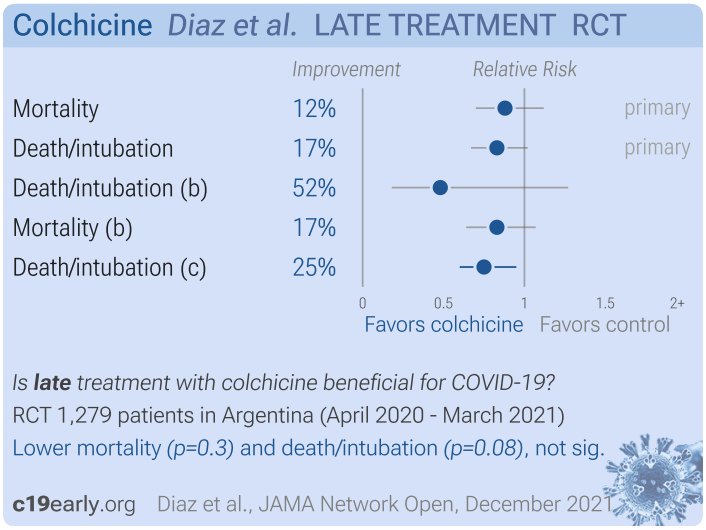
Correa-Rodríguez: Retrospective 244 Behçet disease patients in Spain, showing no significant difference in outcomes with colchicine treatment. Confounding by indication may significantly affect results - colchicine may be prescribed more often for more serious cases, which may have a higher baseline risk for COVID-19.

Deftereos



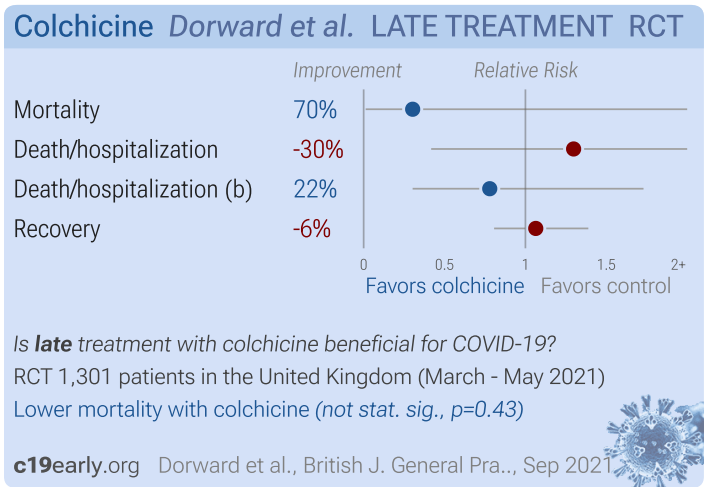
Deftereos: RCT with 55 patients treated with colchicine and 50 control patients, showing lower mortality and ventilation with treatment.

Diaz



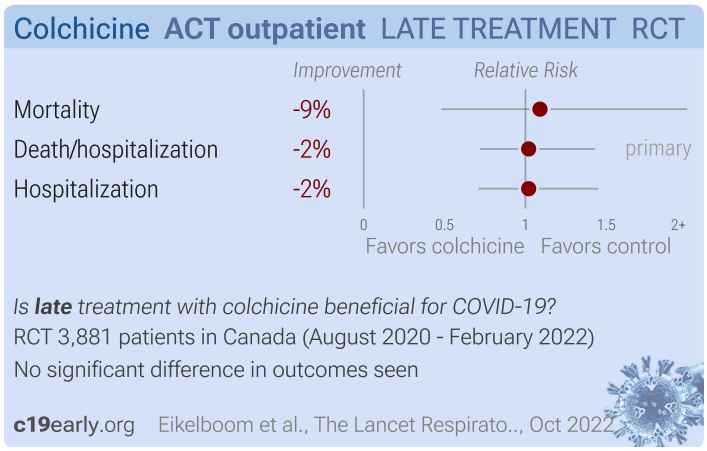
Diaz: Very late stage RCT (O2 88%, 84% on oxygen) with 1,279 hospitalized patients in Argentina, showing lower mortality and lower combined mortality/ventilation, statistically significant only for the combined outcome and per-protocol analysis. NCT04328480. COLCOVID.

Dorward



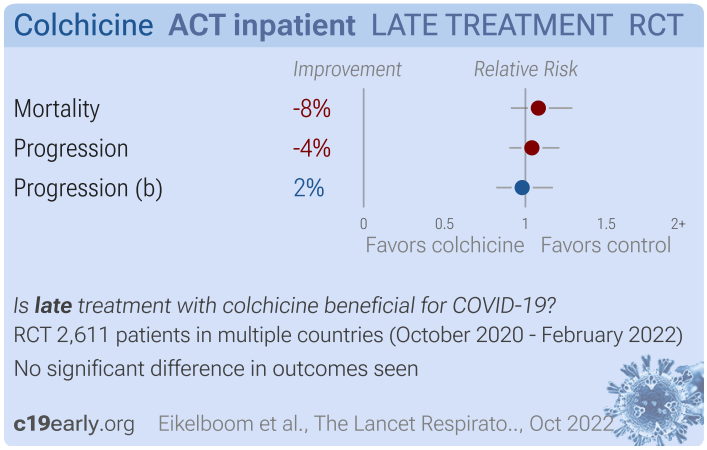
Dorward: Late treatment RCT with 156 colchicine patients in the UK, showing no significant differences. ISRCTN86534580.

Eikelboom



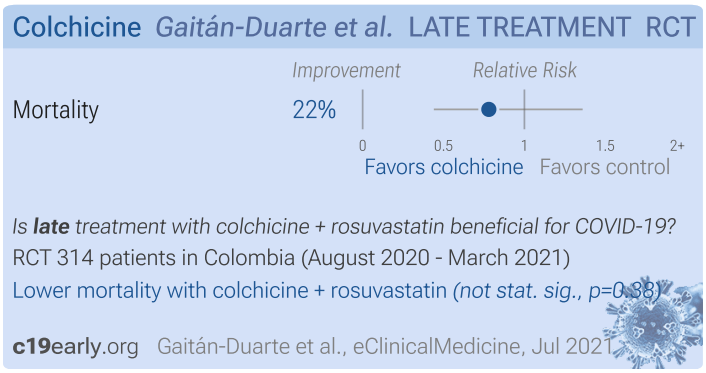
Eikelboom (B): Late (5.4 days) outpatient RCT showing no significant difference in outcomes with colchicine treatment. Authors include a meta analysis of 6 colchicine RCTs, however there were 19 RCTs as of the publication date [c19colchicine.com].

Eikelboom



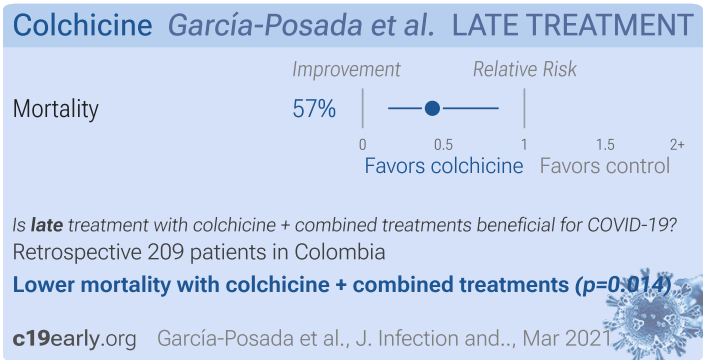
Eikelboom: RCT very late stage (baseline SpO2 80%) patients, showing no significant differences with colchicine treatment.

Gaitán-Duarte



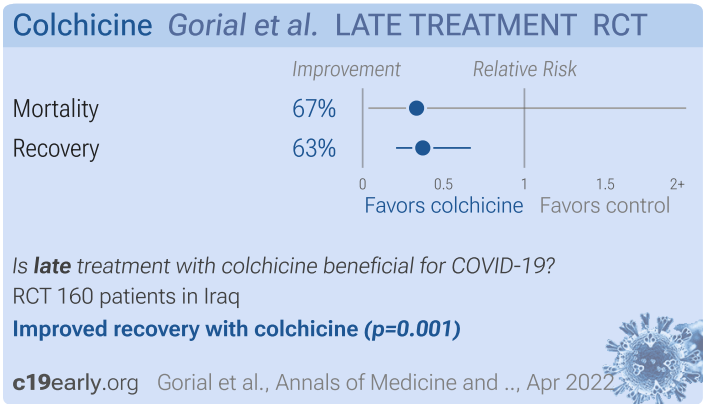
Gaitán-Duarte: RCT 633 hospitalized patients in Colombia, 153 treated with colchicine + rosuvastatin, not showing statistically significant differences in outcomes. Improved results were seen with the combination of emtricitabine/tenofovir disoproxil + rosuvastatin + colchicine. NCT04359095.

García-Posada



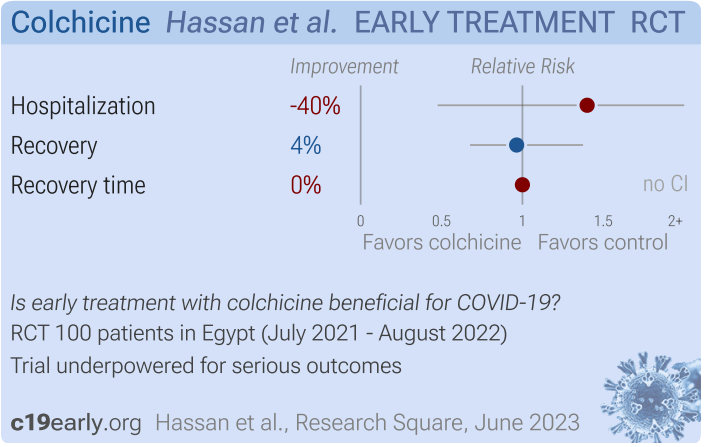
García-Posada: Retrospective 209 hospitalized patients in Colombia, showing lower mortality with antibiotics + LMWH + corticosteroids + colchicine in multivariable analysis.

Gorial



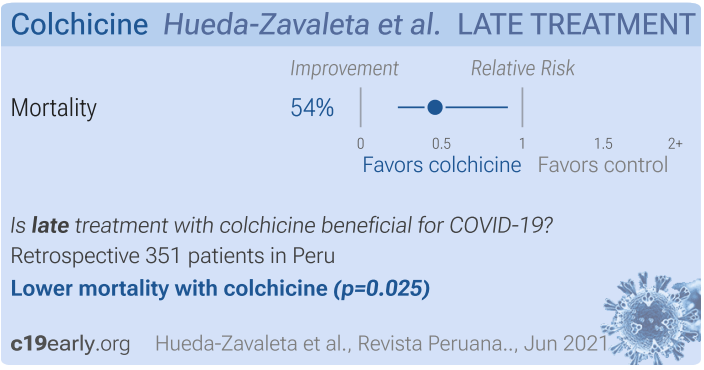
Gorial: RCT with 80 colchicine and 80 control patients, showing improved recovery with treatment. SOC included vitamin C, vitamin D, and zinc.

Hassan



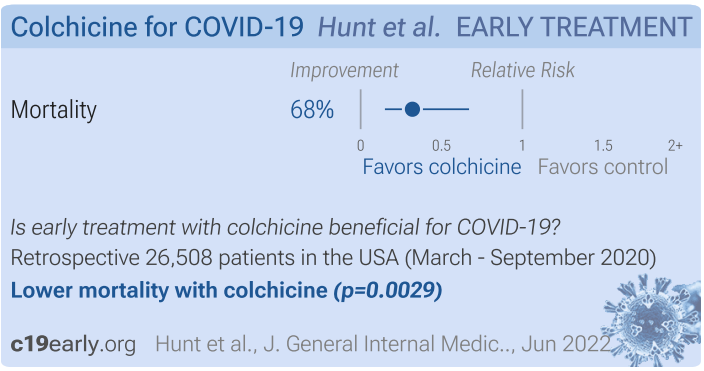
Hassan: RCT 150 patients in Egypt showing no significant difference in outcomes with colchicine. SOC included vitamin C, D, and zinc. Colchicine 0.5mg tid days 1-3, bid days 4-7.

Hueda-Zavaleta



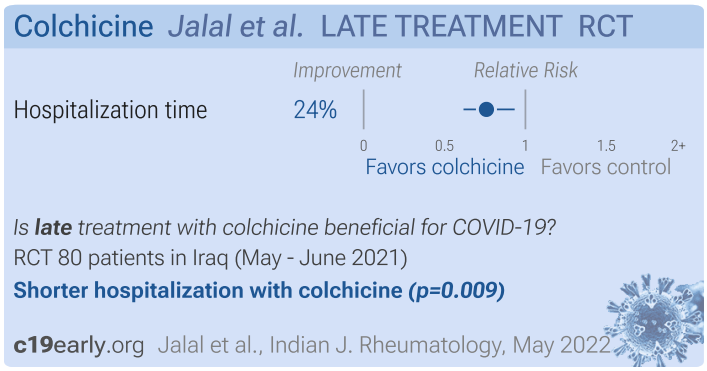
Hueda-Zavaleta: Retrospective 450 late stage (median oxygen saturation 86%) COVID+ hospitalized patients in Peru, showing lower mortality with colchicine treatment.

Hunt



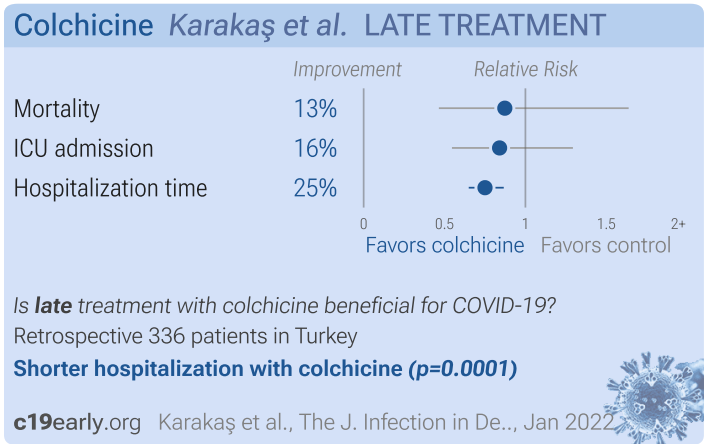
Hunt: Retrospective 26,508 consecutive COVID+ veterans in the USA, showing lower mortality with multiple treatments including colchicine. Treatment was defined as drugs administered ≥50% of the time within 2 weeks post-COVID+, and may be a continuation of prophylactic treatment in some cases, and may be early or late treatment in other cases. Further reduction in mortality was seen with combinations of treatments.

Jalal



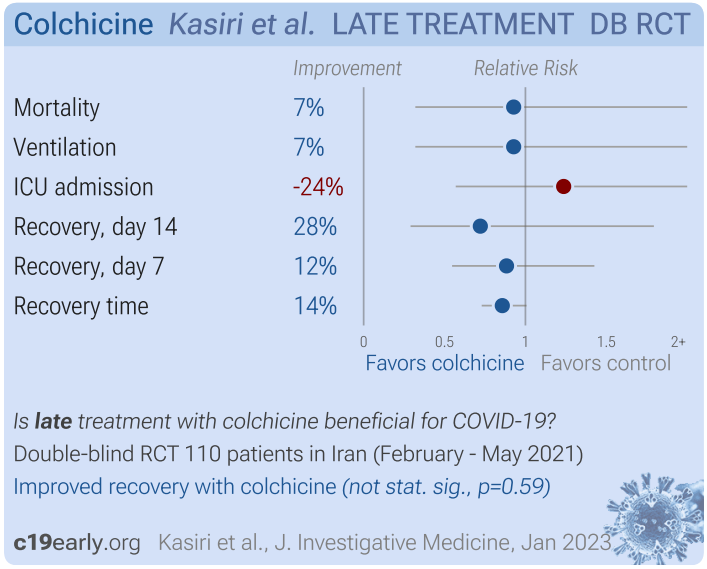
Jalal: Open label RCT of colchicine showing improved recovery with treatment. Only the abstract is currently available. Colchicine 0.5mg bid for 14 days.

Karakaş



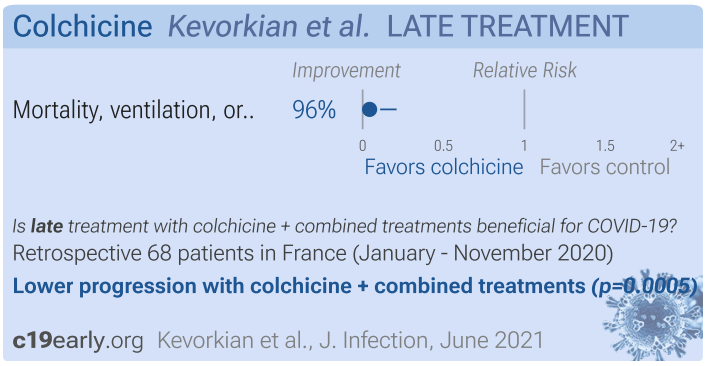
Karakaş: Retrospective 356 hospitalized COVID-19 patients, shorter hospitalization time with colchicine treatment. There were no statistically significant differences for mortality or ICU admission. Significantly lower mortality was seen with higher dosage (1mg/day vs 0.5mg/day). More control patients were on oxygen at baseline (65% vs. 54%).

Kasiri



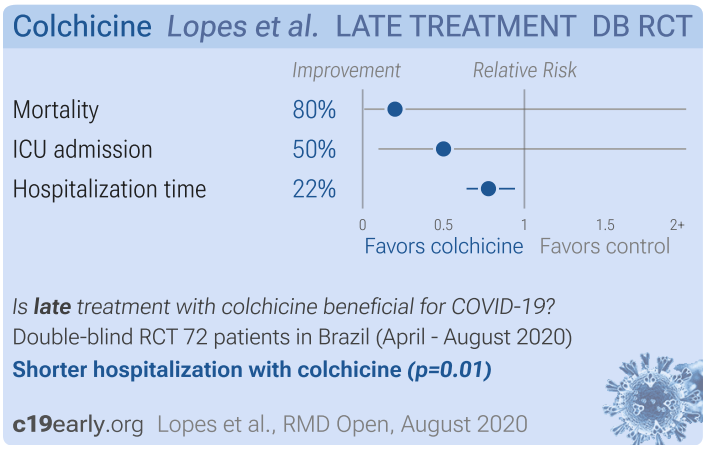
Kasiri: Very late treatment (10 days from onset) RCT 110 patients in Iran, showing no significant difference in outcomes with colchicine. Colchicine 2mg loading dose followed by 0.5mg bid for 7 days.

Kevorkian



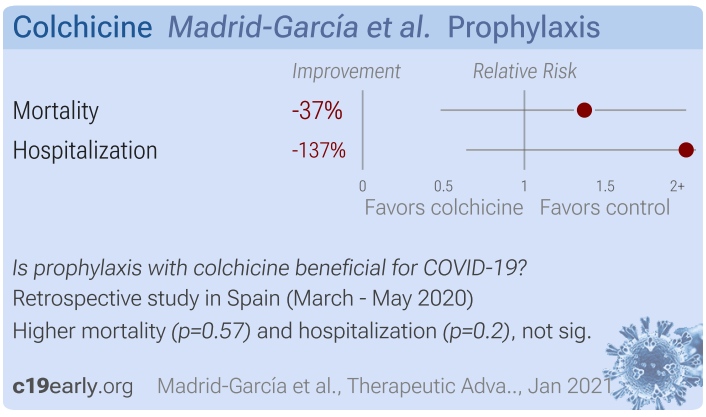
Kevorkian: Observational study in France with 28 hospitalized patients treated with prednisone/furosemide/colchicine/salicylate/direct anti-Xa inhibitor, and 40 control patients, showing lower combined mortality, ventilation, or high-flow oxygen therapy with treatment.

Lopes



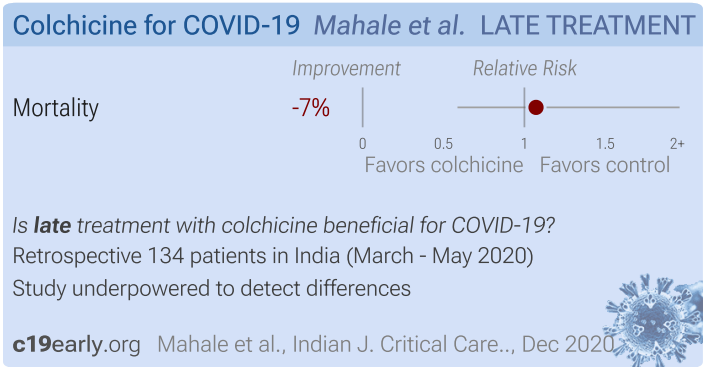
Lopes: RCT with 36 colchicine and 36 control patients, showing reduced length of hospitalization and oxygen therapy with treatment.

Madrid-García



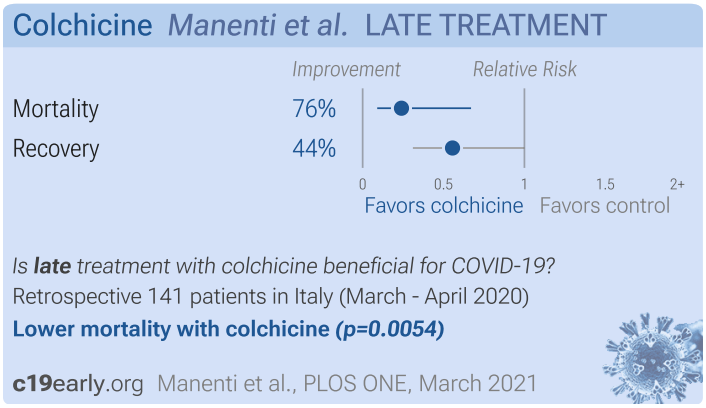
Madrid-García: Retrospective 9,379 patients attending a rheumatology outpatient clinic in Spain, showing higher mortality and hospitalization with colchicine use, without statistical significance.

Mahale



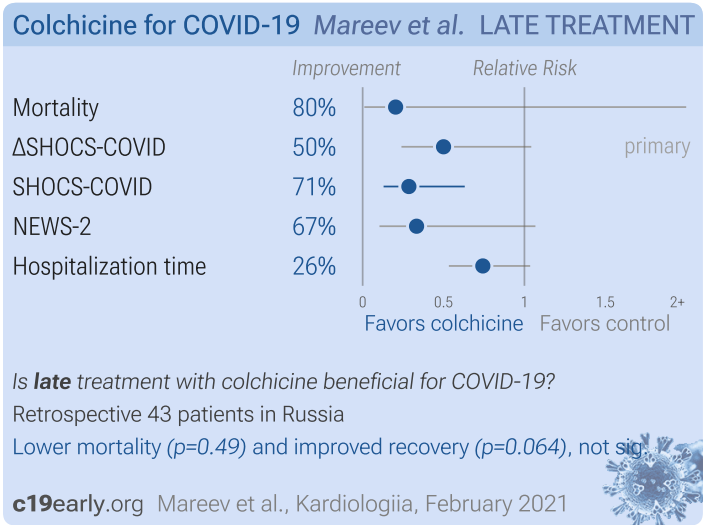
Mahale: Retrospective 134 hospitalized COVID-19 patients in India, showing no significant difference with colchicine treatment in unadjusted results.

Manenti



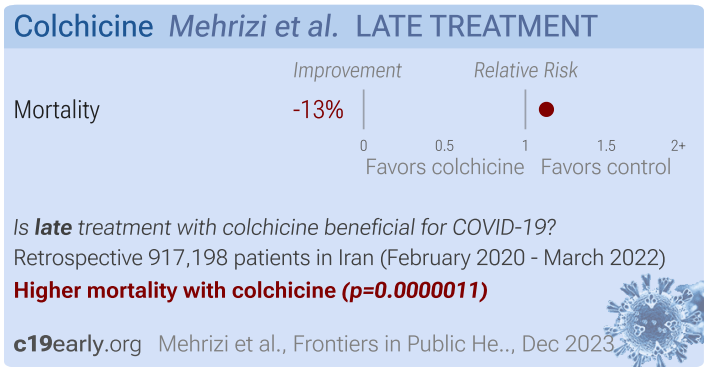
Manenti: IPTW retrospective 141 COVID-19 patients (83% hospitalized), 71 treated with colchicine and 70 matched control patients, showing lower mortality and faster recovery with treatment.

Mareev



Mareev: Small trial with 21 colchicine patients and 22 control patients in Russia, showing improved recovery with treatment. The trial was originally an RCT, however randomization to the control arm was stopped after 5 patients, and 17 retrospective patients were added for comparison.

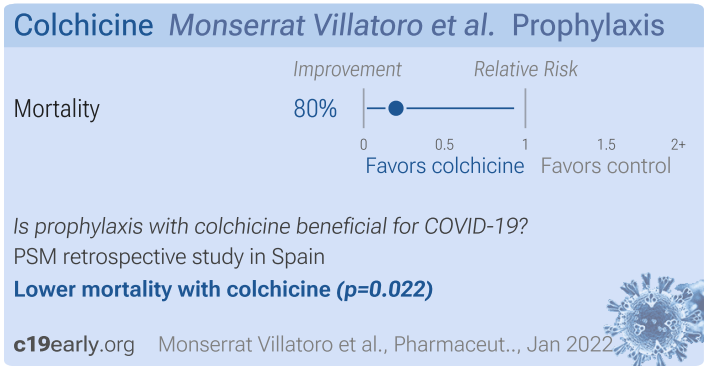
Mehrizi



Mehrizi: Retrospective study of 917,198 hospitalized COVID-19 cases covered by the Iran Health Insurance Organization over 26 months showing that antithrombotics, corticosteroids, and antivirals reduced mortality while diuretics, antibiotics, and antidiabetics increased it. Confounding makes some results very unreliable. For example, diuretics like furosemide are often used to treat fluid overload, which is more likely in ICU or advanced disease requiring aggressive fluid resuscitation. Hospitalization length has increased risk of significant confounding, for example longer hospitalization increases the chance of receiving a medication, and death may result in shorter hospitalization. Mortality results may be more reliable.

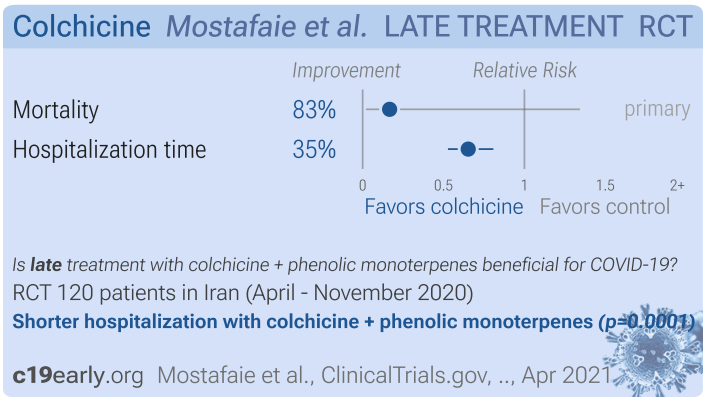
Confounding by indication is likely to be significant for many medications. Authors adjustments have very limited severity information (admission type refers to ward vs. ER department on initial arrival). We can estimate the impact of confounding from typical usage patterns, the prescription frequency, and attenuation or increase of risk for ICU vs. all patients.

Monserrat Villatoro



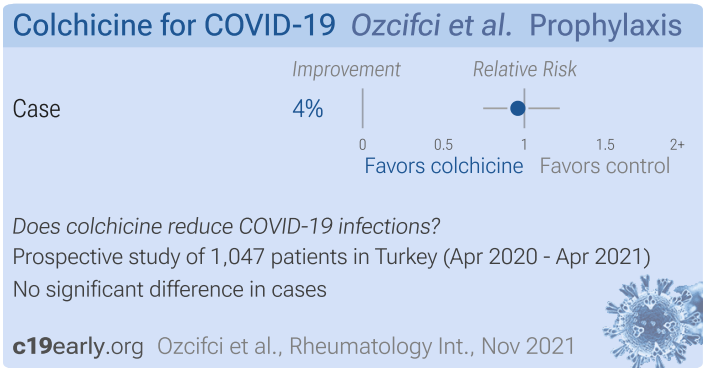
Monserrat Villatoro: PSM retrospective 3,712 hospitalized patients in Spain, showing lower mortality with existing use of azithromycin, bemiparine, budesonide-formoterol fumarate, cefuroxime, colchicine, enoxaparin, ipratropium bromide, loratadine, mepyramine theophylline acetate, oral rehydration salts, and salbutamol sulphate, and higher mortality with acetylsalicylic acid, digoxin, folic acid, mirtazapine, linagliptin, enalapril, atorvastatin, and allopurinol.

Mostafaie



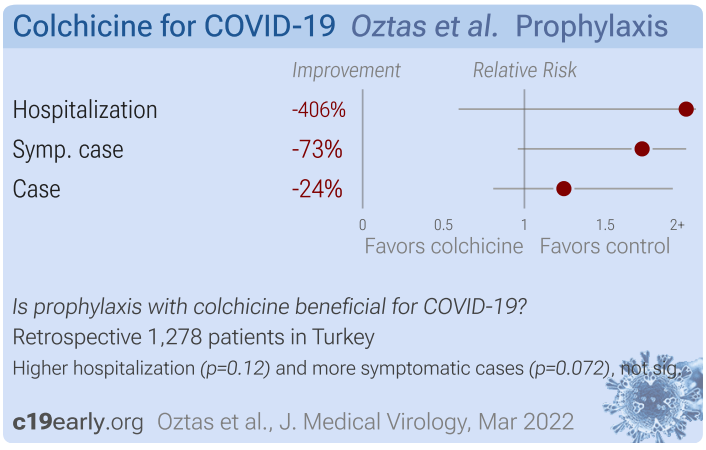
Mostafaie: RCT with 60 patients treated with colchicine and phenolic monoterpenes and 60 control patients in Iran, showing lower mortality with treatment. NCT04392141.

Ozcifci



Ozcifci: Prospective analysis of 1,047 Behçet's syndrome patients in Turkey, showing no significant difference in cases with colchicine use.

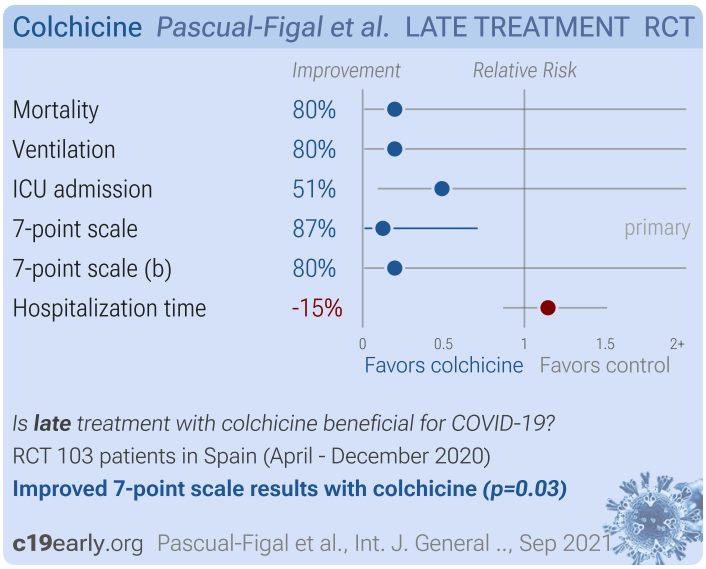
Oztas



Oztas: Retrospective 635 HCQ users and 643 household contacts, showing higher risk with colchicine in unadjusted results.

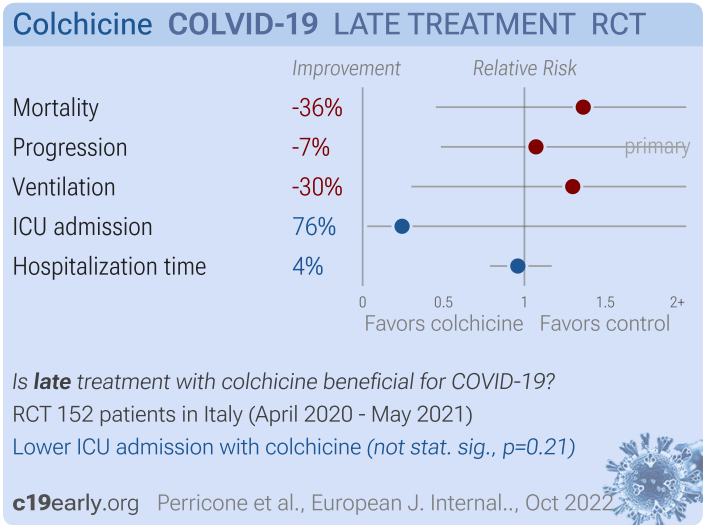
Patients with conditions leading to the use of colchicine may have significantly different baseline risk, e.g. *Topless*.

Pascual-Figal



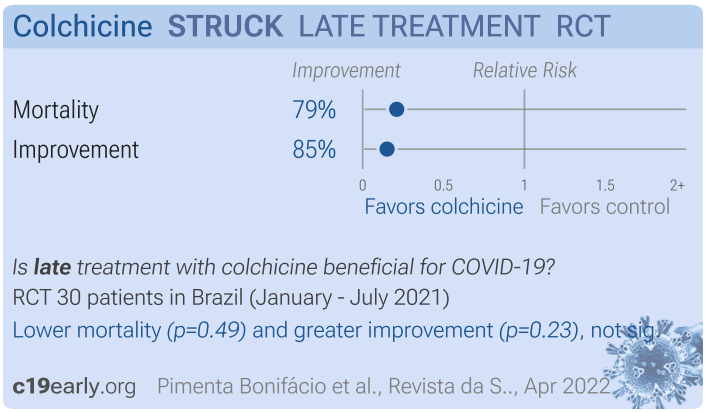
Pascual-Figal: RCT with 52 colchicine patients and 51 control patients, showing lower risk of clinical deterioration with treatment. COL-COVID. NCT04350320.

Perricone



Perricone: RCT 152 hospitalized patients in Italy, showing no significant difference in outcomes with colchicine treatment. Table 2 shows 13% of patients treated with antivirals in the colchicine arm, however 16.9% were treated with one specific antiviral (HCQ).

Pimenta Bonifácio



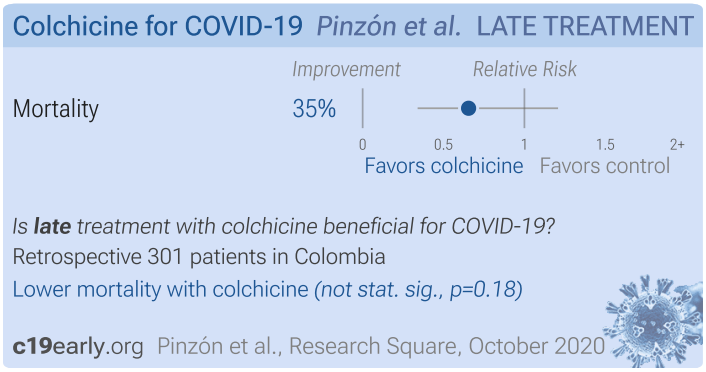
Pimenta Bonifácio: Open label RCT late stage hospitalized patients in Brazil with 14 colchicine and 16 SOC patients, showing lower mortality and improved recovery with treatment, without statistical significance. Authors note that the colchicine group had one patient with SOFA ≥7 vs. zero for SOC, however both groups had one patient intubated and SOC had more patients not requiring high-flow oxygen (12 vs. 8).

The journal version of this paper falsely states: "Ixekizumab, colchicine, and IL-2 were demonstrated to be safe but ineffective".

The pre-print more accurately represents the improved but not statistically significant results:

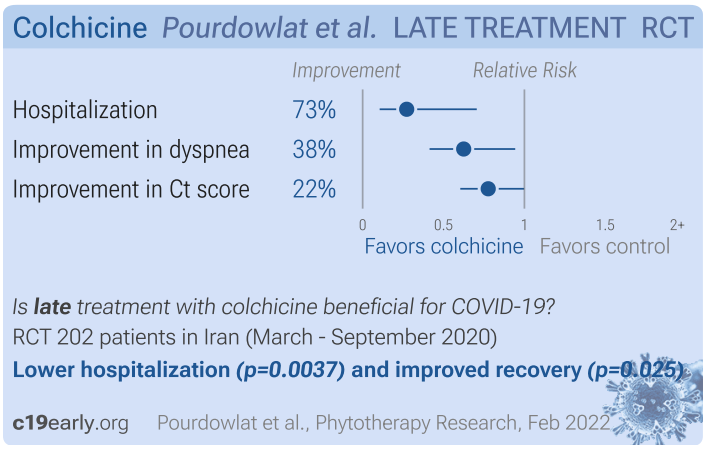
"The colchicine arm presented the lowest mortality rate (0%), while the low dose IL-2 had the highest (21.4%) by day 28 post-enrollment. The frequency of adverse events was lowest in the colchicine group (7.3%). None of the differences observed was statistically significant. Interpretation: Colchicine added to SOC performed better than Ixekizumab, low-dose IL-2, or SOC alone for hospitalized patients with moderate to critical Covid-19 in this exploratory study. Larger studies are needed to confirm these findings."

Pinzón



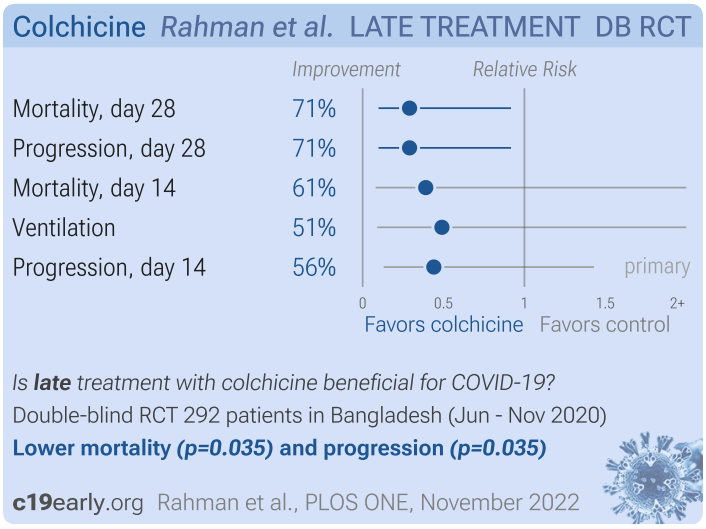
Pinzón: Retrospective 301 pneumonia patients in Colombia showing lower mortality with colchicine treatment.

Pourdowlat



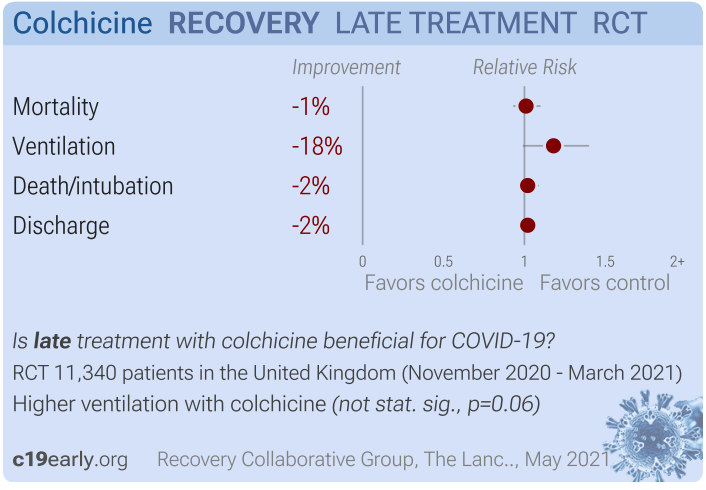
Pourdowlat: RCT 202 patients in Iran, 102 treated with colchicine, showing lower hospitalization and improved clinical outcomes with treatment.

Rahman



Rahman: RCT 300 patients in Bangladesh, published 2 years after completion, showing significantly lower mortality with treatment at 28 days (not significant at 14 days). 1.2mg colchicine on day 1 followed by 0.6mg for 13 days.

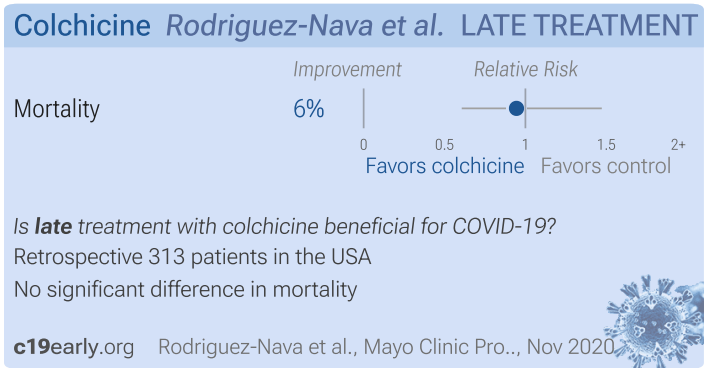
Recovery Collaborative Group



Recovery Collaborative Group: RCT with 5,610 colchicine and 5,730 control patients showing mortality RR 1.01 [0.93-1.10]. Very late stage treatment, median 9 days after symptom onset, baseline 32% ventilation (5% invasive). ISRCTN 50189673.

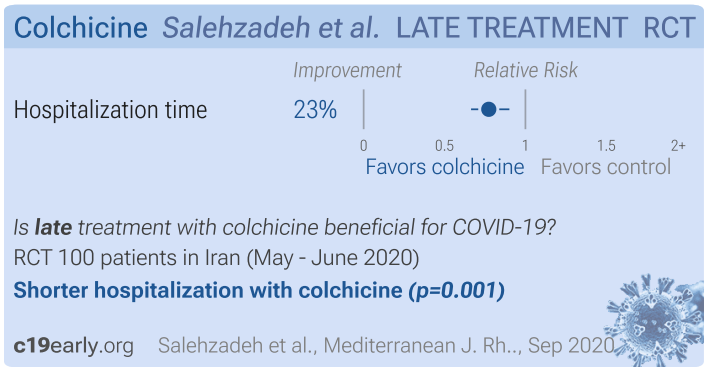
Dose frequency was halved for patients receiving a moderate CYP3A4 inhibitor, patients with an estimated glomerular filtration rate of less than 30 mL/min per 1·73m², and those with an estimated bodyweight of less than 70kg.

Rodriguez-Nava



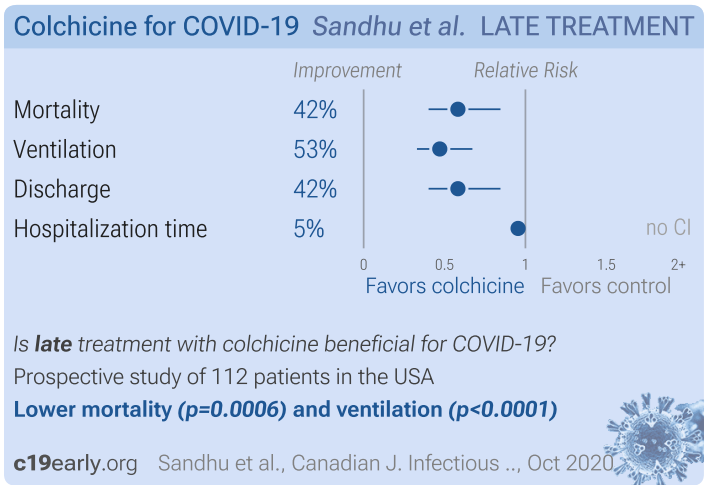
Rodriguez-Nava: Retrospective 313 patients, mostly critical stage and mostly requiring respiratory support. Confounding by indication likely.

Salehzadeh



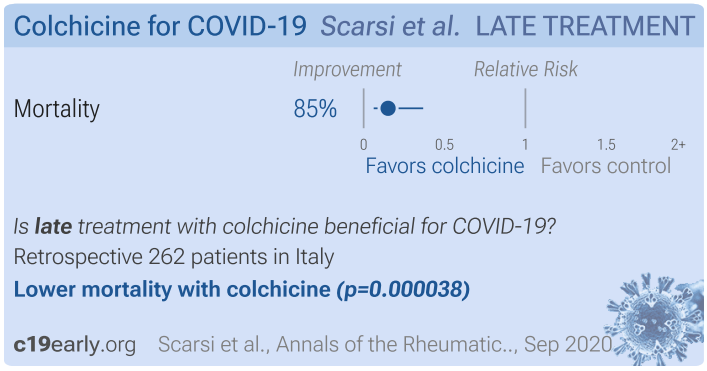
Salehzadeh: Open label RCT with 100 hospitalized patients in Iran, 50 treated with colchicine, showing shorter hospitalization time with treatment. There were no deaths.

Sandhu



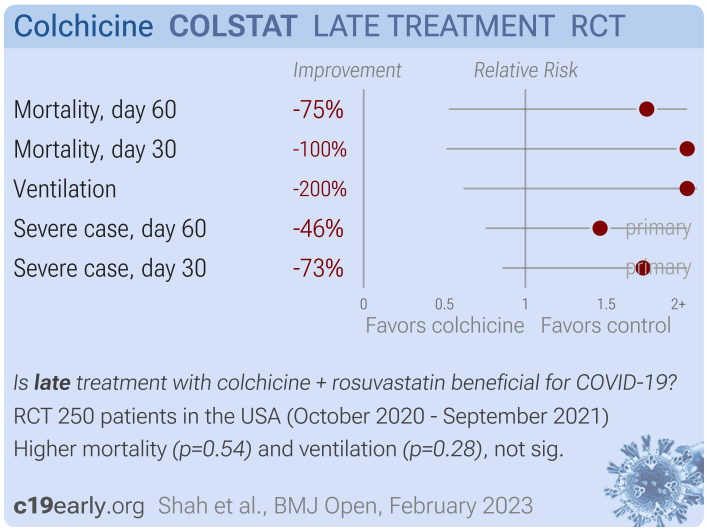
Sandhu: Prospective cohort study of hospitalized patients in the USA, 34 treated with colchicine, showing lower mortality and intubation with treatment.

Scarsi



Scarsi: Retrospective 122 colchicine patients and 140 control patients in Italy, showing lower mortality with treatment.

Shah

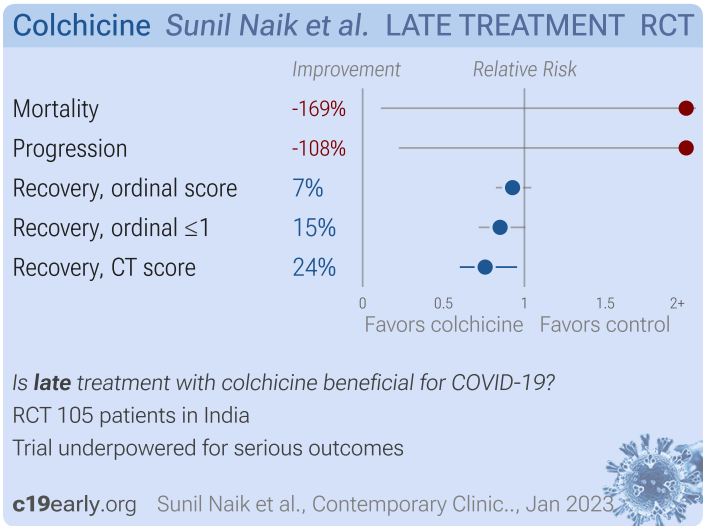


Shah: RCT 250 late stage (80% on oxygen) hospitalized patients in the USA, showing no significant differences with combined colchicine/rosuvastatin treatment.

There was a trend towards increased risk, which authors note may be due to chance because the patients enrolled in the treatment arm were in more serious condition, for example, patients in the treatment arm were more frequently on oxygen, more frequently on HFNC/NIV, and had higher mean SOFA scores.

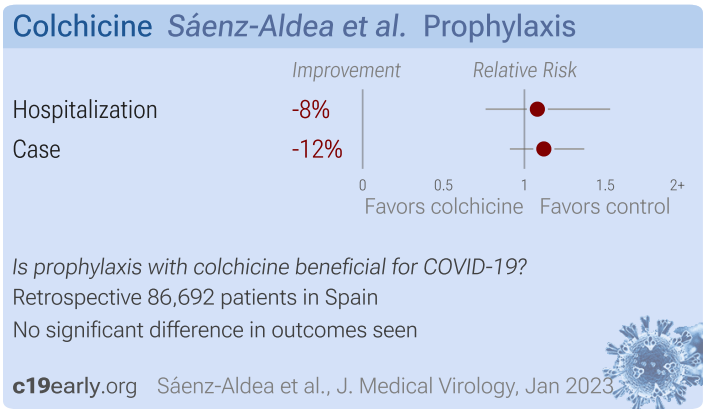
Colchicine 0.6mg two times daily for 3 days followed by 0.6mg daily, and high-intensity rosuvastatin 40mg daily.

Sunil Naik



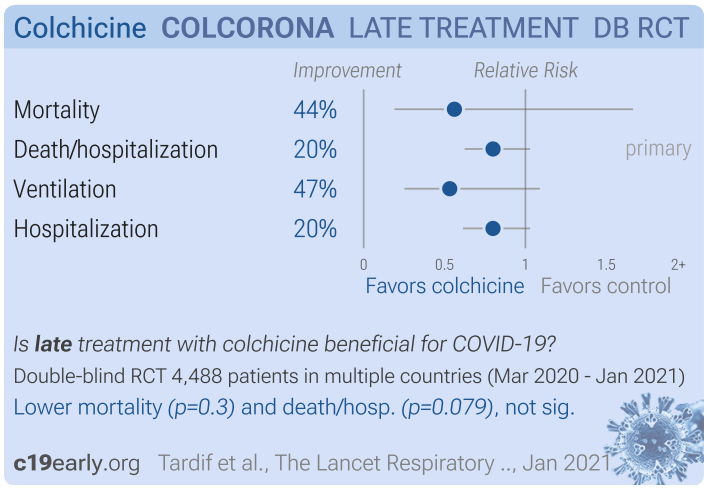
Sunil Naik: RCT 122 hospitalized patients in India, showing improved recovery with colchicine treatment. All patients received aspirin. There was one death and higher progression in the colchicine arm, however 3 patients in the colchicine arm had baseline ordinal scores ≥5, while no patients in the control arm did.

Sáenz-Aldea



Sáenz-Aldea: Retrospective 86,652 patients in Spain, showing no significant difference in cases and hospitalization with colchicine use. The different risk for patients prescribed colchicine may not be fully adjusted for. See *onlinelibrary.wiley.com*.

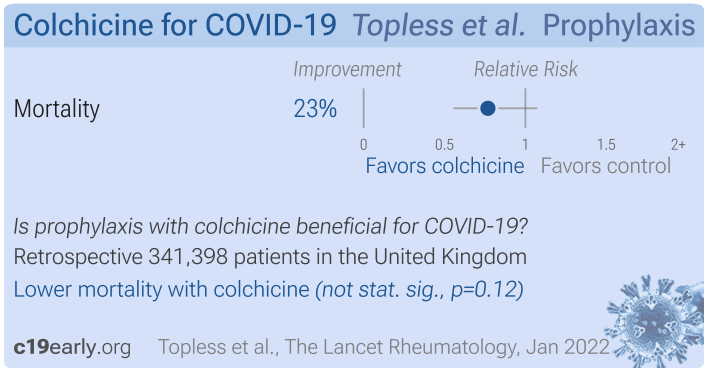
Tardif



Tardif: RCT for relatively low risk outpatients, 2235 treated with colchicine a mean of 5.3 days after the onset of symptoms, and 2253 controls, showing lower mortality, ventilation, and hospitalization with treatment.

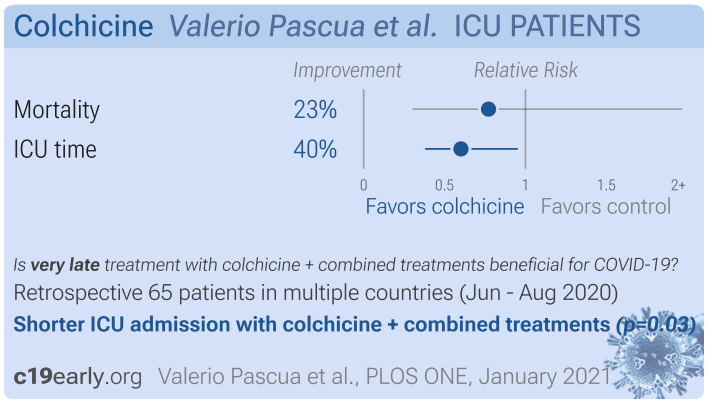
This study was submitted to NEJM which delayed for ~6 months and then said they were not interested, then to JAMA which delayed for ~6 months and then said they were not interested, and then to the Lancet which delayed for ~6 months and then said they were not interested, and finally was published in Lancet Respiratory Medicine [twitter.com].

Topless



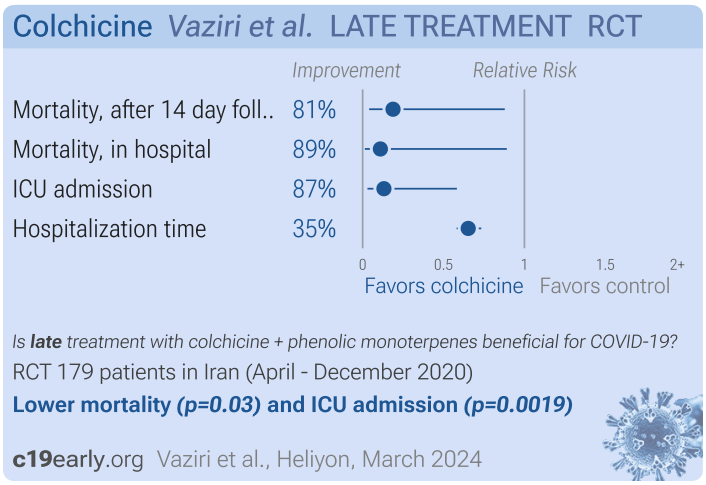
Topless: UK Biobank retrospective showing a higher risk of COVID-19 cases and mortality for patients with gout. Among patients with gout, mortality risk was lower for those on colchicine, OR 1.06 [0.60-1.89], compared to those without colchicine, OR 1.38 [1.08-1.76].

Valerio Pascua



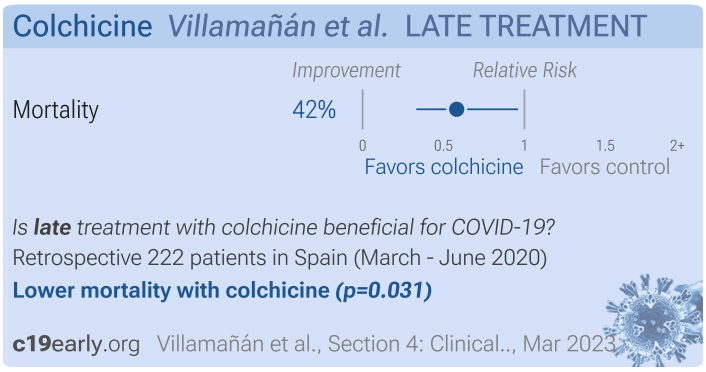
Valerio Pascua: Retrospective 65 ICU patients in the USA and Honduras, showing shorter ICU stay with combined treatment including colchicine, LMWH, tocilizumab, dexamethasone, and methylprednisolone.

Vaziri



Vaziri: RCT 179 hospitalized COVID-19 patients showing lower mortality, ICU admission, and hospitalization duration with colchicine plus phenolic monoterpenes compared to standard care alone. The intervention group received 0.8 mg/day colchicine and 45 mg/day phenolic monoterpenes extracted from nigella sativa and Trachyspermum ammi in addition to standard care (lopinavir/ritonavir). No serious side effects were reported. Baseline SpO2 was significantly lower in the control group, although there was no significant difference in severity according to NIH guidelines.

Villamañán



Villamañán: Retrospective 111 hospitalized COVID-19 pneumonia patients treated with colchicine and 111 matched controls, showing lower mortality with colchicine treatment.

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 colchicine 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 colchicine for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

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

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

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

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

Hassan, 6/13/2023, Randomized Controlled Trial, Egypt, preprint, 6 authors, study period July 2021 - August 2022.	risk of hospitalization, 40.0% higher, RR 1.40, *p* = 0.76, treatment 7 of 50 (14.0%), control 5 of 50 (10.0%).

	risk of no recovery, 3.6% lower, RR 0.96, p = 1.00, treatment 27 of 50 (54.0%), control 28 of 50 (56.0%), NNT 50.
Hunt, 6/29/2022, retrospective, USA, peer-reviewed, 8 authors, study period 1 March, 2020 - 10 September, 2020, dosage not specified.	risk of death, 68.0% lower, RR 0.32, p = 0.003, treatment 9 of 402 (2.2%), control 1,603 of 26,106 (6.1%), NNT 26, adjusted per study, day 30.

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.

Absalón-Aguilar, 11/9/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, peer-reviewed, 18 authors, study period May 2020 - April 2021, dosage 1.5mg day 1, 1mg days 2-10.	risk of death, 28.6% lower, RR 0.71, p = 0.74, treatment 4 of 56 (7.1%), control 6 of 60 (10.0%), NNT 35.
	progression to critical or death, 17.0% lower, OR 0.83, p = 0.67, treatment 56, control 60, primary outcome, RR approximated with OR.
	risk of no recovery, 13.0% higher, RR 1.13, p = 0.59, treatment 56, control 60, Kaplan–Meier.
Alsultan, 12/31/2021, Randomized Controlled Trial, Syria, peer-reviewed, 11 authors, dosage 2mg day 1, 1mg days 2-5.	risk of death, 35.7% lower, RR 0.64, p = 0.70, treatment 3 of 14 (21.4%), control 7 of 21 (33.3%), NNT 8.4.
Brunetti, 9/14/2020, retrospective, propensity score matching, USA, peer-reviewed, baseline oxygen required 86.4%, 7 authors, dosage 1.2mg daily.	risk of death, 72.7% lower, RR 0.27, p = 0.03, treatment 3 of 33 (9.1%), control 11 of 33 (33.3%), NNT 4.1, PSM.
	risk of no hospital discharge, 72.7% lower, RR 0.27, p = 0.03, treatment 3 of 33 (9.1%), control 11 of 33 (33.3%), NNT 4.1, PSM.
Cecconi, 6/2/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Spain, peer-reviewed, mean age 65.0, 31 authors, study period August 2020 - March 2021, average treatment delay 9.0 days, dosage 1mg day 1, 0.5mg days 2-5.	risk of death, 29.4% lower, RR 0.71, p = 0.62, treatment 7 of 119 (5.9%), control 10 of 120 (8.3%), NNT 41.
	risk of mechanical ventilation, 49.6% lower, RR 0.50, p = 0.29, treatment 5 of 119 (4.2%), control 10 of 120 (8.3%), NNT 24.
	risk of ICU admission, 20.8% lower, RR 0.79, p = 0.67, treatment 11 of 119 (9.2%), control 14 of 120 (11.7%), NNT 41.
	combined NIV/ICU/ventilation/death, 15.3% lower, RR 0.85, p = 0.62, treatment 21 of 119 (17.6%), control 25 of 120 (20.8%), NNT 31, primary outcome.
Deftereos, 6/24/2020, Randomized Controlled Trial, Greece, peer-reviewed, baseline oxygen required 62.9%, 49 authors, study period 3 April, 2020 - 27 April, 2020, dosage 2mg day 1, 1mg days 2-21, trial NCT04326790 (history) (GRECCO-19).	risk of death, 77.3% lower, RR 0.23, p = 0.19, treatment 1 of 55 (1.8%), control 4 of 50 (8.0%), NNT 16.
	risk of mechanical ventilation, 81.8% lower, RR 0.18, p = 0.10, treatment 1 of 55 (1.8%), control 5 of 50 (10.0%), NNT 12.

	risk of clinical deterioration, 87.4% lower, RR 0.13, $p = 0.046$, treatment 1 of 55 (1.8%), control 7 of 50 (14.0%), NNT 8.2, odds ratio converted to relative risk.
Diaz, 12/29/2021, Randomized Controlled Trial, Argentina, peer-reviewed, 101 authors, study period 17 April, 2020 - 28 March, 2021, dosage 2mg day 1, 1mg days 2-14, trial NCT04328480 (history), excluded in exclusion analyses: very late stage, oxygen saturation <90% at baseline; very late stage, >80% on oxygen/ventilation at baseline.	**risk of death, 12.0% lower, HR 0.88, $p = 0.30$**, treatment 131 of 640 (20.5%), control 142 of 639 (22.2%), NNT 57, adjusted per study, Cox proportional hazards, primary outcome.
	risk of death/intubation, 17.0% lower, HR 0.83, $p = 0.08$, treatment 160 of 640 (25.0%), control 184 of 639 (28.8%), NNT 26, adjusted per study, Cox proportional hazards, primary outcome.
	risk of death/intubation, 52.0% lower, HR 0.48, $p = 0.60$, treatment 6 of 93 (6.5%), control 13 of 102 (12.7%), NNT 16, adjusted per study, subset not on supplemental oxygen, Cox proportional hazards.
	risk of death, 17.0% lower, HR 0.83, $p = 0.30$, treatment 98 of 515 (19.0%), control 140 of 634 (22.1%), NNT 33, adjusted per study, PP, Cox proportional hazards.
	risk of death/intubation, 25.0% lower, HR 0.75, $p = 0.02$, treatment 117 of 515 (22.7%), control 181 of 634 (28.5%), NNT 17, adjusted per study, PP, Cox proportional hazards.
Dorward, 9/23/2021, Randomized Controlled Trial, United Kingdom, peer-reviewed, 21 authors, study period 4 March, 2021 - 26 May, 2021, average treatment delay 6.0 days, dosage 0.5mg days 1-14.	**risk of death, 69.7% lower, RR 0.30, $p = 0.43$**, treatment 0 of 156 (0.0%), control 1 of 120 (0.8%), NNT 120, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of death/hospitalization, 29.8% higher, RR 1.30, $p = 0.66$, treatment 6 of 156 (3.8%), control 4 of 133 (3.0%), odds ratio converted to relative risk, concurrent randomisation.
	risk of death/hospitalization, 22.1% lower, RR 0.78, $p = 0.59$, treatment 6 of 156 (3.8%), control 119 of 1,145 (10.4%), odds ratio converted to relative risk, including control patients before the colchicine arm started.
	risk of no recovery, 6.4% higher, HR 1.06, $p = 0.67$, treatment 156, control 133, inverted to make HR<1 favor treatment, time to alleviation of symptoms, concurrent randomisation.
Eikelboom (B), 10/10/2022, Randomized Controlled Trial, Canada, peer-reviewed, mean age 45.0, 31 authors, study period 27 August, 2020 - 10 February, 2022, average treatment delay 5.4 days, dosage 1.2mg days 1-3, 0.6mg days 4-28, trial NCT04324463 (history) (ACT outpatient).	**risk of death, 9.0% higher, HR 1.09, $p = 0.84$**, treatment 12 of 1,939 (0.6%), control 11 of 1,942 (0.6%).
	risk of death/hospitalization, 2.0% higher, HR 1.02, $p = 0.93$, treatment 66 of 1,939 (3.4%), control 65 of 1,942 (3.3%), primary outcome.
	risk of hospitalization, 2.0% higher, HR 1.02, $p = 0.92$, treatment 62 of 1,939 (3.2%), control 61 of 1,942 (3.1%).
Eikelboom, 10/10/2022, Randomized Controlled Trial, multiple countries, peer-reviewed, mean age 56.0, 29 authors, study period 2 October, 2020 - 10	**risk of death, 8.0% higher, HR 1.08, $p = 0.38$**, treatment 264 of 1,304 (20.2%), control 249 of 1,307 (19.1%).

February, 2022, average treatment delay 7.0 days, dosage 1.8mg day 1, 1.2mg days 2-28, trial NCT04324463 (history) (ACT inpatient), excluded in exclusion analyses: very late stage, oxygen saturation <90% at baseline.	risk of progression, 4.0% higher, HR 1.04, p = 0.58, treatment 368 of 1,304 (28.2%), control 356 of 1,307 (27.2%), high-flow oxygen, ventilation, or death.
	risk of progression, 2.0% lower, HR 0.98, p = 0.84, treatment 246 of 1,304 (18.9%), control 252 of 1,307 (19.3%), NNT 241, high-flow oxygen or ventilation.
Gaitán-Duarte, 7/10/2021, Randomized Controlled Trial, Colombia, peer-reviewed, 17 authors, study period 24 August, 2020 - 20 March, 2021, average treatment delay 10.0 days, dosage 0.5mg days 1-14, this trial uses multiple treatments in the treatment arm (combined with rosuvastatin) - results of individual treatments may vary, trial NCT04359095 (history).	risk of death, 22.0% lower, HR 0.78, p = 0.38, treatment 22 of 153 (14.4%), control 28 of 161 (17.4%), NNT 33, adjusted per study, Cox proportional hazards.
García-Posada, 3/6/2021, retrospective, Colombia, peer-reviewed, 8 authors, dosage not specified, this trial uses multiple treatments in the treatment arm (combined with antibiotics, LMWH, and corticosteroidsPERIOD:5/20-8/20) - results of individual treatments may vary.	risk of death, 56.9% lower, RR 0.43, p = 0.01, treatment 48 of 99 (48.5%), control 59 of 110 (53.6%), adjusted per study, odds ratio converted to relative risk, multivariable.
Gorial, 4/12/2022, Randomized Controlled Trial, Iraq, peer-reviewed, 6 authors, dosage 1mg days 1-7, 0.5mg days 8-15.	risk of death, 66.7% lower, RR 0.33, p = 0.62, treatment 1 of 80 (1.2%), control 3 of 80 (3.8%), NNT 40.
	risk of no recovery, 62.8% lower, HR 0.37, p < 0.001, treatment 80, control 80, inverted to make HR<1 favor treatment, Cox proportional hazards.
Hueda-Zavaleta, 6/10/2021, retrospective, Peru, peer-reviewed, 6 authors, dosage not specified.	risk of death, 54.0% lower, HR 0.46, p = 0.03, treatment 10 of 50 (20.0%), control 109 of 301 (36.2%), NNT 6.2, adjusted per study, multivariable.
Jalal, 5/5/2022, Randomized Controlled Trial, Iraq, peer-reviewed, 3 authors, study period 8 May, 2021 - 18 June, 2021, trial NCT04867226 (history), excluded in exclusion analyses: minimal details provided.	hospitalization time, 24.1% lower, relative time 0.76, p = 0.009, treatment 36, control 44.
Karakaş, 1/31/2022, retrospective, Turkey, peer-reviewed, 11 authors, dosage 1mg daily, 0.5mg for 37 patients, excluded in exclusion analyses: excessive unadjusted differences between groups.	risk of death, 12.7% lower, RR 0.87, p = 0.72, treatment 16 of 165 (9.7%), control 19 of 171 (11.1%), NNT 71.
	risk of ICU admission, 16.0% lower, RR 0.84, p = 0.50, treatment 30 of 165 (18.2%), control 37 of 171 (21.6%), NNT 29.
	hospitalization time, 25.0% lower, relative time 0.75, p < 0.001, treatment 165, control 171.
Kasiri, 1/16/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, mean age 54.6, 6 authors, study period February 2021 - May 2021, average treatment delay 10.0 days, trial IRCT20190804044429N5.	risk of death, 7.3% lower, RR 0.93, p = 1.00, treatment 6 of 55 (10.9%), control 6 of 51 (11.8%), NNT 117.
	risk of mechanical ventilation, 7.3% lower, RR 0.93, p = 1.00, treatment 6 of 55 (10.9%), control 6 of 51 (11.8%), NNT 117.

	risk of ICU admission, 23.6% higher, RR 1.24, *p* = 0.63, treatment 12 of 55 (21.8%), control 9 of 51 (17.6%).
	risk of no recovery, 27.9% lower, RR 0.72, *p* = 0.59, treatment 7 of 55 (12.7%), control 9 of 51 (17.6%), NNT 20, day 14.
	risk of no recovery, 11.7% lower, RR 0.88, *p* = 0.69, treatment 20 of 55 (36.4%), control 21 of 51 (41.2%), NNT 21, day 7.
	recovery time, 14.3% lower, relative time 0.86, *p* = 0.06, treatment 55, control 51.
Kevorkian, 6/30/2021, retrospective, France, peer-reviewed, 11 authors, study period 9 January, 2020 - 30 November, 2020, this trial uses multiple treatments in the treatment arm (combined with prednisone, furosemide, salicylate, direct anti-Xa inhibitor) - results of individual treatments may vary.	**risk of mortality, ventilation, or high-flow oxygen therapy, 95.7% lower, OR 0.04, *p* < 0.001**, treatment 28, control 40, adjusted per study, multivariable, RR approximated with OR.
Lopes, 8/12/2020, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, baseline oxygen required 93.0%, median age 54.5 (treatment) 55.0 (control), 34 authors, study period 11 April, 2020 - 30 August, 2020, average treatment delay 9.5 (treatment) 8.0 (control) days, dosage 1.5mg days 1-5, 1mg days 6-10.	**risk of death, 80.0% lower, RR 0.20, *p* = 0.49**, treatment 0 of 36 (0.0%), control 2 of 36 (5.6%), NNT 18, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 50.0% lower, RR 0.50, *p* = 0.67, treatment 2 of 36 (5.6%), control 4 of 36 (11.1%), NNT 18.
	hospitalization time, 22.2% lower, relative time 0.78, *p* < 0.01, treatment 36, control 36.
Mahale, 12/31/2020, retrospective, India, peer-reviewed, 22 authors, study period 22 March, 2020 - 21 May, 2020, dosage not specified, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 7.2% higher, RR 1.07, *p* = 0.83**, treatment 11 of 39 (28.2%), control 25 of 95 (26.3%).
Manenti, 3/24/2021, retrospective, Italy, peer-reviewed, 24 authors, study period 1 March, 2020 - 10 April, 2020, dosage 1mg days 1-21.	**risk of death, 76.0% lower, HR 0.24, *p* = 0.005**, treatment 71, control 70, adjusted per study, propensity score weighting.
	risk of no recovery, 44.4% lower, RR 0.56, *p* = 0.048, treatment 71, control 70, adjusted per study, inverted to make RR<1 favor treatment, propensity score weighting.
Mareev, 2/28/2021, retrospective, Russia, peer-reviewed, 21 authors, dosage 1mg days 1-3.	**risk of death, 79.6% lower, RR 0.20, *p* = 0.49**, treatment 0 of 21 (0.0%), control 2 of 22 (9.1%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	ΔSHOCS-COVID, 50.0% lower, RR 0.50, *p* = 0.06, treatment 21, control 22, ΔSHOCS-COVID score, primary outcome.
	SHOCS-COVID, 71.4% lower, RR 0.29, *p* = 0.002, treatment 21, control 22, SHOCS-COVID score.
	NEWS-2, 66.7% lower, RR 0.33, *p* = 0.06, treatment 21, control 22, inverted to make RR<1 favor treatment, NEWS-2 score.

	hospitalization time, 25.7% lower, relative time 0.74, $p = 0.08$, treatment 21, control 22.
Mehrizi, 12/18/2023, retrospective, Iran, peer-reviewed, 10 authors, study period 1 February, 2020 - 20 March, 2022.	risk of death, 13.0% higher, OR 1.13, $p < 0.001$, RR approximated with OR.
Mostafaie, 4/20/2021, Randomized Controlled Trial, Iran, preprint, 1 author, study period 1 April, 2020 - 1 November, 2020, dosage not specified, this trial uses multiple treatments in the treatment arm (combined with phenolic monoterpenes) - results of individual treatments may vary, trial NCT04392141 (history).	risk of death, 83.3% lower, RR 0.17, $p = 0.11$, treatment 1 of 60 (1.7%), control 6 of 60 (10.0%), NNT 12, primary outcome.
	hospitalization time, 34.7% lower, relative time 0.65, $p < 0.001$, treatment 59, control 54.
Pascual-Figal, 9/11/2021, Randomized Controlled Trial, Spain, peer-reviewed, 14 authors, study period 30 April, 2020 - 4 December, 2020, dosage 1.5mg day 1, 1mg days 2-8, 0.5mg days 9-36, trial NCT04350320 (history).	risk of death, 80.2% lower, RR 0.20, $p = 0.24$, treatment 0 of 52 (0.0%), control 2 of 51 (3.9%), NNT 26, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 80.2% lower, RR 0.20, $p = 0.24$, treatment 0 of 52 (0.0%), control 2 of 51 (3.9%), NNT 26, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 51.0% lower, RR 0.49, $p = 0.44$, treatment 2 of 52 (3.8%), control 4 of 51 (7.8%), NNT 25.
	risk of 7-point scale, 87.5% lower, RR 0.13, $p = 0.03$, treatment 3 of 52 (5.8%), control 7 of 51 (13.7%), adjusted per study, odds ratio converted to relative risk, deterioration ≥1 point, multivariable, primary outcome.
	risk of 7-point scale, 80.2% lower, RR 0.20, $p = 0.24$, treatment 0 of 52 (0.0%), control 2 of 51 (3.9%), NNT 26, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), deterioration ≥2 points.
	hospitalization time, 14.6% higher, relative time 1.15, $p = 0.34$, treatment 52, control 51.
Perricone, 10/31/2022, Randomized Controlled Trial, Italy, peer-reviewed, mean age 69.1, 40 authors, study period 18 April, 2020 - 12 May, 2021, dosage 1.5mg daily, 2mg daily for >100kg, trial NCT04375202 (history) (COLVID-19).	risk of death, 36.4% higher, RR 1.36, $p = 0.77$, treatment 7 of 77 (9.1%), control 5 of 75 (6.7%).
	risk of progression, 7.1% higher, RR 1.07, $p = 1.00$, treatment 11 of 77 (14.3%), control 10 of 75 (13.3%), mechanical ventilation, ICU, or death, primary outcome.
	risk of mechanical ventilation, 29.9% higher, RR 1.30, $p = 1.00$, treatment 4 of 77 (5.2%), control 3 of 75 (4.0%).
	risk of ICU admission, 75.6% lower, RR 0.24, $p = 0.21$, treatment 1 of 77 (1.3%), control 4 of 75 (5.3%), NNT 25.
	hospitalization time, 4.1% lower, relative time 0.96, $p = 0.69$, treatment mean 14.1 (±10.4) n=77, control mean 14.7 (±8.1)

	n=75.
Pimenta Bonifácio, 4/28/2022, Randomized Controlled Trial, Brazil, peer-reviewed, mean age 48.9, 18 authors, study period 5 January, 2021 - 30 July, 2021, dosage 1.5mg days 1-3, 1mg days 4-28, trial NCT04724629 (history) (STRUCK).	risk of death, 78.9% lower, RR 0.21, $p = 0.49$, treatment 0 of 14 (0.0%), control 2 of 16 (12.5%), NNT 8.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no improvement, 84.9% lower, RR 0.15, $p = 0.23$, treatment 0 of 14 (0.0%), control 3 of 16 (18.8%), NNT 5.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Pinzón, 10/23/2020, retrospective, Colombia, preprint, 9 authors, dosage 1mg days 1-14.	risk of death, 34.5% lower, RR 0.65, $p = 0.18$, treatment 14 of 145 (9.7%), control 23 of 156 (14.7%), NNT 20, odds ratio converted to relative risk.
Pourdowlat, 2/2/2022, Randomized Controlled Trial, Iran, peer-reviewed, 18 authors, study period 26 March, 2020 - 30 September, 2020.	risk of hospitalization, 72.8% lower, RR 0.27, $p = 0.004$, treatment 5 of 102 (4.9%), control 18 of 100 (18.0%), NNT 7.6.
	relative improvement in dyspnea, 37.5% better, RR 0.62, $p = 0.03$, treatment 89, control 63, excluding 5 treatment and 37 control patients that needed hospitalization/other interventions.
	relative improvement in Ct score, 22.4% better, RR 0.78, $p = 0.048$, treatment 89, control 63, excluding 5 treatment and 37 control patients that needed hospitalization/other interventions.
Rahman, 11/16/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Bangladesh, peer-reviewed, 14 authors, study period June 2020 - November 2020, dosage 1.2mg day 1, 0.6mg days 2-14, trial NCT04527562 (history).	risk of death, 71.0% lower, HR 0.29, $p = 0.04$, treatment 4 of 146 (2.7%), control 13 of 146 (8.9%), NNT 16, Cox proportional hazards, day 28.
	risk of progression, 71.0% lower, HR 0.29, $p = 0.04$, treatment 4 of 146 (2.7%), control 13 of 146 (8.9%), NNT 16, 2 point deterioration, Cox proportional hazards, day 28.
	risk of death, 61.0% lower, HR 0.39, $p = 0.26$, treatment 2 of 146 (1.4%), control 5 of 146 (3.4%), NNT 49, Cox proportional hazards, day 14.
	risk of mechanical ventilation, 51.0% lower, HR 0.49, $p = 0.41$, treatment 2 of 146 (1.4%), control 4 of 146 (2.7%), NNT 73, Cox proportional hazards, day 14.
	risk of progression, 56.0% lower, HR 0.44, $p = 0.17$, treatment 4 of 146 (2.7%), control 9 of 146 (6.2%), NNT 29, 2 point deterioration, Cox proportional hazards, day 14, primary outcome.
Recovery Collaborative Group, 5/18/2021, Randomized Controlled Trial, United Kingdom, peer-reviewed, 35 authors, study period 27 November, 2020 - 4 March, 2021, average treatment delay 9.0 days, dosage 1.5mg day 1, 1mg days 2-10, dose for days 2-10 halved for certain patients, trial NCT04381936 (history) (RECOVERY), excluded in exclusion analyses: very late stage, 9 days since symptoms started, 32% baseline ventilation.	risk of death, 1.0% higher, RR 1.01, $p = 0.77$, treatment 1,173 of 5,610 (20.9%), control 1,190 of 5,730 (20.8%).
	risk of mechanical ventilation, 18.0% higher, RR 1.18, $p = 0.06$, treatment 259 of 3,815 (6.8%), control 228 of 3,962 (5.8%).
	risk of death/intubation, 2.0% higher, RR 1.02, $p = 0.47$, treatment 1,344 of 5,342 (25.2%), control 1,343 of 5,469 (24.6%).

	risk of no hospital discharge, 2.0% higher, RR 1.02, $p = 0.44$, treatment 1,709 of 5,610 (30.5%), control 1,698 of 5,730 (29.6%), inverted to make RR<1 favor treatment.
Rodriguez-Nava, 11/5/2020, retrospective, USA, peer-reviewed, median age 68.0, 8 authors, dosage not specified, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; excessive unadjusted differences between groups; unadjusted results with no group details.	risk of death, 5.5% lower, RR 0.94, $p = 0.87$, treatment 16 of 52 (30.8%), control 85 of 261 (32.6%), NNT 56, unadjusted.
Salehzadeh, 9/21/2020, Randomized Controlled Trial, Iran, peer-reviewed, median age 56.0, 3 authors, study period 21 May, 2020 - 20 June, 2020, average treatment delay 6.28 (treatment) 8.12 (control) days, trial IRCT20200418047126N1.	hospitalization time, 22.7% lower, relative time 0.77, $p = 0.001$, treatment 50, control 50.
Sandhu, 10/27/2020, prospective, USA, peer-reviewed, 4 authors, dosage 1.2mg days 1-3, 0.6mg days 4-15.	risk of death, 41.7% lower, RR 0.58, $p < 0.001$, treatment 16 of 34 (47.1%), control 63 of 78 (80.8%), NNT 3.0.
	risk of mechanical ventilation, 52.9% lower, RR 0.47, $p < 0.001$, treatment 16 of 34 (47.1%), control 68 of 68 (100.0%), NNT 1.9.
	risk of no hospital discharge, 41.7% lower, RR 0.58, $p < 0.001$, treatment 16 of 34 (47.1%), control 63 of 78 (80.8%), NNT 3.0.
Scarsi, 9/14/2020, retrospective, Italy, peer-reviewed, 28 authors, dosage 1mg daily.	risk of death, 84.9% lower, HR 0.15, $p < 0.001$, treatment 122, control 140.
Shah, 2/24/2023, Randomized Controlled Trial, USA, peer-reviewed, median age 61.0, 23 authors, study period October 2020 - September 2021, this trial uses multiple treatments in the treatment arm (combined with rosuvastatin) - results of individual treatments may vary, trial NCT04472611 (history) (COLSTAT), excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline.	risk of death, 75.0% higher, RR 1.75, $p = 0.54$, treatment 7 of 125 (5.6%), control 4 of 125 (3.2%), day 60.
	risk of death, 100% higher, RR 2.00, $p = 0.50$, treatment 6 of 125 (4.8%), control 3 of 125 (2.4%), day 30.
	risk of mechanical ventilation, 200.0% higher, RR 3.00, $p = 0.28$, treatment 6 of 125 (4.8%), control 2 of 125 (1.6%).
	risk of severe case, 46.2% higher, RR 1.46, $p = 0.34$, treatment 19 of 125 (15.2%), control 13 of 125 (10.4%), day 60, primary outcome.
	risk of severe case, 72.7% higher, RR 1.73, $p = 0.17$, treatment 19 of 125 (15.2%), control 11 of 125 (8.8%), day 30, primary outcome.
Sunil Naik, 1/21/2023, Randomized Controlled Trial, India, peer-reviewed, 3 authors, trial CTRI/2021/03/032060.	risk of death, 169.4% higher, RR 2.69, $p = 1.00$, treatment 1 of 62 (1.6%), control 0 of 43 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of progression, 108.1% higher, RR 2.08, $p = 0.64$, treatment 3 of 62 (4.8%), control 1 of 43 (2.3%).
	recovery, 7.3% lower, RR 0.93, $p = 0.21$, treatment 62, control 43, relative improvement in ordinal score.

	risk of no recovery, 15.0% lower, RR 0.85, p = 0.06, treatment 49 of 62 (79.0%), control 40 of 43 (93.0%), NNT 7.1, ordinal score ≤1.
	recovery, 24.3% lower, RR 0.76, p = 0.02, treatment 62, control 43, relative improvement in CT score.
Tardif, 1/27/2021, Double Blind Randomized Controlled Trial, multiple countries, peer-reviewed, 44 authors, study period 23 March, 2020 - 21 January, 2021, average treatment delay 5.3 days, dosage 1mg days 1-3, 0.5mg days 4-30, trial NCT04322682 (history) (COLCORONA).	**risk of death, 43.9% lower, RR 0.56, p = 0.30**, treatment 5 of 2,235 (0.2%), control 9 of 2,253 (0.4%), NNT 569, odds ratio converted to relative risk.
	risk of death/hospitalization, 20.0% lower, RR 0.80, p = 0.08, treatment 104 of 2,235 (4.7%), control 131 of 2,253 (5.8%), NNT 86, odds ratio converted to relative risk, primary outcome.
	risk of mechanical ventilation, 46.8% lower, RR 0.53, p = 0.09, treatment 11 of 2,235 (0.5%), control 21 of 2,253 (0.9%), NNT 227, odds ratio converted to relative risk.
	risk of hospitalization, 20.0% lower, RR 0.80, p = 0.09, treatment 101 of 2,235 (4.5%), control 128 of 2,253 (5.7%), NNT 86, odds ratio converted to relative risk.
Valerio Pascua, 1/7/2021, retrospective, multiple countries, peer-reviewed, 19 authors, study period 10 June, 2020 - 6 August, 2020, average treatment delay 6.1 days, dosage 1.5mg day 1, 1mg days 2-5, varied by location, this trial uses multiple treatments in the treatment arm (combined with LMWH, tocilizumab, dexamethasone, methylprednisolone) - results of individual treatments may vary.	**risk of death, 22.8% lower, RR 0.77, p = 0.60**, treatment 5 of 35 (14.3%), control 12 of 30 (40.0%), NNT 3.9, adjusted per study, odds ratio converted to relative risk, multivariable.
	ICU time, 39.9% lower, relative time 0.60, p = 0.03, treatment 35, control 30, adjusted per study, multivariable.
Vaziri, 3/6/2024, Randomized Controlled Trial, Iran, peer-reviewed, mean age 54.2, 11 authors, study period April 2020 - December 2020, this trial uses multiple treatments in the treatment arm (combined with phenolic monoterpenes) - results of individual treatments may vary, trial NCT04392141 (history), excluded in exclusion analyses: randomization resulted in significant baseline differences that were not adjusted for.	**risk of death, 81.2% lower, RR 0.19, p = 0.03**, treatment 2 of 108 (1.9%), control 7 of 71 (9.9%), NNT 12, after 14 day followup.
	risk of death, 89.0% lower, RR 0.11, p = 0.02, treatment 1 of 108 (0.9%), control 6 of 71 (8.5%), NNT 13, in hospital.
	risk of ICU admission, 86.9% lower, RR 0.13, p = 0.002, treatment 2 of 108 (1.9%), control 10 of 71 (14.1%), NNT 8.2.
	hospitalization time, 34.7% lower, relative time 0.65, p < 0.001, treatment mean 4.17 (±1.34) n=108, control mean 6.39 (±2.59) n=71.
Villamañán, 3/23/2023, retrospective, Spain, peer-reviewed, median age 79.0, 10 authors, study period March 2020 - June 2020.	**risk of death, 41.9% lower, RR 0.58, p = 0.03**, treatment 19 of 111 (17.1%), control 32 of 111 (28.8%), NNT 8.5, odds ratio converted to relative risk.

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.

Avanoglu Guler, 7/21/2022, retrospective, Turkey, peer-reviewed, median age 39.5, 14 authors.	risk of oxygen therapy, 78.8% lower, RR 0.21, $p = 0.04$, treatment 6 of 66 (9.1%), control 3 of 7 (42.9%), NNT 3.0, inverted to make RR<1 favor treatment, odds ratio converted to relative risk.
Chevalier, 3/22/2023, retrospective, France, peer-reviewed, mean age 70.3, 24 authors.	risk of death, 27.8% higher, RR 1.28, $p = 0.54$, treatment 5 of 21 (23.8%), control 111 of 569 (19.5%), odds ratio converted to relative risk.
	risk of hospitalization, 7.6% lower, RR 0.92, $p = 0.83$, treatment 15 of 116 (12.9%), control 180 of 1,097 (16.4%), odds ratio converted to relative risk.
Correa-Rodríguez, 9/19/2022, retrospective, Spain, peer-reviewed, mean age 44.0, 6 authors.	risk of oxygen therapy, 149.7% higher, RR 2.50, $p = 1.00$, treatment 1 of 163 (0.6%), control 0 of 81 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 149.7% higher, RR 2.50, $p = 1.00$, treatment 1 of 163 (0.6%), control 0 of 81 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of no recovery, 7.1% lower, RR 0.93, $p = 1.00$, treatment 13 of 24 (54.2%), control 7 of 12 (58.3%), NNT 24, full recovery at 6 months.
	risk of case, 0.6% lower, RR 0.99, $p = 1.00$, treatment 24 of 163 (14.7%), control 12 of 81 (14.8%), NNT 1100.
Madrid-García, 1/31/2021, retrospective, Spain, peer-reviewed, 8 authors, study period 1 March, 2020 - 20 May, 2020.	risk of death, 37.1% higher, HR 1.37, $p = 0.57$.
	risk of hospitalization, 137.0% higher, HR 2.37, $p = 0.20$, GBM.
Monserrat Villatoro, 1/8/2022, retrospective, propensity score matching, Spain, peer-reviewed, 18 authors.	risk of death, 80.0% lower, OR 0.20, $p = 0.02$, RR approximated with OR.
Ozcifci, 11/25/2021, prospective, Turkey, peer-reviewed, 13 authors, study period 1 April, 2020 - 30 April, 2021.	risk of case, 4.0% lower, RR 0.96, $p = 0.72$, treatment 130 of 616 (21.1%), control 85 of 421 (20.2%), odds ratio converted to relative risk.
Oztas, 3/21/2022, retrospective, Turkey, peer-reviewed, 15 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	risk of hospitalization, 406.3% higher, RR 5.06, $p = 0.12$, treatment 5 of 635 (0.8%), control 1 of 643 (0.2%).
	risk of symptomatic case, 72.7% higher, RR 1.73, $p = 0.07$, treatment 29 of 635 (4.6%), control 17 of 643 (2.6%).
	risk of case, 24.4% higher, RR 1.24, $p = 0.35$, treatment 43 of 635 (6.8%), control 35 of 643 (5.4%).
Sáenz-Aldea, 1/13/2023, retrospective, Spain, peer-reviewed, 8 authors.	risk of hospitalization, 8.0% higher, OR 1.08, $p = 0.68$, treatment 36 of 3,060 (1.2%) cases, 459 of 56,785 (0.8%) controls, case control OR.

	risk of case, 12.0% higher, OR 1.12, p = 0.68, treatment 140 of 29,817 (0.5%) cases, 459 of 56,875 (0.8%) controls, NNT 9.0, case control OR.
Topless, 1/28/2022, retrospective, database analysis, United Kingdom, peer-reviewed, 6 authors, dosage not specified.	risk of death, 23.2% lower, OR 0.77, p = 0.12, relative odds for patients with gout, model 2, RR approximated with OR.

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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