Famotidine reduces COVID-19 risk: real-time meta analysis of 30 studies

@CovidAnalysis, July 2025, Version 23
https://c19early.org/fmmeta.html

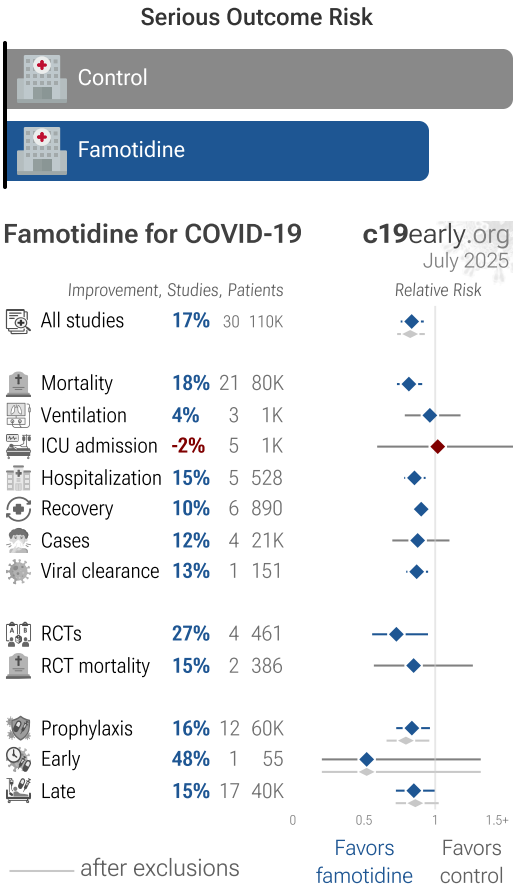
Abstract

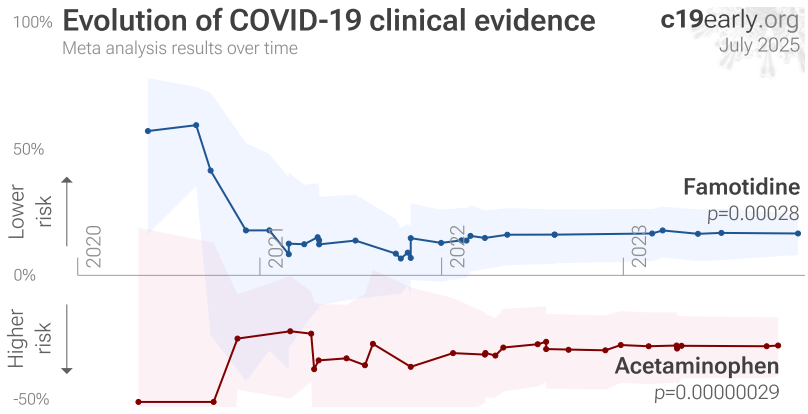
Significantly lower risk is seen for mortality, hospitalization, recovery, and viral clearance. 15 studies from 15 independent teams in 7 countries show significant benefit.

Meta analysis using the most serious outcome reported shows 17% [8-24%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Early treatment is more effective than late treatment.

1 RCT with 528 patients has not reported results (1.5 years late) [1].

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. All data and sources to reproduce this analysis are in the appendix.





FAMOTIDINE FOR COVID-19 — HIGHLIGHTS

Famotidine reduces risk with very high confidence for mortality, hospitalization, recovery, and in pooled analysis, and low confidence for viral clearance, however increased risk is seen with low confidence for progression.

Early treatment is more effective than late treatment.

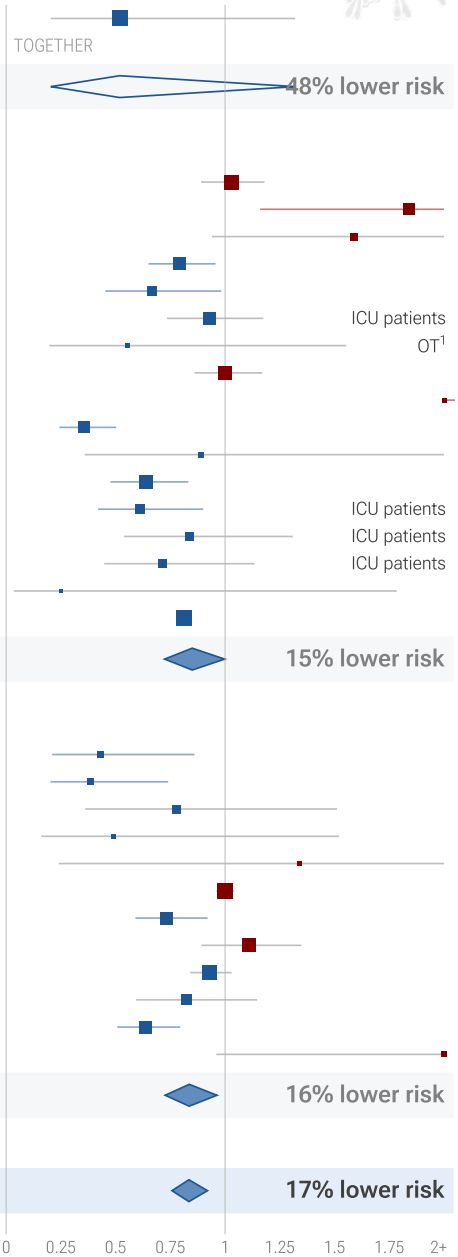
29th treatment shown effective in October 2021, now with $p = 0.00028$ from 30 studies, recognized in 2 countries.

Real-time updates and corrections with a consistent protocol for 172 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

30 famotidine COVID-19 studies (+1 unreported RCT)

c19early.org
July 2025

	Improvement	RR [CI]		Treatment	Control
Brennan (DB RCT)	48%	0.52 [0.20-1.32]	no recov.	5/27	10/28
Together.. (DB RCT)	unknown, >1.5 years late			528 (total)	
Early treatment	48%	0.52 [0.20-1.32]		5/27	10/28
$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.17$					
	Improvement	RR [CI]		Treatment	Control
Shoaibi	-3%	1.03 [0.89-1.18]	death	1,816 (n)	26,820 (n)
Zhou (PSM)	-84%	1.84 [1.16-2.92]	severe case	72/519	198/2,595
Yeramaneni	-59%	1.59 [0.94-2.71]	death	410 (n)	746 (n)
Mura (PSM)	21%	0.79 [0.65-0.96]	death	563 (n)	563 (n)
Samim.. (SB RCT)	33%	0.67 [0.45-0.98]	hosp. time	10 (n)	10 (n)
Elhadi (ICU)	7%	0.93 [0.73-1.17]	death	34/60	247/405
Taşdemir	45%	0.55 [0.20-1.55]	death	5/85	10/94
Kuno (PSM)	0%	1.00 [0.86-1.17]	death	1,593 (n)	7,972 (n)
Stolow	-519%	6.19 [2.10-18.3]	death	137 (n)	352 (n)
Wagner	64%	0.36 [0.24-0.50]	death	82/638	182/819
Pahwani (RCT)	11%	0.89 [0.36-2.20]	death	8/89	9/89
Siraj	36%	0.64 [0.48-0.83]	death	183/711	122/289
Zangeneh (ICU)	39%	0.61 [0.42-0.90]	death	n/a	n/a
Chowdhury (RCT)	16%	0.84 [0.54-1.31]	death	26/104	31/104
Özden (ICU)	29%	0.71 [0.45-1.13]	death	14/30	19/29
Shamsi	75%	0.25 [0.04-1.78]	death	1/27	23/156
Mehrizi	19%	0.81 [0.79-0.83]	death	population-based cohort	
Late treatment	15%	0.85 [0.72-1.00]		425/6,792	841/41,043
$Tau^2 = 0.07$, $I^2 = 88.5\%$, $p = 0.047$					
	Improvement	RR [CI]		Treatment	Control
Freedberg (PSM)	57%	0.43 [0.21-0.86]	death/int.	8/84	332/1,536
Mather (PSM)	61%	0.39 [0.20-0.74]	death	83 (n)	689 (n)
Balouch	22%	0.78 [0.36-1.51]	symp. case	18/80	49/227
Yeramaneni	51%	0.49 [0.16-1.52]	death	351 (n)	6,807 (n)
Cheung	-34%	1.34 [0.24-6.06]	severe case	23 (n)	929 (n)
Fung	0%	1.00 [0.96-1.04]	death	population-based cohort	
Razjouyan	27%	0.73 [0.59-0.92]	death	93 (n)	9,981 (n)
Wallace	-11%	1.11 [0.89-1.35]	death	98/423	1,436/7,521
MacFadden	7%	0.93 [0.84-1.03]	cases	n/a	n/a
Loucera	18%	0.82 [0.59-1.15]	death	207 (n)	15,761 (n)
Kim (PSM)	36%	0.64 [0.51-0.80]	cases	105/5,594	480/15,432
Kwon	-107%	2.07 [0.96-4.47]	progression	204 (n)	204 (n)
Prophylaxis	16%	0.84 [0.73-0.96]		229/7,142	2,297/59,087
$Tau^2 = 0.03$, $I^2 = 76.8\%$, $p = 0.013$					
All studies	17%	0.83 [0.76-0.92]		659/13,961	3,148/100,158



[1] OT: comparison with other treatment

$Tau^2 = 0.04$, $I^2 = 88.4\%$, $p = 0.00028$

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

A

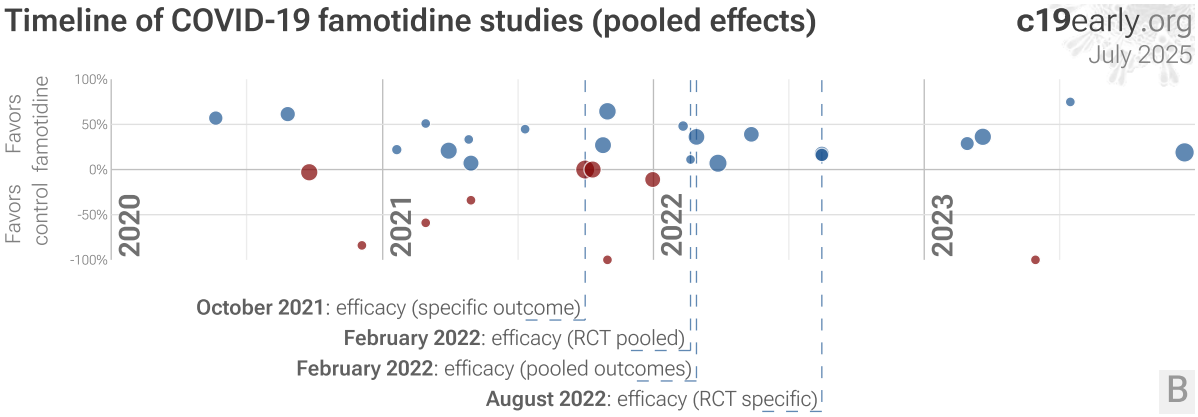


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in famotidine studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, pooled outcomes in RCTs, and one or more specific outcome in RCTs. Efficacy based on RCTs only was delayed by 4.7 months, compared to using all studies. Efficacy based on specific outcomes in RCTs was delayed by 5.8 months, compared to using pooled outcomes in RCTs.

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury[3-15] and cognitive deficits[6,11], cardiovascular complications[16-20], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[21]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

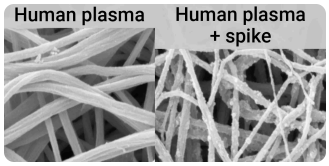


***Figure 2.* SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[2].**

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,22-29], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[30], 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 famotidine 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 3 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.

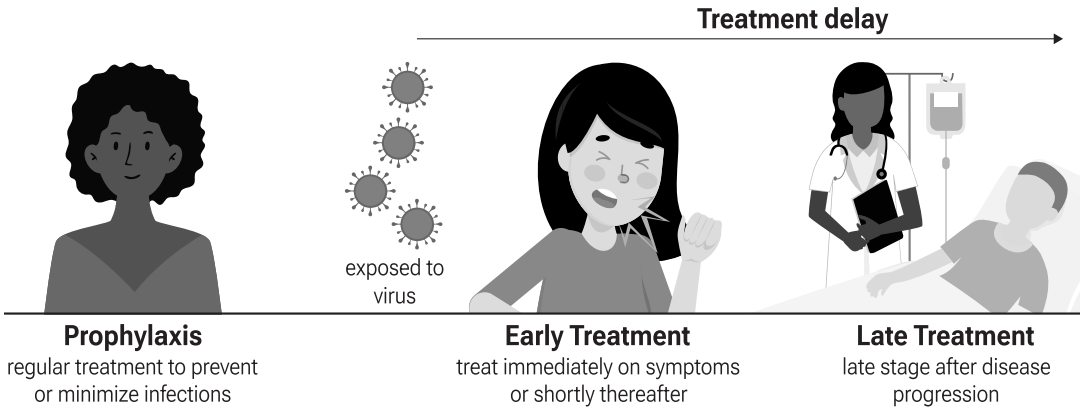


Figure 3. Treatment stages.

Preclinical Research

An *In Vitro* study supports the efficacy of famotidine[31].

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

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

	Relative Risk	Studies	Patients
All studies	0.83 [0.76-0.92] ***	30	110K
After exclusions	0.82 [0.73-0.93] **	26	110K
Peer-reviewed	0.84 [0.76-0.93] ***	29	110K
RCTs	0.73 [0.56-0.95] *	4	461
Mortality	0.82 [0.73-0.91] ***	21	80K
Ventilation	0.96 [0.79-1.18]	3	1,694
ICU admission	1.02 [0.59-1.75]	5	1,056
Hospitalization	0.85 [0.78-0.93] ***	5	528
Recovery	0.90 [0.86-0.95] ****	6	890
Cases	0.88 [0.70-1.10]	4	20K
RCT mortality	0.85 [0.57-1.26]	2	386
RCT hospitalization	0.83 [0.78-0.88] ****	3	349

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the relative risk 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	0.52 [0.20-1.32]	0.85 [0.72-1.00] *	0.84 [0.73-0.96] *
After exclusions	0.52 [0.20-1.32]	0.86 [0.72-1.02]	0.79 [0.66-0.96] *
Peer-reviewed	0.52 [0.20-1.32]	0.86 [0.73-1.02]	0.84 [0.73-0.96] *
RCTs	0.52 [0.20-1.32]	0.75 [0.57-0.99] *	
Mortality		0.80 [0.69-0.94] **	0.85 [0.71-1.04]
Ventilation		0.96 [0.79-1.18]	
ICU admission		1.02 [0.59-1.75]	
Hospitalization		0.83 [0.79-0.87] ****	0.94 [0.91-0.97] ***
Recovery	0.52 [0.20-1.32]	0.90 [0.86-0.95] ****	0.63 [0.26-1.54]
Cases			0.88 [0.70-1.10]
RCT mortality		0.85 [0.57-1.26]	
RCT hospitalization		0.83 [0.78-0.88] ****	

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

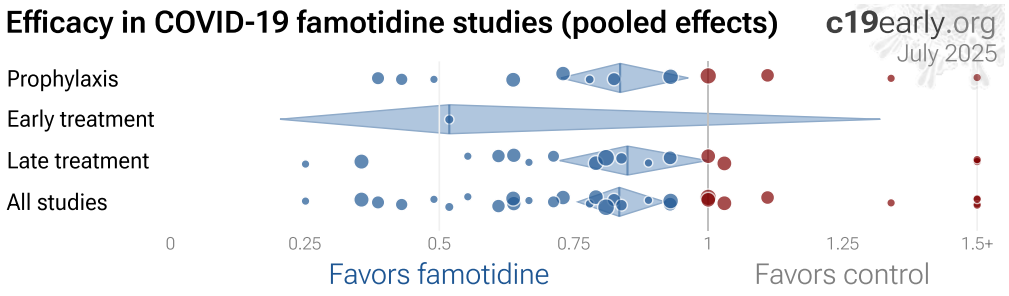


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

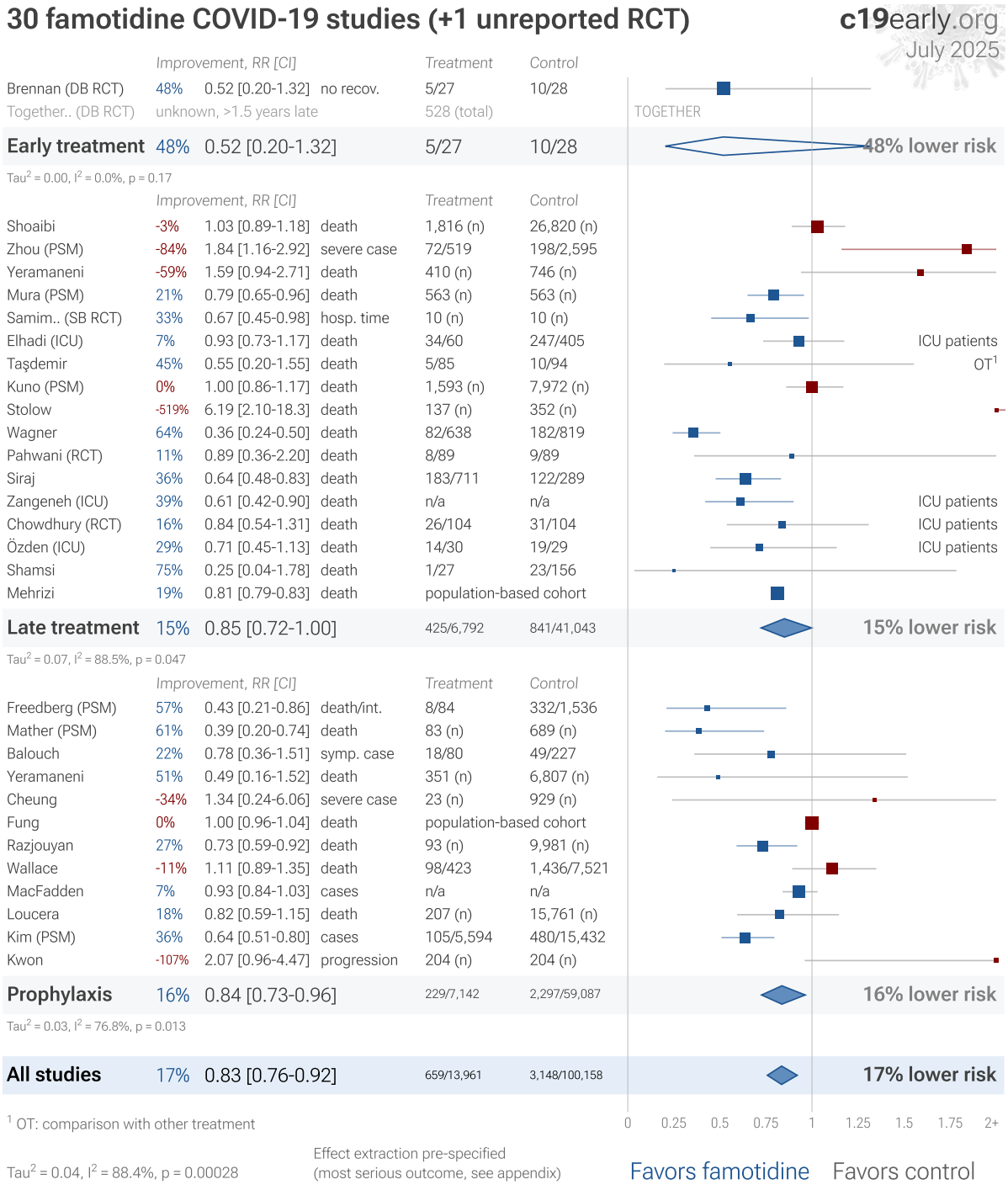


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

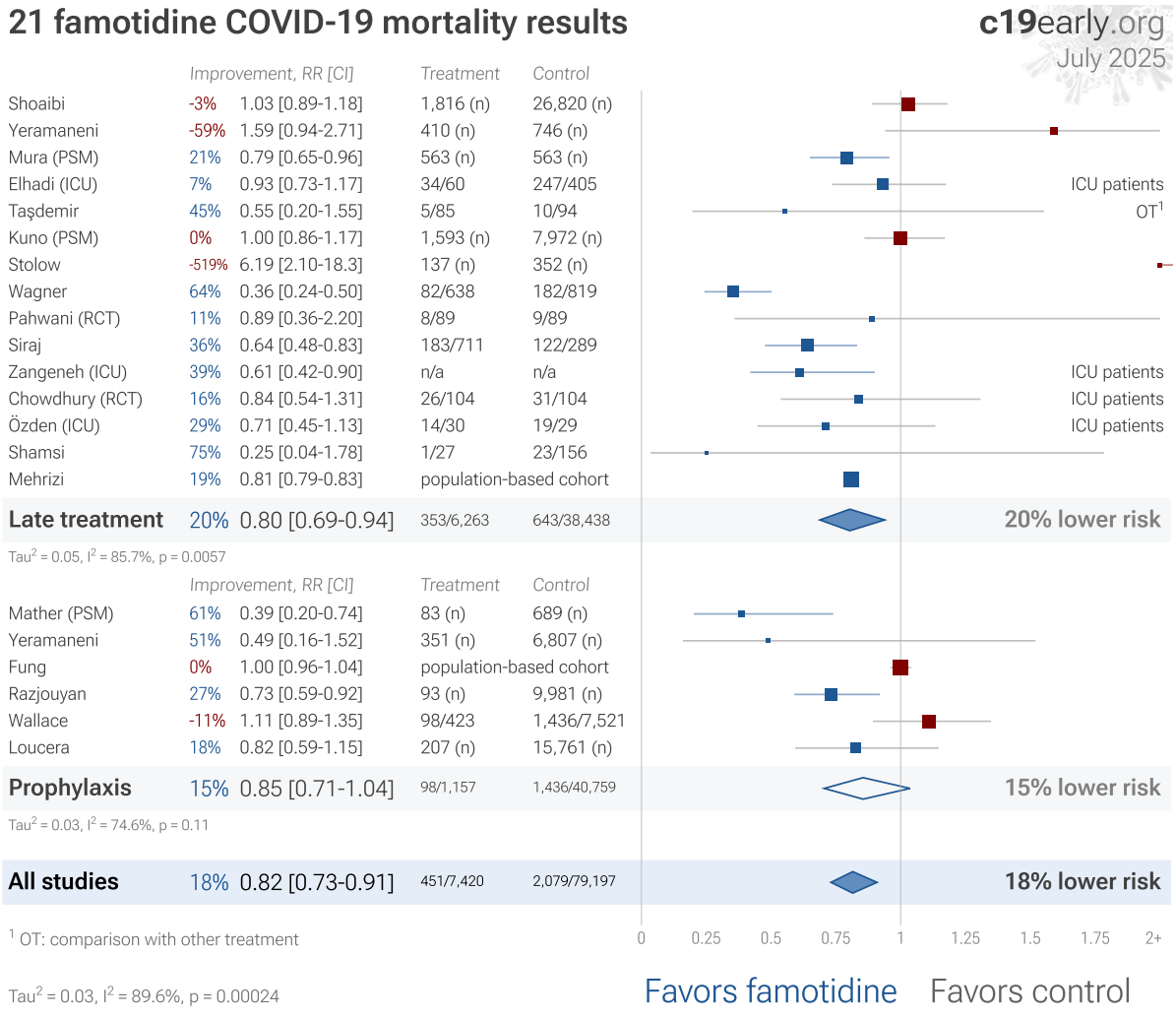


Figure 6. Random effects meta-analysis for mortality results.

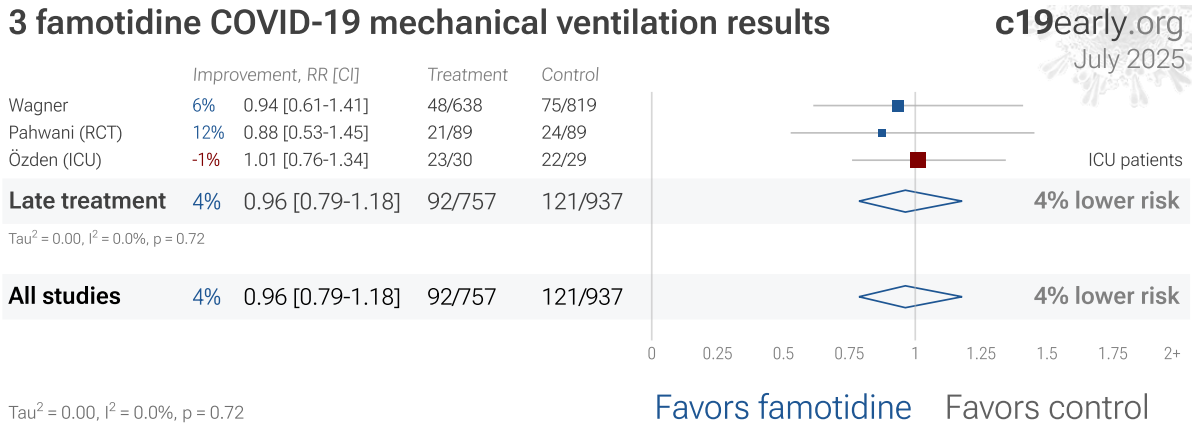


Figure 7. Random effects meta-analysis for ventilation.

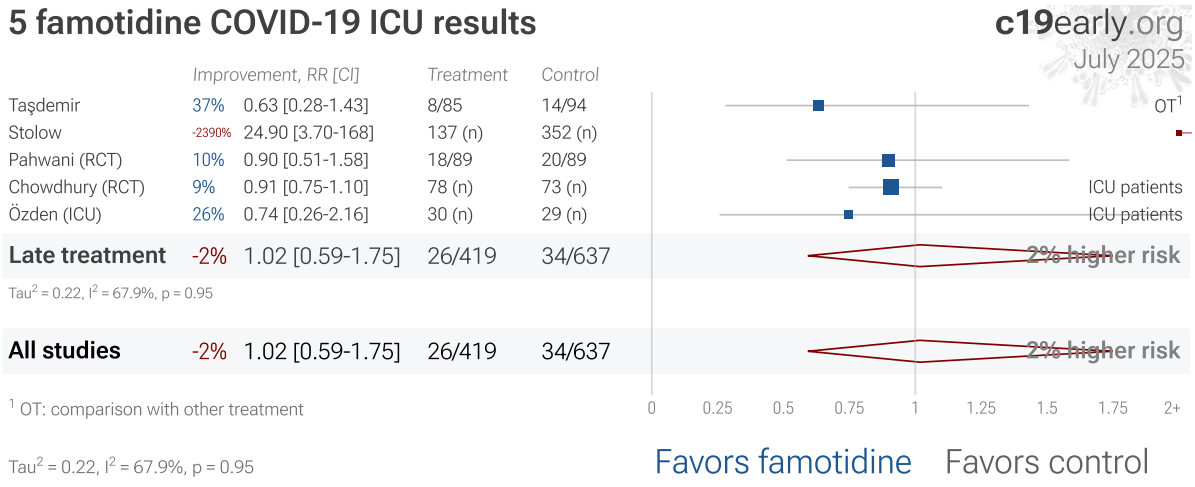


Figure 8. Random effects meta-analysis for ICU admission.

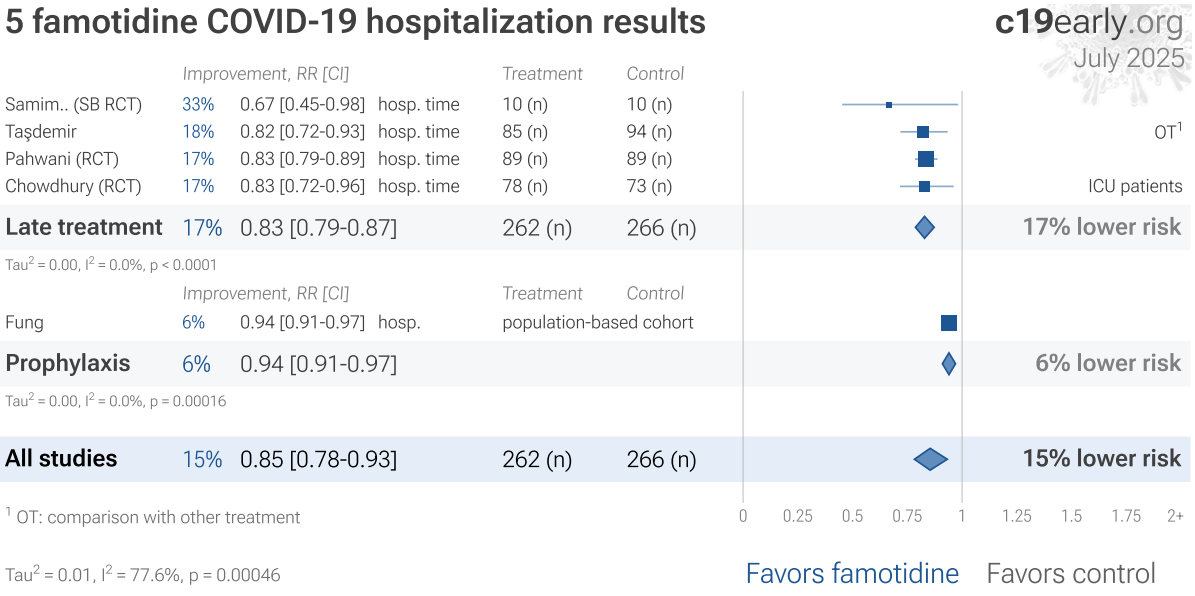


Figure 9. Random effects meta-analysis for hospitalization.

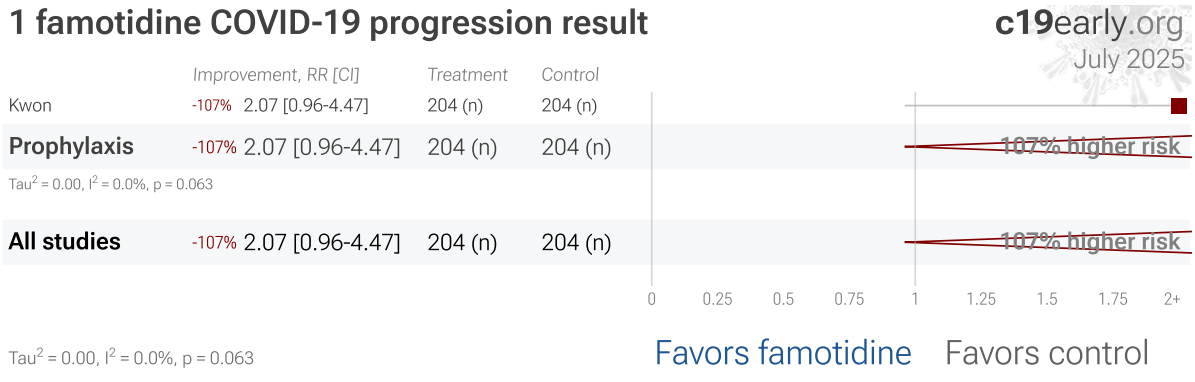


Figure 10. Random effects meta-analysis for progression.

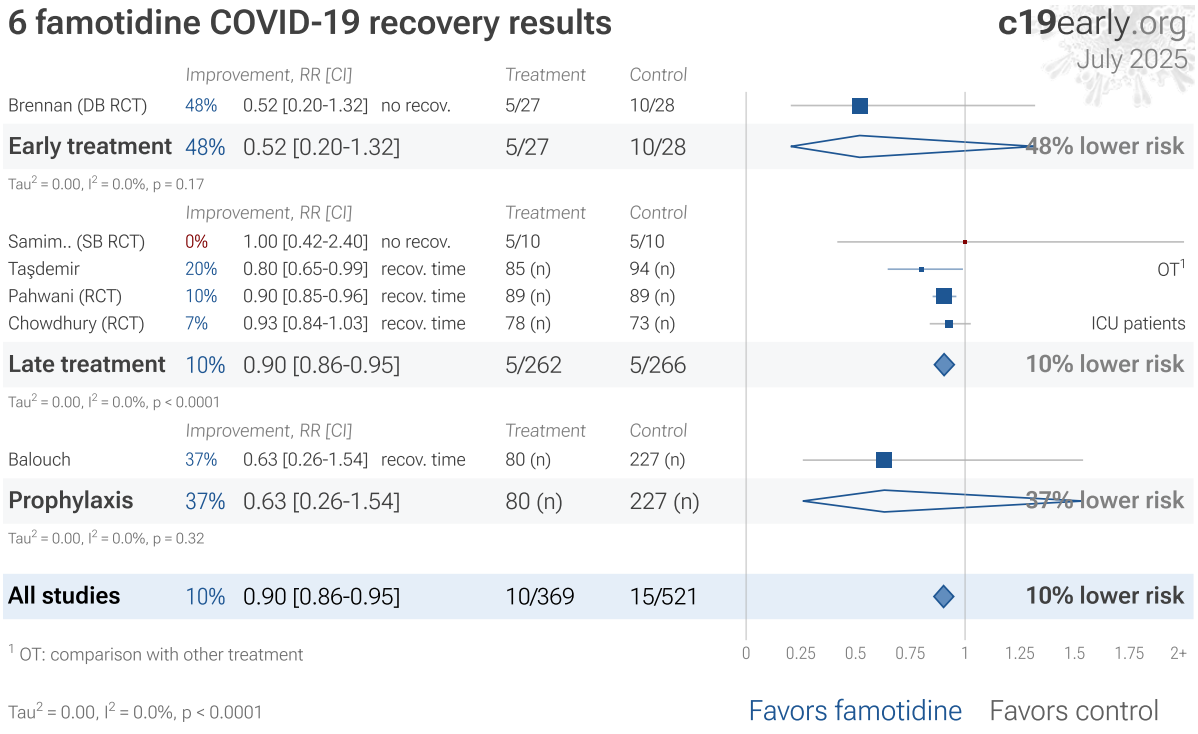


Figure 11. Random effects meta-analysis for recovery.

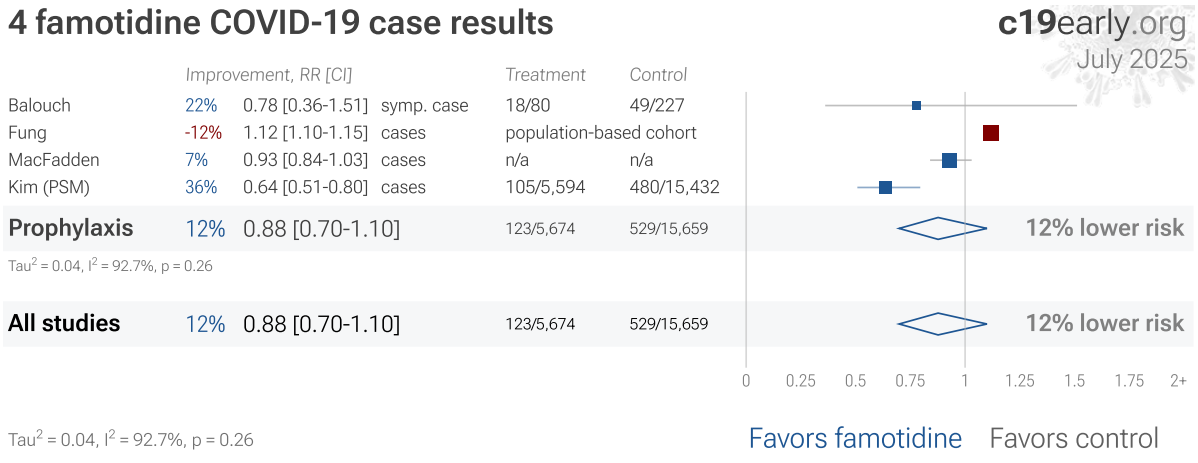


Figure 12. Random effects meta-analysis for cases.

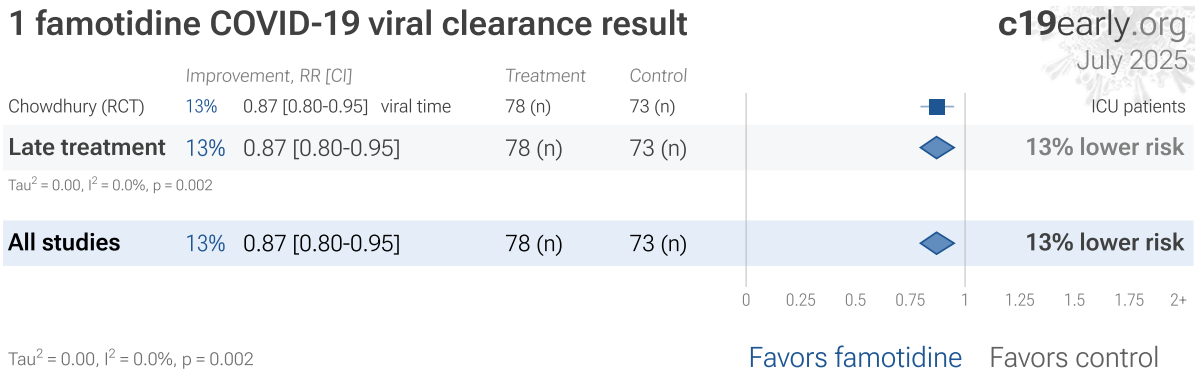


Figure 13. Random effects meta-analysis for viral clearance.

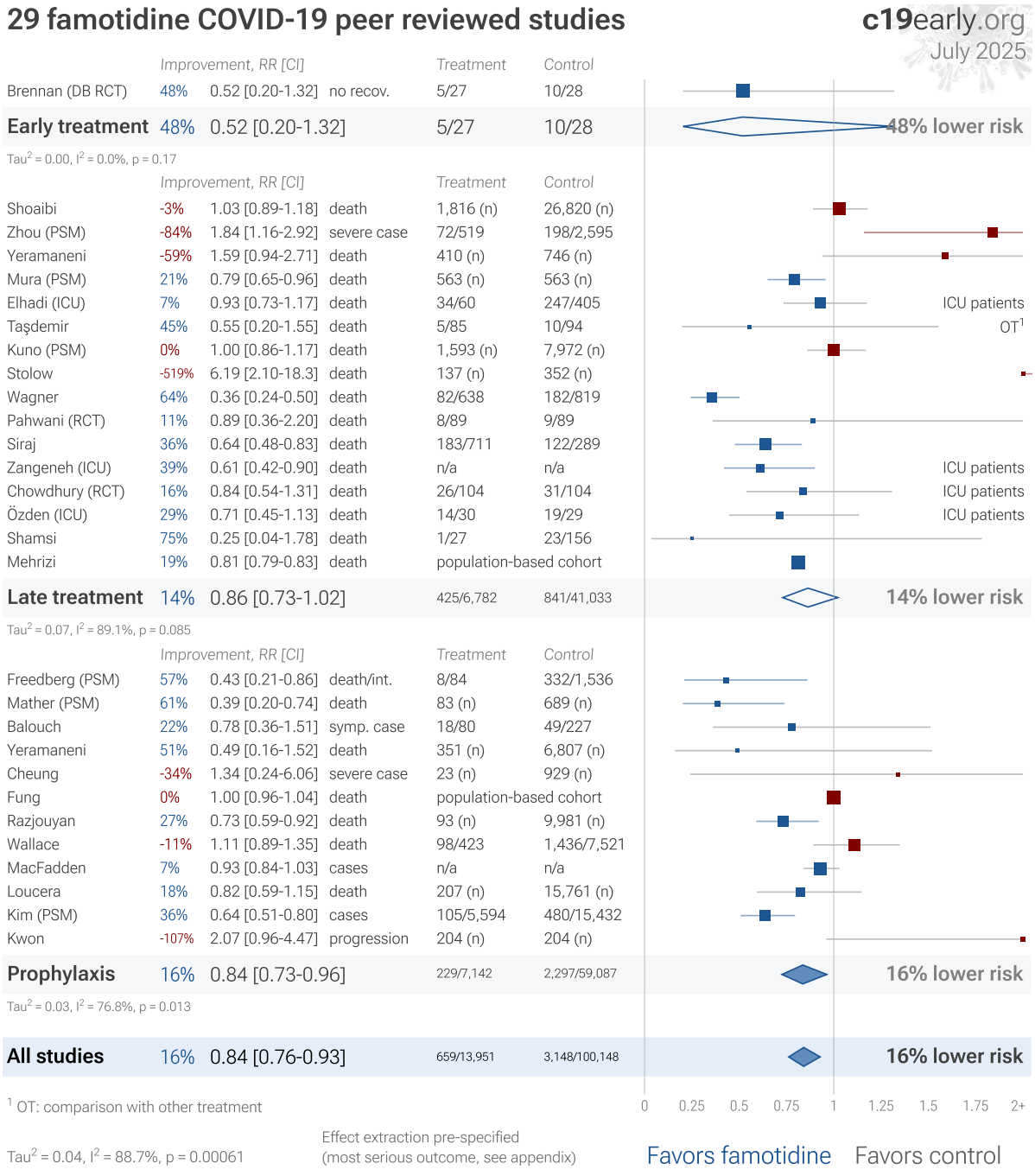


Figure 14. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 15 shows a comparison of results for RCTs and observational studies. Random effects meta analysis of RCTs shows 27% improvement, compared to 16% for other studies. Figure 16, 17, and 18 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

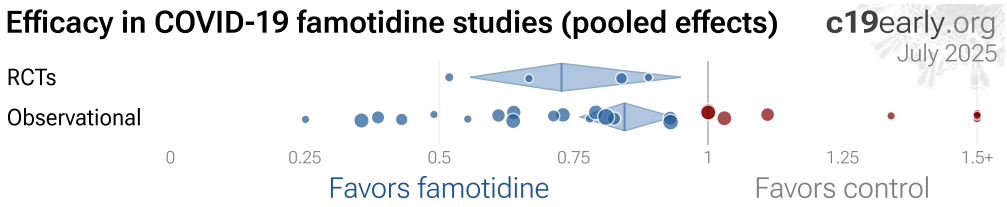


Figure 15. **Results for RCTs and observational studies.**

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases[34], and analysis of double-blind RCTs has identified extreme levels of bias[35]. 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 172 treatments we have analyzed, 67% 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.

Observational studies have been shown to be reliable

Evidence shows that observational studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* analyzed reviews comparing RCTs to observational studies and found little evidence for

significant differences in effect estimates. We performed a similar analysis across the 172 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.98 [0.92-1.05][40]. Similar results are found for all low-cost treatments, RR 1.00 [0.91-1.09]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the supplementary data. *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 remote 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[42,43].

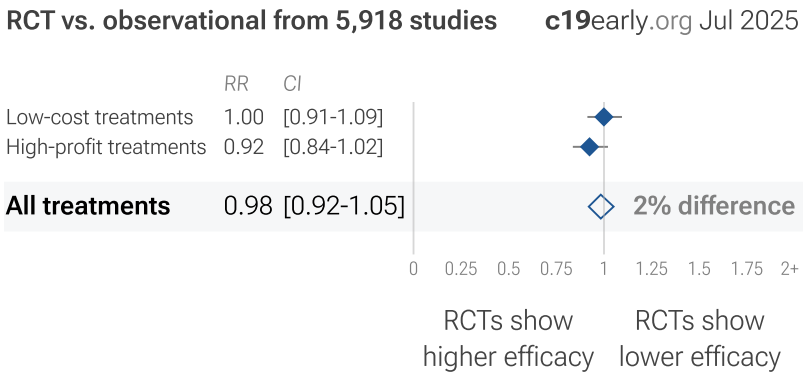


Figure 19. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[37].**

Using all studies identifies efficacy 8+ months faster (9+ months for low-cost treatments)

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 58% have been confirmed in RCTs, with a mean delay of 7.7 months (64% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

Summary

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

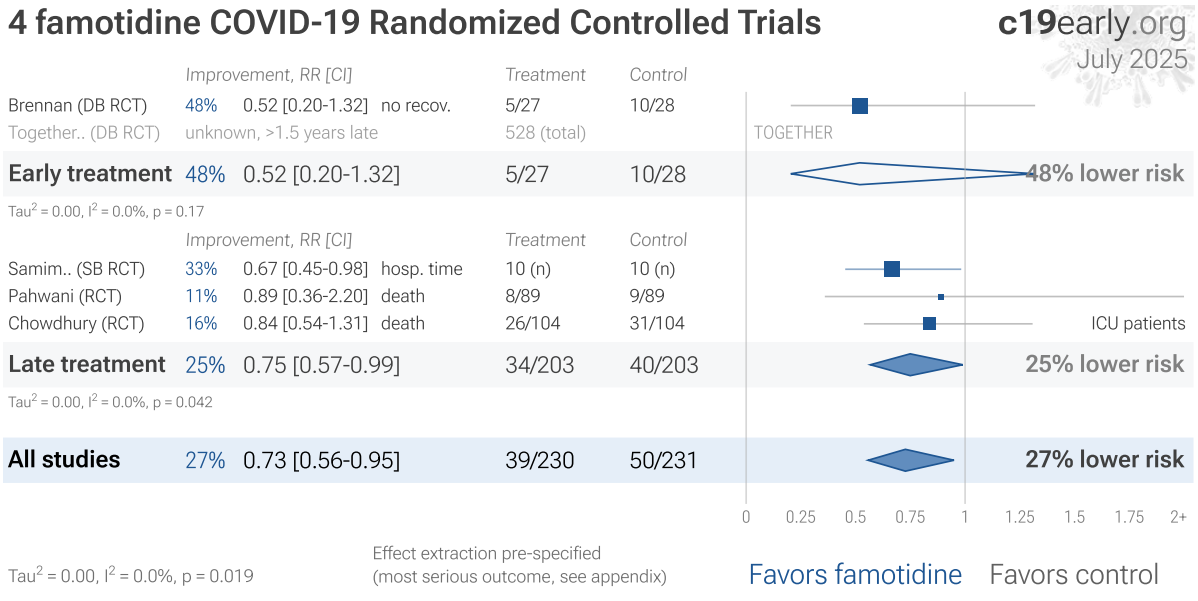


Figure 16. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

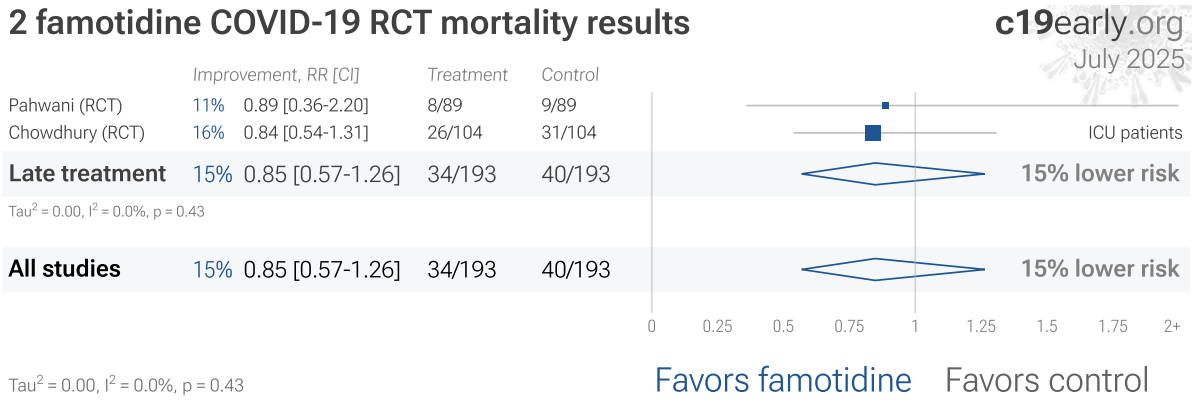


Figure 17. Random effects meta-analysis for RCT mortality results.

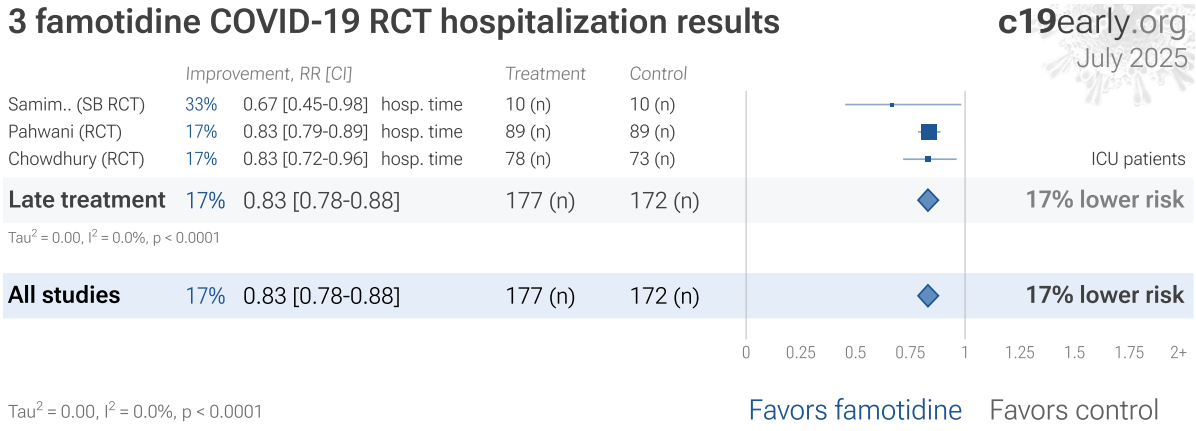


Figure 18. Random effects meta-analysis for RCT hospitalization results.

Unreported RCTs

1 famotidine RCT has not reported results[1]. The trial reports total actual enrollment of 528 patients. The result is delayed over 1.5 years.

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 20 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Elhadi, unadjusted results with no group details.

Fung, not fully adjusting for the different baseline risk of systemic autoimmune patients.

Shamsi, unadjusted results with no group details.

Taşdemir, excessive unadjusted differences between groups.

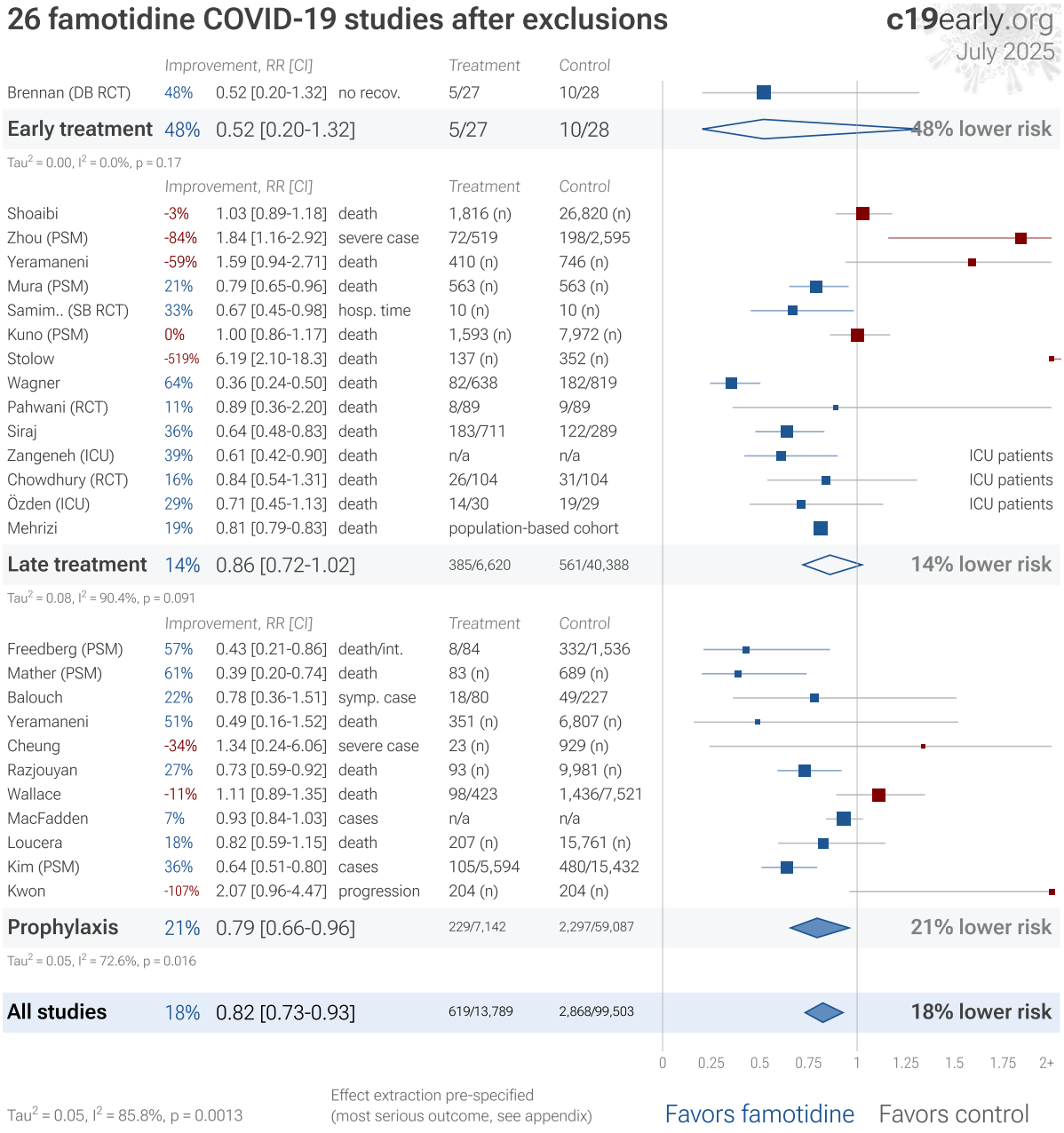


Figure 20. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

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[48,49]. Baloxavir marboxil 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 [50]
<24 hours	-33 hours symptoms [51]
24-48 hours	-13 hours symptoms [51]
Inpatients	-2.5 hours to improvement [52]

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

Figure 21 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

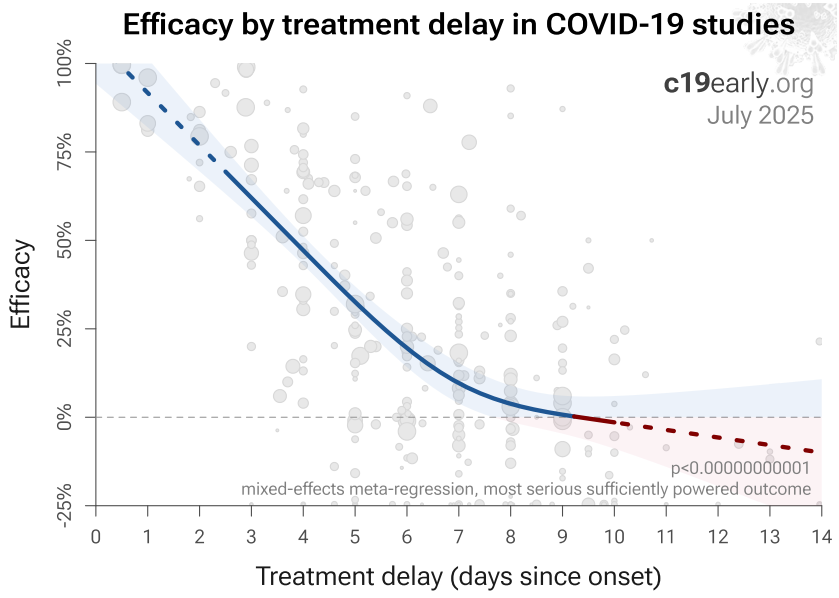


Figure 21. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

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

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [54], for example the Gamma variant shows significantly different characteristics [55-58]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which

TMPRSS2 contributes to viral entry can differ across variants[59,60].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

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.

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic[63-79], therefore efficacy may depend strongly on combined treatments.

Effect measured

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

Meta analysis

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Pooled effects are no longer required to show efficacy as of October 2021

This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however pooled effects are no longer required for famotidine as of October 2021. Efficacy is now known based on specific outcomes for all studies and when restricted to RCTs. Efficacy based on specific outcomes in RCTs was delayed by 5.8 months compared to using pooled outcomes in RCTs.

Combining studies is required

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

allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Specific outcome and pooled analyses

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

Ethical and practical issues limit high-risk trials

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

Validating pooled outcome analysis for COVID-19

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

Analysis of the the association between different outcomes across studies from all 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 22 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 23 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 24 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.000000082$ to $p = 0.0000000033$.

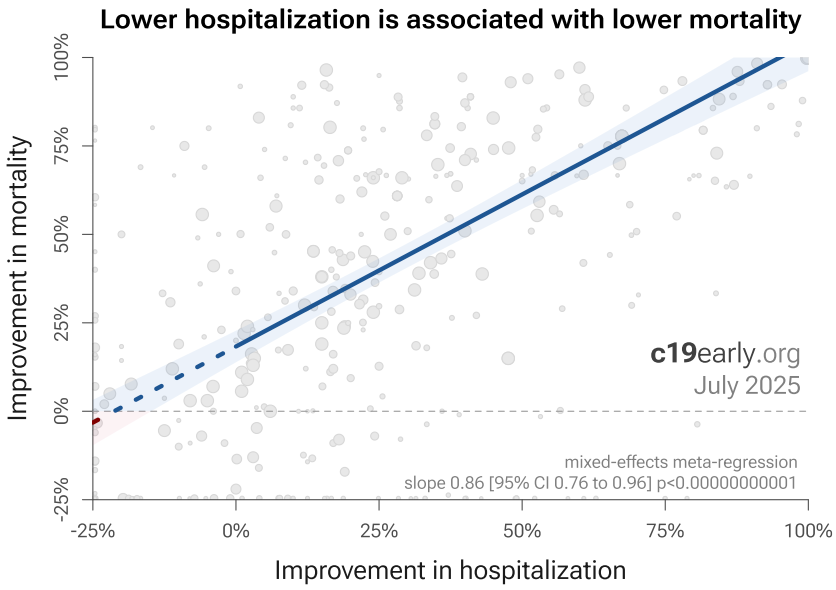


Figure 22. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

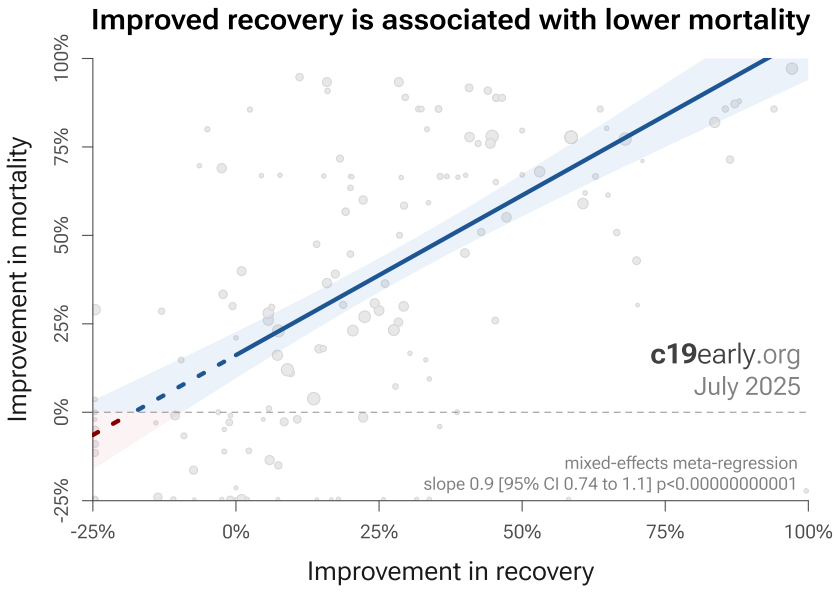


Figure 23. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

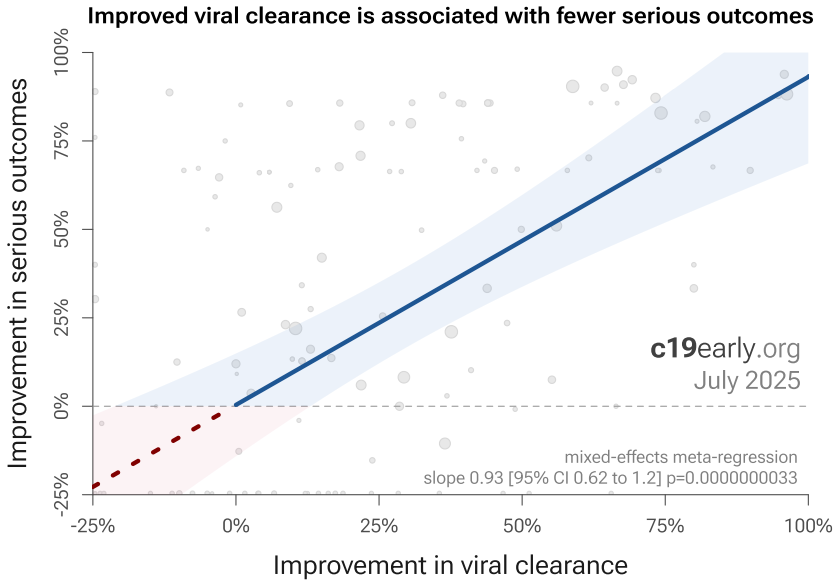


Figure 22. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 25 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

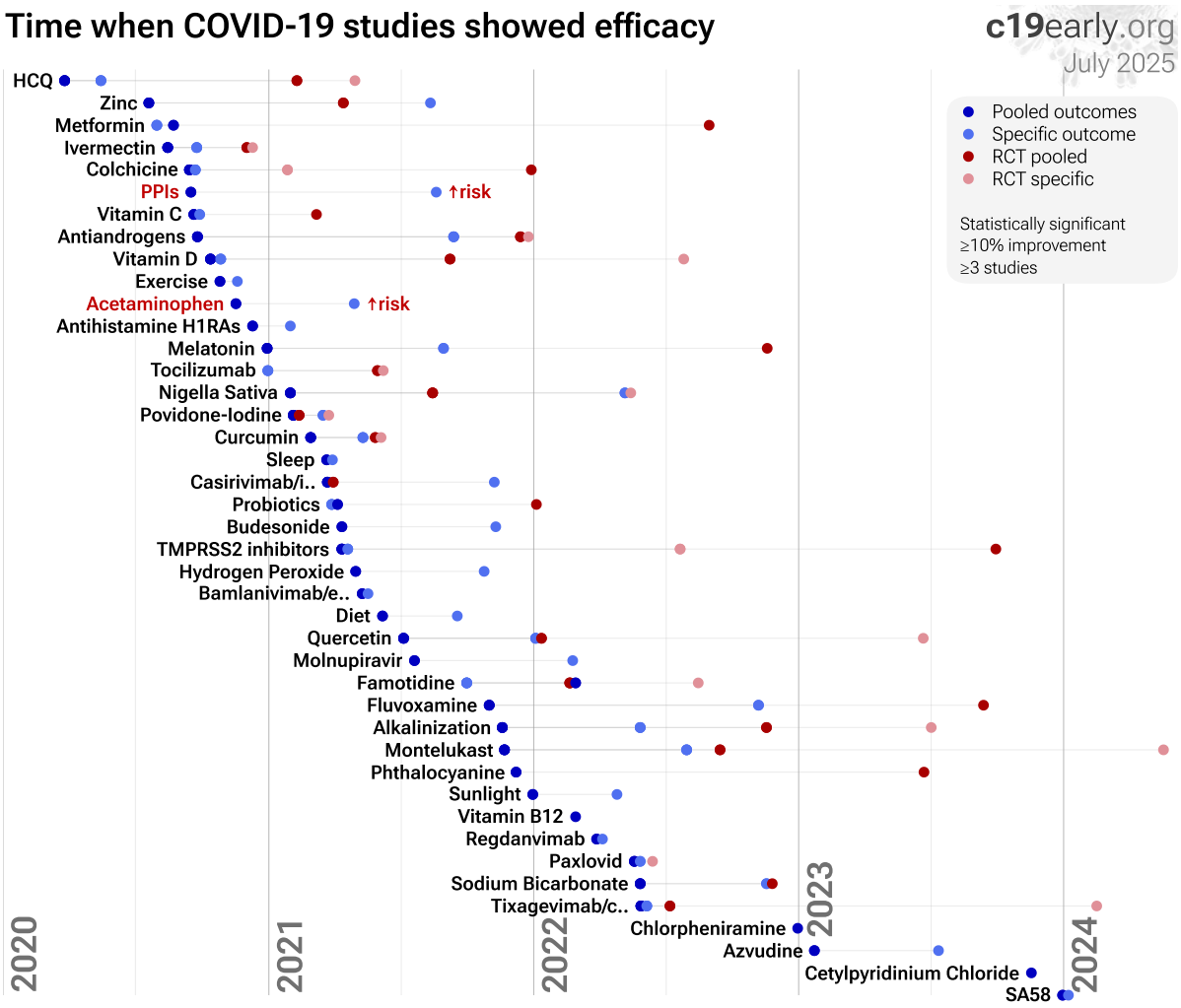


Figure 25. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations

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

Summary

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

Discussion

Publication bias

Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that

value media recognition), and there are many reports of difficulty publishing positive results[81-84]. For famotidine, there is currently not enough data to evaluate publication bias with high confidence.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 26 shows a scatter plot of results for prospective and retrospective studies. 44% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 80% of prospective studies, consistent with a bias toward publishing negative results. The median effect size for retrospective studies is 21% improvement, compared to 16% for prospective studies, showing similar results.

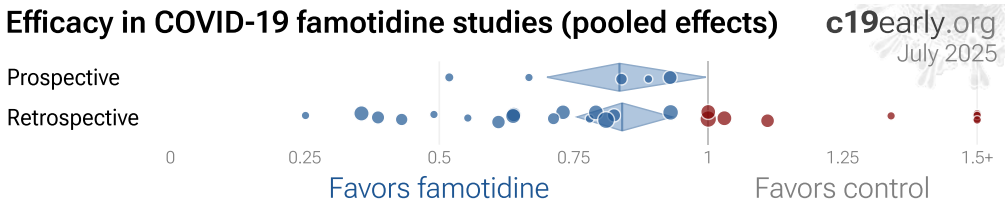


Figure 26. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 27 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 $p < 0.05$[85-92]. 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.

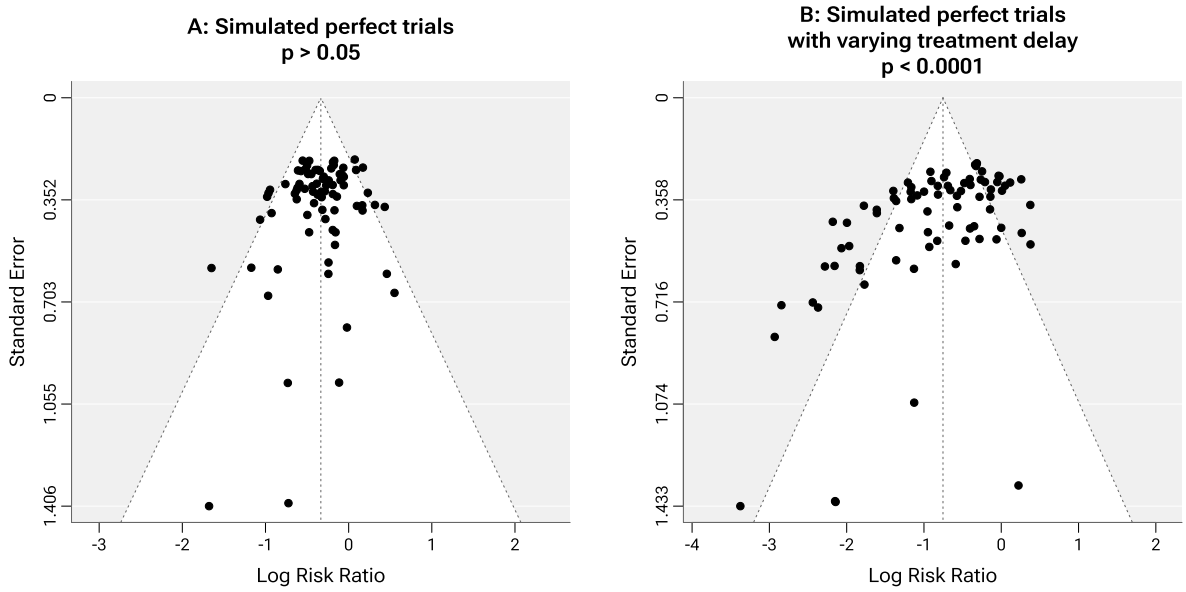


Figure 27. **Example funnel plot analysis for simulated perfect trials.**

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

Limitations

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

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone [63-79]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

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

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

Notes

1 of the 30 studies compare against other treatments, which may reduce the effect seen.

Reviews

Multiple reviews cover famotidine for COVID-19, presenting additional background on mechanisms and related results, including [93,94].

Other studies

Additional preclinical or review papers suggesting potential benefits of famotidine for COVID-19 include [121-137]. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors [22-29], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [30], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 28 shows an overview of the results for famotidine in the context of multiple COVID-19 treatments, and Figure 29 shows a plot of efficacy vs. cost for COVID-19 treatments.

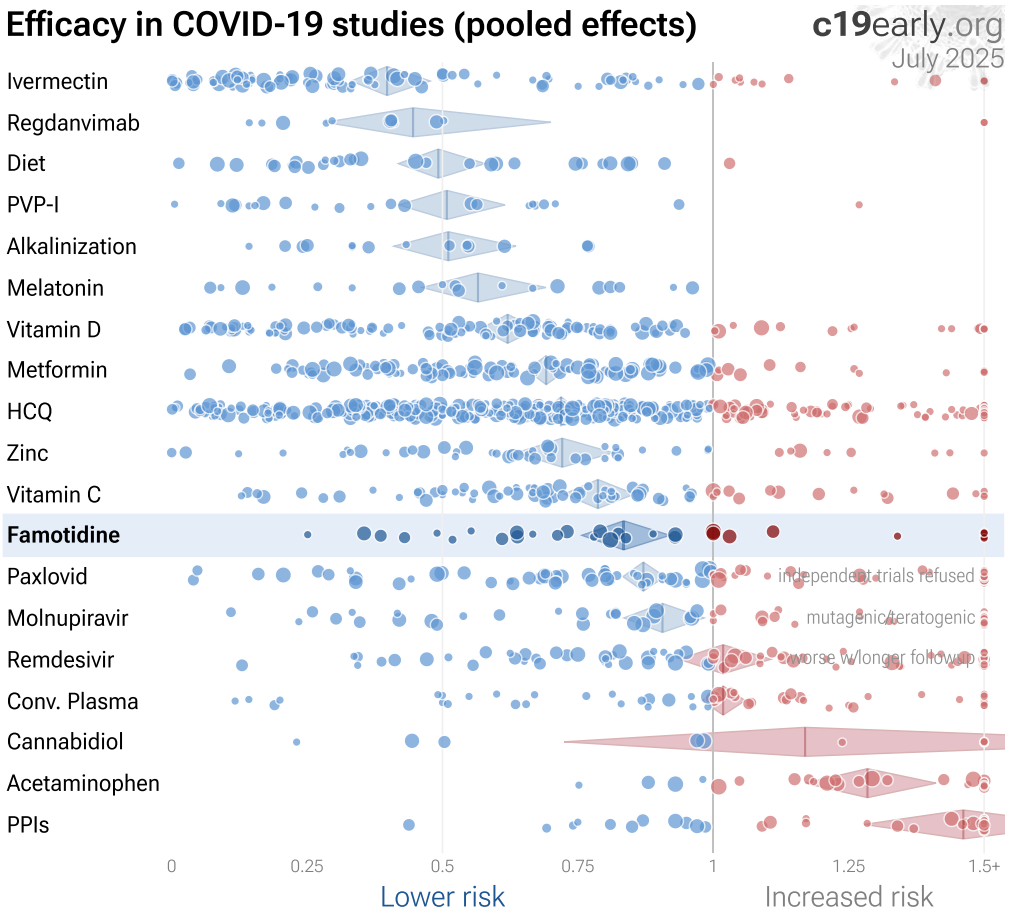


Figure 28. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [138].

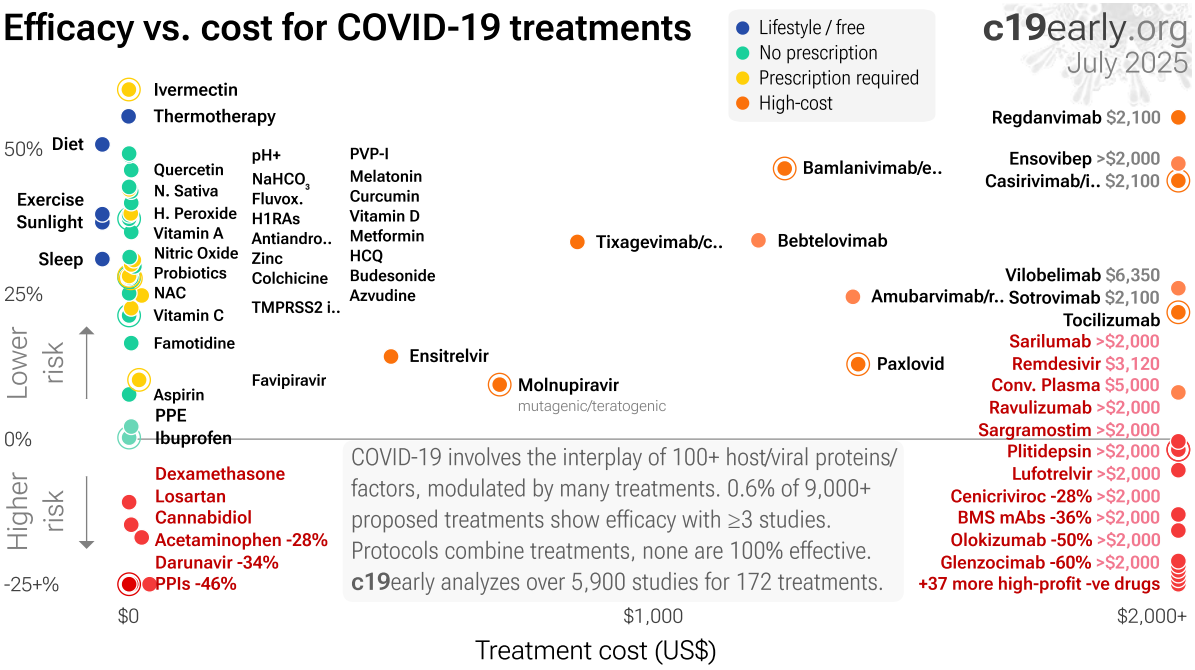


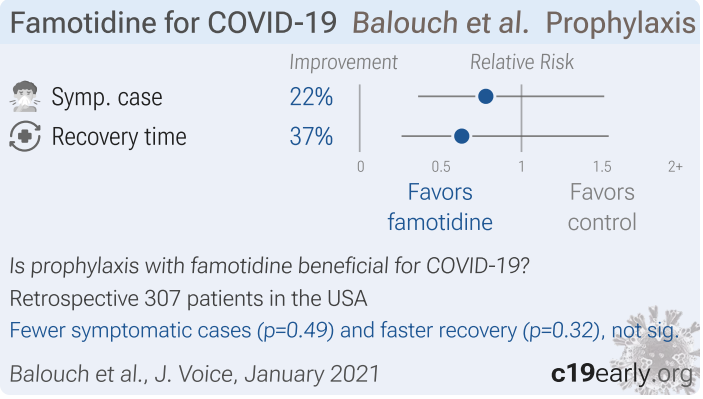
Figure 29. **Efficacy vs. cost for COVID-19 treatments.**

Conclusion

Famotidine is an effective treatment for COVID-19. Significantly lower risk is seen for mortality, hospitalization, recovery, and viral clearance. 15 studies from 15 independent teams in 7 countries show significant benefit. Meta analysis using the most serious outcome reported shows 17% [8-24%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Early treatment is more effective than late treatment.

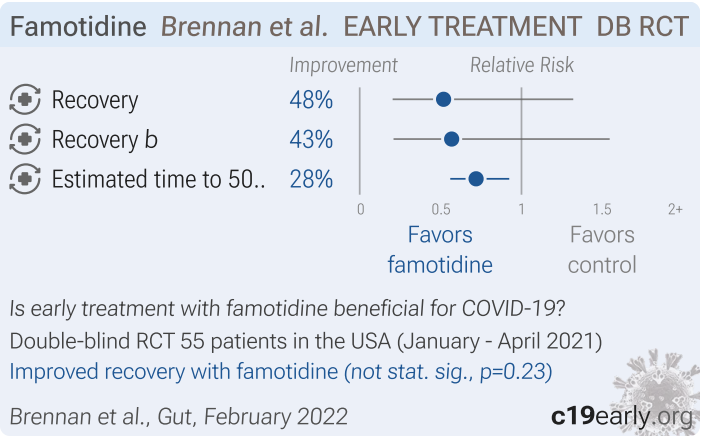
Study Notes

Balouch



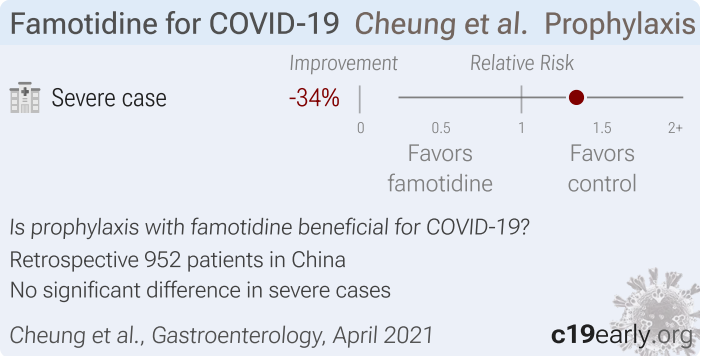
Survey of 307 patients in the USA, showing no significant difference in COVID-19 cases with famotidine use.

Brennan



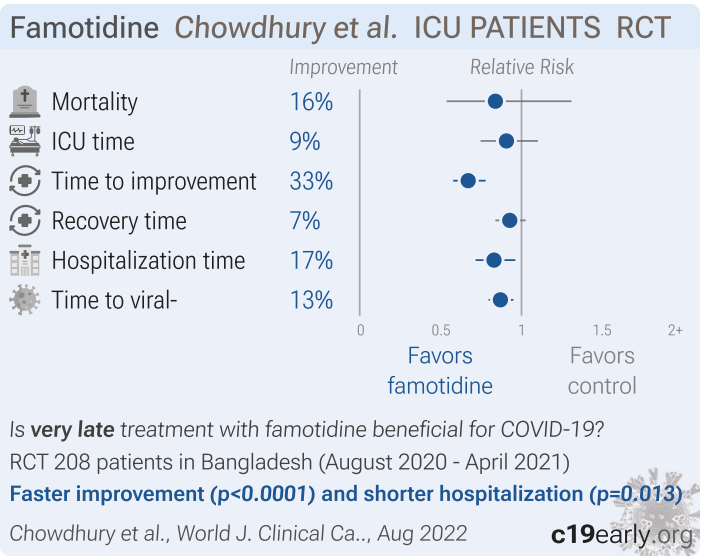
Small RCT with 27 famotidine and 28 placebo patients, showing improved recovery with treatment. Recovery was faster with treatment for 14 of 16 symptoms. There was no mortality or hospitalization. NCT04724720.

Cheung



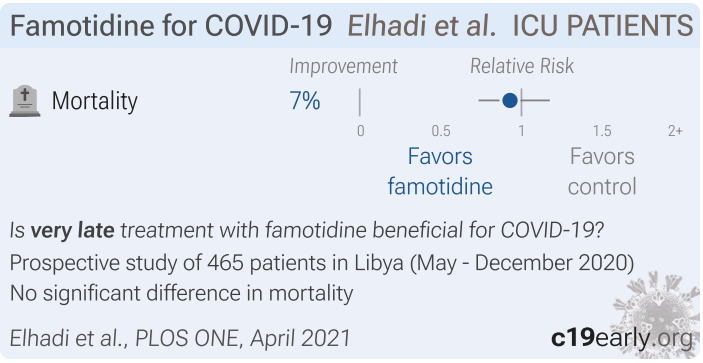
Retrospective 952 COVID-19 patients in Hong Kong, showing no significant difference in severe disease with famotidine use or PPI use.

Chowdhury



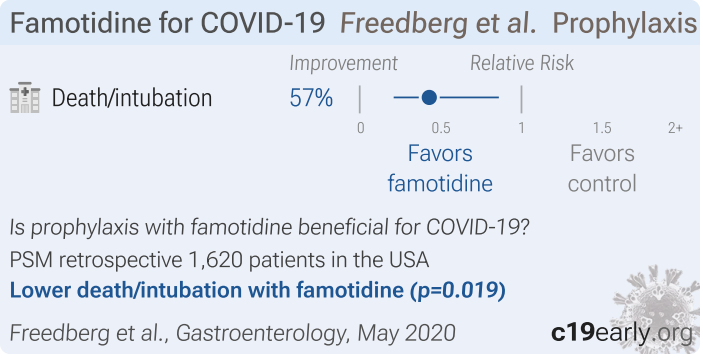
RCT 208 ICU patients in Bangladesh, showing improved recovery with famotidine. Famotidine 40mg (<60kg) or 60mg every 8 hours.

Elhadi



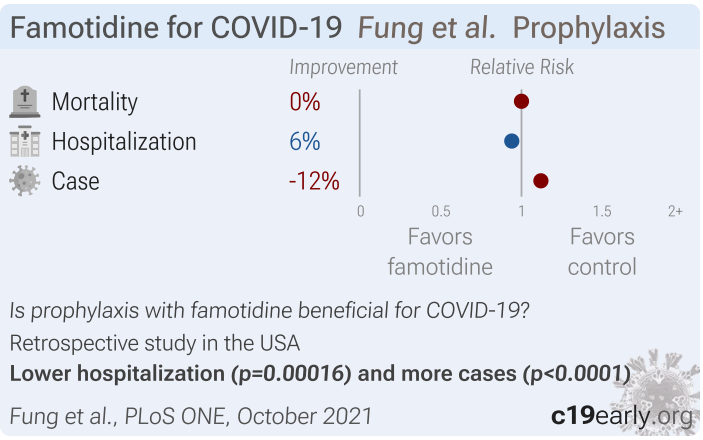
Prospective study of 465 COVID-19 ICU patients in Libya showing no significant differences with treatment.

Freedberg



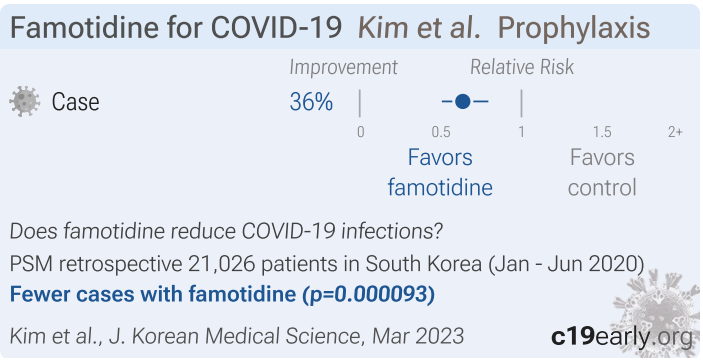
PSM retrospective 1,620 hospitalized patients in the USA, 84 with existing famotidine use, showing lower risk of combined death/intubation with treatment.

Fung



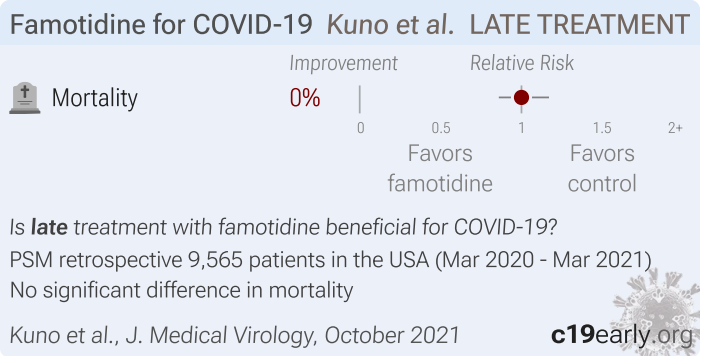
Retrospective database analysis of 374,229 patients in the USA, showing higher cases, lower hospitalizations, and no change in mortality with famotidine use.

Kim



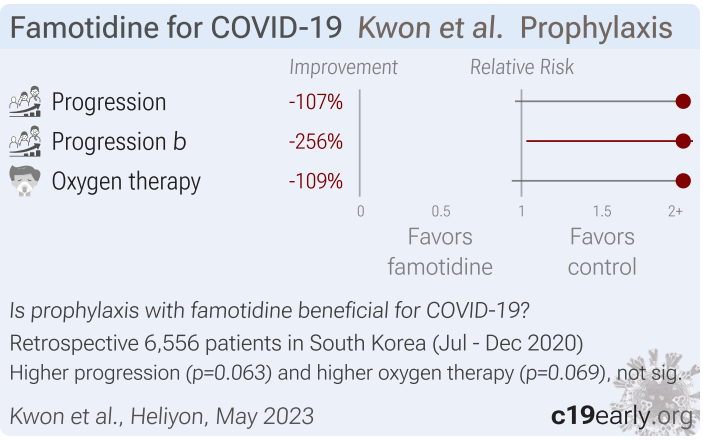
PSM retrospective in South Korea, showing lower risk of COVID-19 cases with H2RA (including famotidine) and PPI use, but no significant difference in severe outcomes (results provided for the combined groups only).

Kuno



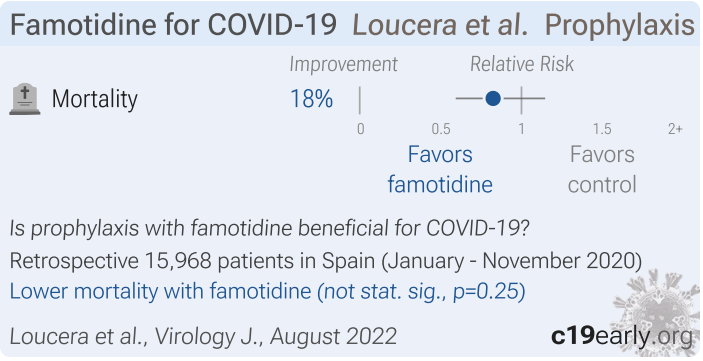
PSM retrospective 9,565 COVID-19 hospitalized patients in the USA, 1,593 receiving famotidine, showing no significant difference in mortality.

Kwon



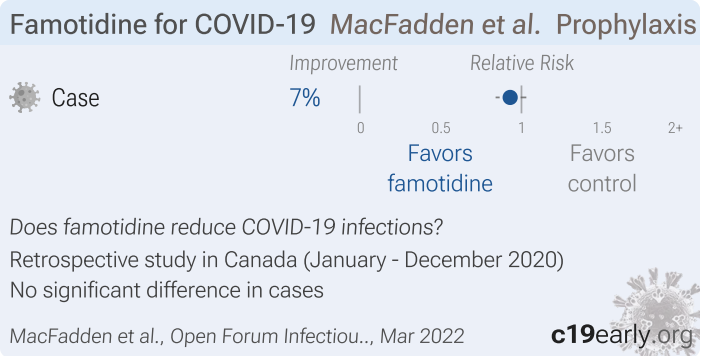
PSM retrospective 6,556 COVID-19 patients in South Korea, showing higher risk of poor outcomes with famotidine vs. other H2-blocker use.

Loucera



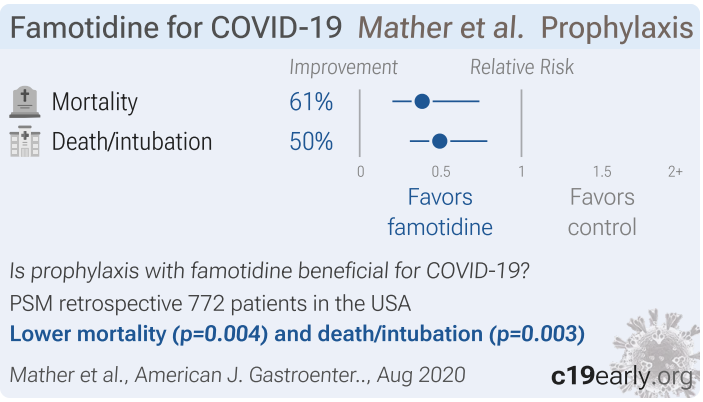
Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

MacFadden



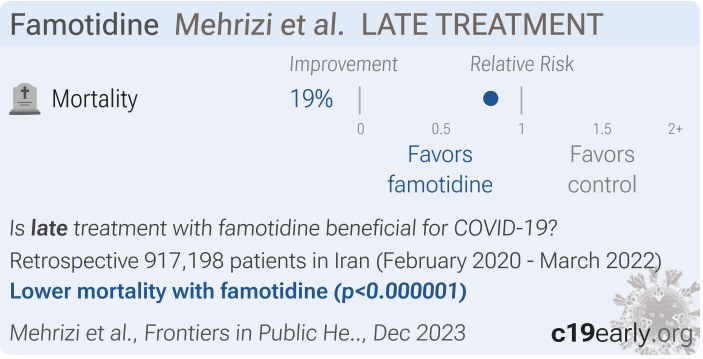
Retrospective 26,121 cases and 2,369,020 controls ≥65yo in Canada, showing no significant difference in cases with chronic use of famotidine.

Mather



PSM retrospective 878 hospitalized patients in the USA, 83 with existing famotidine use, showing significantly lower mortality with treatment.

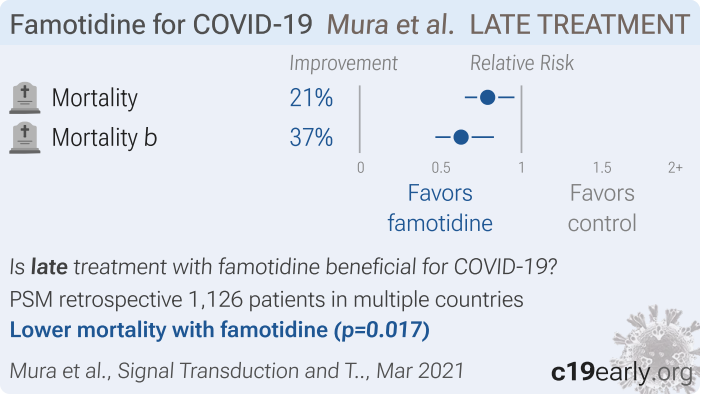
Mehrizi



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.

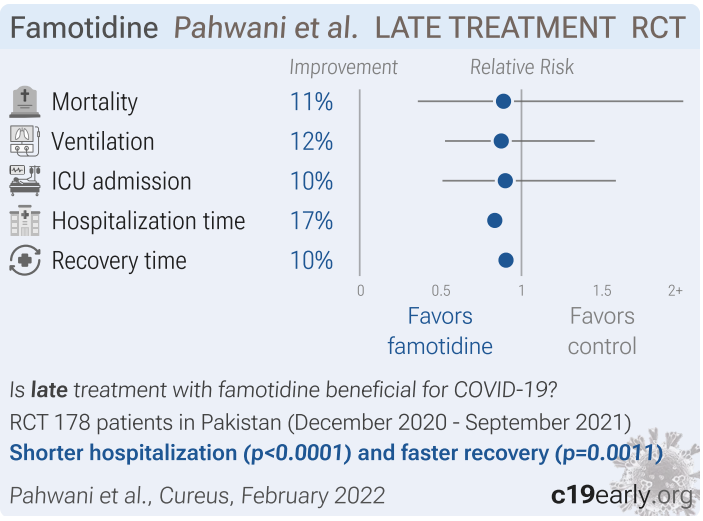
Confounding by indication is likely to be significant for many medications. Authors adjustments have very limited severity information (admission type refers to ward vs. ER department on initial arrival). We can estimate the impact of confounding from typical usage patterns, the prescription frequency,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

Mura



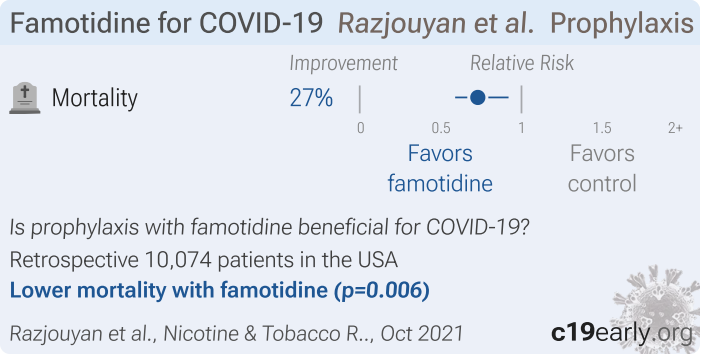
PSM retrospective TriNetX database analysis of 1,379 severe COVID-19 patients requiring respiratory support, showing lower mortality with aspirin (not reaching statistical significance) and famotidine, and improved results from the combination of both.

Pahwani



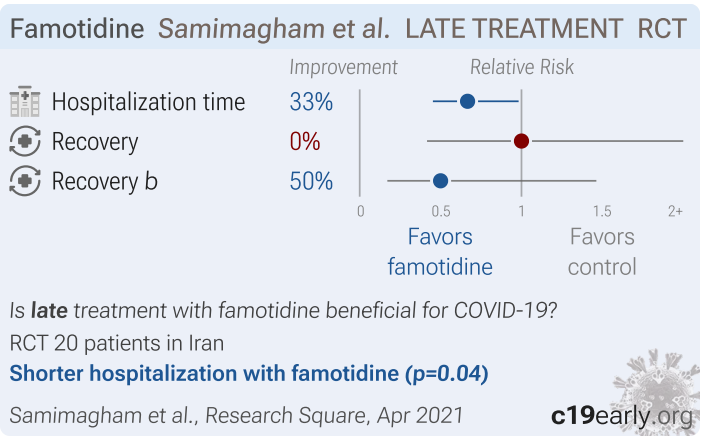
RCT with 89 famotidine and 89 control patients in Pakistan, showing faster recovery but no significant difference in mortality. 40mg oral famotidine daily.

Razjouyan



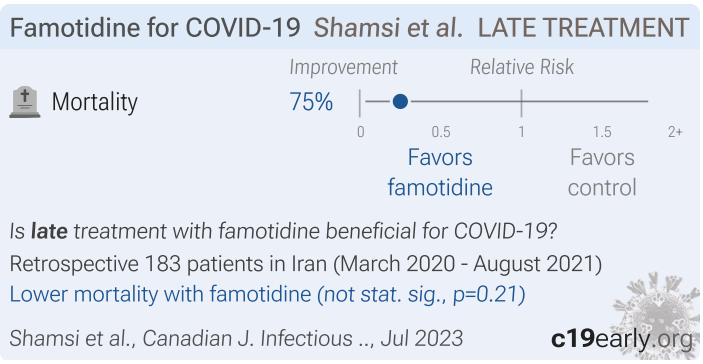
Retrospective 10,074 hospitalized veterans with COVID-19 in the USA, showing lower mortality with existing famotidine use.

Samimagham



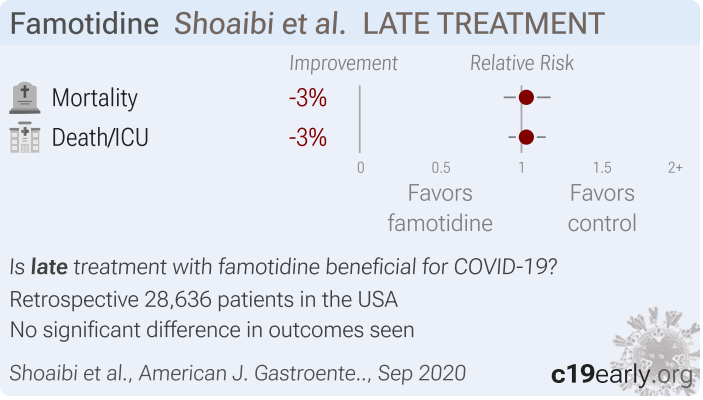
Very small RCT with 20 patients in Iran, showing shorter hospitalization time with famotidine treatment. There was no mortality or ICU admission. Famotidine 160mg four times a day. IRCT20200509047364N2.

Shamsi



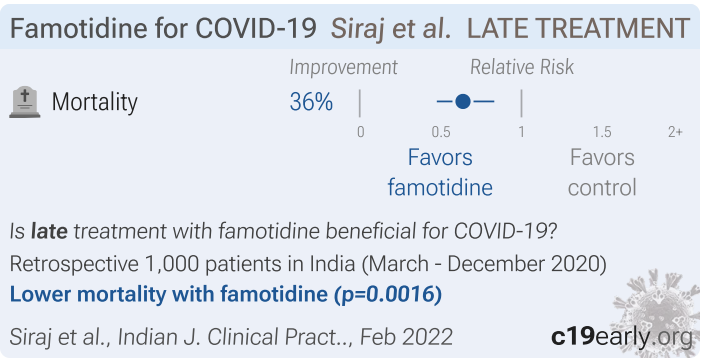
Retrospective 183 hospitalized pediatric COVID-19 patients in Iran, showing no significant difference in mortality with famotidine in unadjusted results.

Shoaibi



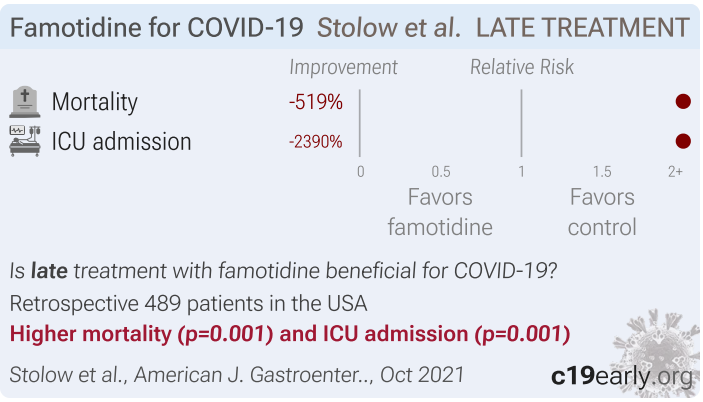
Retrospective 1,816 famotidine users and 26,820 non-users hospitalized for COVID-19 in the USA, showing no significant differences with treatment.

Siraj



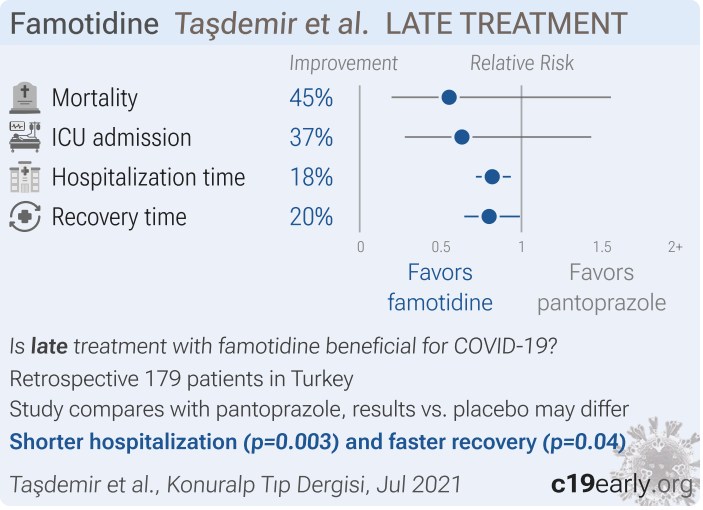
Retrospective 1,000 COVID+ hospitalized patients in India, showing lower mortality with famotidine and remdesivir in multivariable logistic regression.

Stolow



Retrospective 489 COVID+ hospitalized patients in the USA, showing higher mortality with famotidine treatment.

Taşdemir

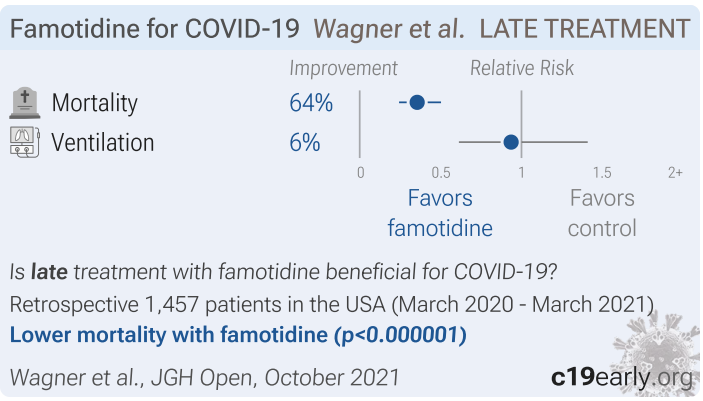


Retrospective 179 hospitalized patients in Turkey, 85 treated with famotidine and 94 treated with pantoprazole, showing faster recovery with famotidine in unadjusted results.

Together Trial

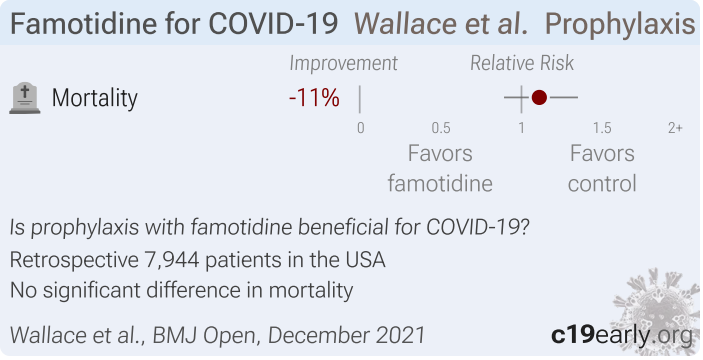
528 patient famotidine early treatment RCT with results not reported over 1.5 years after completion.

Wagner



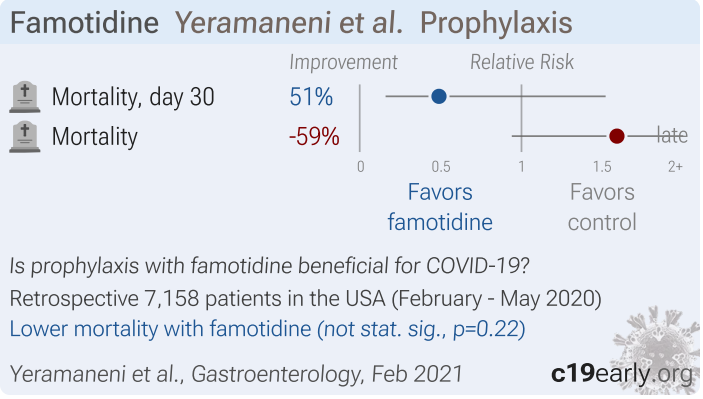
Retrospective 2,184 hospitalized patients in the USA, 638 treated with famotidine, showing lower mortality with treatment.

Wallace



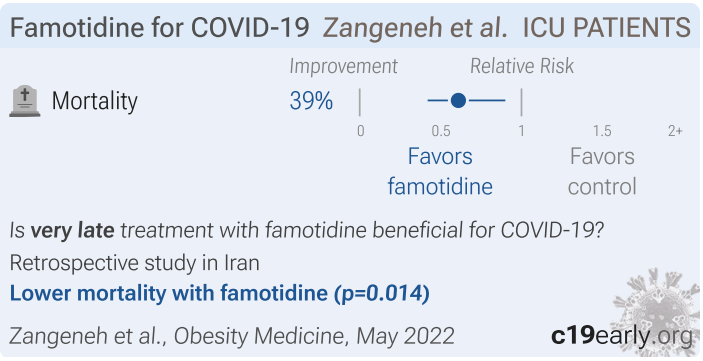
Retrospective 9,532 hospitalized COVID+ veterans in the USA, showing no significant difference in mortality with famotidine use. The study provides results for use before, after, and before+after. Before+after should more accurately represent prophylaxis up to COVID-19 infection (and continued use). Before included use up to 2 years before, and after included use up to 60 days later.

Yeramaneni



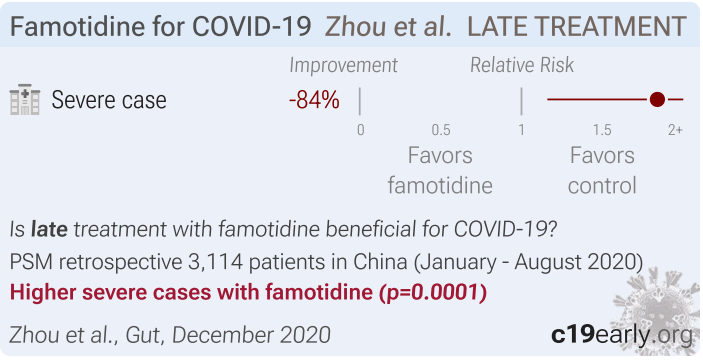
Retrospective 7,158 hospitalized COVID-19 patients in the USA, showing higher risk or mortality with in-hospital famotidine use, but lower risk when there was pre-existing at-home use, without statistical significance in both cases.

Zangeneh



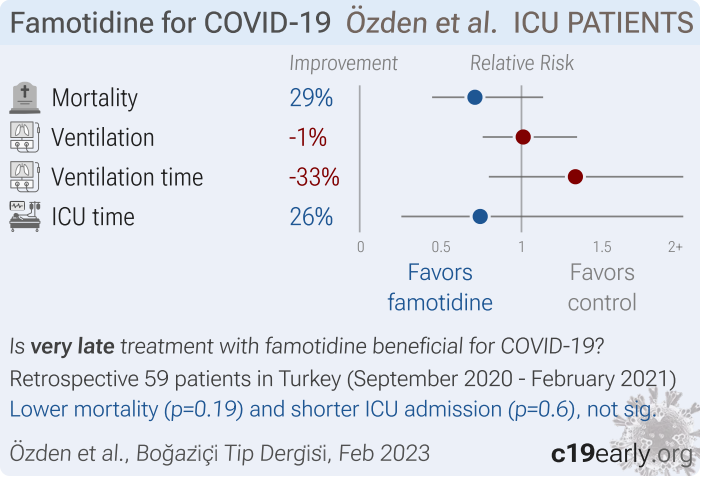
Retrospective 193 ICU patients in Iran, showing lower mortality with famotidine treatment.

Zhou



Retrospective 4,445 COVID+ patients in China, showing higher risk of combined death/intubation/ICU with famotidine and with PPIs.

Özden



Retrospective 59 ICU patients in Turkey, showing no significant difference in 30-day mortality or invasive mechanical ventilation with 160mg/day famotidine treatment. However, the famotidine group had lower fibrinogen and procalcitonin, suggesting possible benefits for coagulation, inflammation, and secondary infections. Limitations include the small sample size, lack of randomization, and other confounding treatments.

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 famotidine 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 famotidine 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. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

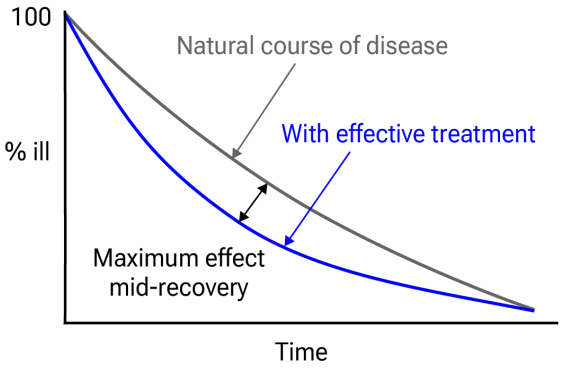


Figure 30. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use 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 outcomes. 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. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction [139]. 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 et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used 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 [143]. 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 (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

Forest plots are computed using PythonMeta [144] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 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 [48,49].

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/fmmeta.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.

Brennan, 2/10/2022, Double Blind Randomized Controlled Trial, USA, peer-reviewed, 31 authors, study period January 2021 - April 2021, average treatment delay 4.0 days, trial NCT04724720 (history).	risk of no recovery, 48.1% lower, RR 0.52, $p = 0.23$, treatment 5 of 27 (18.5%), control 10 of 28 (35.7%), NNT 5.8, day 28, ITT.
	risk of no recovery, 43.2% lower, RR 0.57, $p = 0.34$, treatment 4 of 19 (21.1%), control 10 of 27 (37.0%), NNT 6.3, day 28, PP.
	estimated time to 50% resolution, 28.1% lower, relative time 0.72, $p < 0.01$, treatment 27, control 28.
Together Trial, 11/1/2023, Double Blind Randomized Controlled Trial, placebo-controlled, trial NCT04727424 (history) (TOGETHER).	528 patient RCT with results unknown and over 1.5 years late.

Late treatment

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

Chowdhury, 8/16/2022, Randomized Controlled Trial, Bangladesh, peer-reviewed, mean age 57.1, 11 authors, study period 1 August, 2020 - 15 April, 2021, trial NCT04504240 (history).	risk of death, 16.1% lower, RR 0.84, $p = 0.53$, treatment 26 of 104 (25.0%), control 31 of 104 (29.8%), NNT 21.
	ICU time, 9.3% lower, relative time 0.91, $p = 0.33$, treatment 78, control 73.
	time to improvement, 32.9% lower, relative time 0.67, $p < 0.001$, treatment mean 9.53 (±5.0) n=78, control mean 14.21 (±5.6) n=73, time to clinical improvement.
	recovery time, 7.3% lower, relative time 0.93, $p = 0.14$, treatment mean 17.9 (±5.4) n=78, control mean 19.3 (±6.3) n=73, time to symptomatic recovery.
	hospitalization time, 17.0% lower, relative time 0.83, $p = 0.01$, treatment 78, control 73.
	time to viral-, 13.0% lower, relative time 0.87, $p = 0.002$, treatment 78, control 73.
Elhadi, 4/30/2021, prospective, Libya, peer-reviewed, 21 authors, study period 29 May, 2020 - 30 December, 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 7.1% lower, RR 0.93, $p = 0.57$, treatment 34 of 60 (56.7%), control 247 of 405 (61.0%), NNT 23.
Kuno, 10/11/2021, retrospective, propensity score matching, USA, peer-reviewed, 4 authors, study period 1 March, 2020 - 30 March, 2021.	risk of death, no change, OR 1.00, $p = 0.97$, treatment 1,593, control 7,972, RR approximated with OR.
Mehrizi, 12/18/2023, retrospective, Iran, peer-reviewed, 10 authors, study period 1 February, 2020 - 20 March, 2022.	risk of death, 19.0% lower, OR 0.81, $p < 0.001$, RR approximated with OR.
Mura, 3/31/2021, retrospective, database analysis, multiple countries, peer-reviewed, 6 authors.	risk of death, 20.9% lower, RR 0.79, $p = 0.02$, treatment 563, control 563, odds ratio converted to relative risk, famotidine only, control prevalence approximated with treatment prevalence, propensity score matching.
	risk of death, 37.3% lower, RR 0.63, $p = 0.001$, treatment 305, control 305, odds ratio converted to relative risk, famotidine and aspirin, control prevalence approximated with treatment prevalence, propensity score matching.
Pahwani, 2/20/2022, Randomized Controlled Trial, Pakistan, peer-reviewed, mean age 52.0, 8 authors, study period December 2020 - September 2021.	risk of death, 11.1% lower, RR 0.89, $p = 1.00$, treatment 8 of 89 (9.0%), control 9 of 89 (10.1%), NNT 89.
	risk of mechanical ventilation, 12.5% lower, RR 0.88, $p = 0.73$, treatment 21 of 89 (23.6%), control 24 of 89 (27.0%), NNT 30.
	risk of ICU admission, 10.0% lower, RR 0.90, $p = 0.86$, treatment 18 of 89 (20.2%), control 20 of 89 (22.5%), NNT 44.
	hospitalization time, 16.5% lower, relative time 0.83, $p < 0.001$, treatment mean 8.6 (±1.6) n=89, control mean 10.3 (±2.2) n=89.

	recovery time, 9.6% lower, relative time 0.90, p = 0.001, treatment mean 8.5 (±1.7) n=89, control mean 9.4 (±1.9) n=89.
Samimagham, 4/27/2021, Single Blind Randomized Controlled Trial, placebo-controlled, Iran, preprint, 6 authors.	**hospitalization time, 33.3% lower, relative time 0.67, p = 0.04**, treatment 10, control 10.
	risk of no recovery, no change, RR 1.00, p = 1.00, treatment 5 of 10 (50.0%), control 5 of 10 (50.0%), >50% CT lung involvment.
	risk of no recovery, 50.0% lower, RR 0.50, p = 0.37, treatment 3 of 10 (30.0%), control 6 of 10 (60.0%), NNT 3.3, no improvement in cough.
Shamsi, 7/17/2023, retrospective, Iran, peer-reviewed, 4 authors, study period 1 March, 2020 - 1 August, 2021, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 74.9% lower, RR 0.25, p = 0.21**, treatment 1 of 27 (3.7%), control 23 of 156 (14.7%), NNT 9.1.
Shoaibi, 9/24/2020, retrospective, database analysis, USA, peer-reviewed, 5 authors.	**risk of death, 3.0% higher, RR 1.03, p = 0.67**, treatment 1,816, control 26,820.
	risk of death/ICU, 3.0% higher, RR 1.03, p = 0.62, treatment 1,816, control 26,820.
Siraj, 2/28/2022, retrospective, India, peer-reviewed, median age 56.0, 13 authors, study period March 2020 - December 2020.	**risk of death, 36.2% lower, RR 0.64, p = 0.002**, treatment 183 of 711 (25.7%), control 122 of 289 (42.2%), NNT 6.1, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariable.
Stolow, 10/31/2021, retrospective, USA, peer-reviewed, 9 authors.	**risk of death, 518.9% higher, OR 6.19, p < 0.001**, treatment 137, control 352, RR approximated with OR.
	risk of ICU admission, 2389.6% higher, OR 24.90, p < 0.001, treatment 137, control 352, RR approximated with OR.
Taşdemir, 7/12/2021, retrospective, Turkey, peer-reviewed, 7 authors, this trial compares with another treatment - results may be better when compared to placebo, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 44.7% lower, RR 0.55, p = 0.29**, treatment 5 of 85 (5.9%), control 10 of 94 (10.6%), NNT 21.
	risk of ICU admission, 36.8% lower, RR 0.63, p = 0.36, treatment 8 of 85 (9.4%), control 14 of 94 (14.9%), NNT 18.
	hospitalization time, 18.1% lower, relative time 0.82, p = 0.003, treatment 85, control 94.
	recovery time, 20.0% lower, relative time 0.80, p = 0.04, treatment 85, control 94, duration of fever.
Wagner, 10/31/2021, retrospective, USA, peer-reviewed, 5 authors, study period 1 March, 2020 - 1 March, 2021.	**risk of death, 64.5% lower, RR 0.36, p < 0.001**, treatment 82 of 638 (12.9%), control 182 of 819 (22.2%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of mechanical ventilation, 6.4% lower, RR 0.94, p = 0.77, treatment 48 of 638 (7.5%), control 75 of 819 (9.2%), adjusted per study, odds ratio converted to relative risk, multivariable.
Yeramaneni, 2/28/2021, retrospective, USA, peer-reviewed, 6 authors, study period 11 February, 2020 - 8 May, 2020.	**risk of death, 59.0% higher, OR 1.59, p = 0.09**, treatment 410, control 746, adjusted per study, hospital use only, multivariable, RR approximated with OR, late treatment result.
Zangeneh, 5/13/2022, retrospective, Iran, peer-reviewed, 3 authors.	**risk of death, 39.0% lower, HR 0.61, p = 0.01**, Cox proportional hazards.

Zhou, 12/4/2020, retrospective, propensity score matching, China, peer-reviewed, 7 authors, study period 1 January, 2020 - 22 August, 2020.	risk of severe case, 84.0% higher, HR 1.84, $p < 0.001$, treatment 72 of 519 (13.9%), control 198 of 2,595 (7.6%), adjusted per study, death/intubation/ICU, propensity score matching, multivariable, Cox proportional hazards.
Özden, 2/28/2023, retrospective, Turkey, peer-reviewed, mean age 65.3, 2 authors, study period September 2020 - February 2021, trial NCT05122208 (history).	risk of death, 28.8% lower, RR 0.71, $p = 0.19$, treatment 14 of 30 (46.7%), control 19 of 29 (65.5%), NNT 5.3.
	risk of mechanical ventilation, 1.1% higher, RR 1.01, $p = 1.00$, treatment 23 of 30 (76.7%), control 22 of 29 (75.9%).
	ventilation time, 33.3% higher, relative time 1.33, $p = 0.28$, treatment 30, control 29.
	ICU time, 25.5% lower, relative time 0.74, $p = 0.60$, treatment 30, control 29.

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.

Balouch, 1/20/2021, retrospective, USA, peer-reviewed, 5 authors.	risk of symptomatic case, 22.0% lower, RR 0.78, $p = 0.49$, treatment 18 of 80 (22.5%), control 49 of 227 (21.6%), adjusted per study, odds ratio converted to relative risk, multivariable.
	recovery time, 36.9% lower, relative time 0.63, $p = 0.32$, treatment 80, control 227.
Cheung, 4/30/2021, retrospective, China, peer-reviewed, 3 authors.	risk of severe case, 34.0% higher, OR 1.34, $p = 0.72$, treatment 23, control 929, adjusted per study, multivariable, RR approximated with OR.
Freedberg, 5/21/2020, retrospective, propensity score matching, USA, peer-reviewed, 15 authors.	risk of death/intubation, 57.0% lower, HR 0.43, $p = 0.02$, treatment 8 of 84 (9.5%), control 332 of 1,536 (21.6%), NNT 8.3, adjusted per study, propensity score matching, multivariable, Cox proportional hazards.
Fung, 10/1/2021, retrospective, population-based cohort, USA, peer-reviewed, 6 authors, excluded in exclusion analyses: not fully adjusting for the different baseline risk of systemic autoimmune patients.	risk of death, no change, HR 1.00, $p = 1.00$, vs. never used.
	risk of hospitalization, 6.0% lower, HR 0.94, $p < 0.001$, vs. never used.
	risk of case, 12.0% higher, HR 1.12, $p < 0.001$, vs. never used.
Kim, 3/21/2023, retrospective, South Korea, peer-reviewed, 8 authors, study period 1 January, 2020 - 4 June, 2020.	risk of case, 36.3% lower, RR 0.64, $p < 0.001$, treatment 105 of 5,594 (1.9%), control 480 of 15,432 (3.1%), NNT 81, adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable, model 3.
Kwon, 5/31/2023, retrospective, South Korea, peer-reviewed, 8 authors, study period 1 July, 2020 - 31 December, 2020.	risk of progression, 107.0% higher, OR 2.07, $p = 0.06$, treatment 204, control 204, adjusted per study, ICU, mechanical ventilation, or death, famotidine vs. other H2-blocker use, multivariable, RR approximated with OR.
	risk of progression, 256.0% higher, OR 3.56, $p = 0.04$, treatment 204, control 204, adjusted per study, high oxygen, ICU, mechanical ventilation, or death, famotidine vs. other H2-blocker use, multivariable, RR approximated with OR.

	risk of oxygen therapy, 109.0% higher, OR 2.09, p = 0.07, treatment 204, control 204, adjusted per study, famotidine vs. other H2-blocker use, multivariable, RR approximated with OR.
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	risk of death, 17.5% lower, HR 0.82, p = 0.25, treatment 207, control 15,761, Cox proportional hazards, day 30.
MacFadden, 3/29/2022, retrospective, Canada, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.	risk of case, 7.0% lower, OR 0.93, p = 0.16, RR approximated with OR.
Mather, 8/26/2020, retrospective, USA, peer-reviewed, 3 authors.	risk of death, 61.4% lower, HR 0.39, p = 0.004, treatment 83, control 689, propensity score matching, Cox proportional hazards.
	risk of death/intubation, 50.5% lower, HR 0.49, p = 0.003, treatment 83, control 689, propensity score matching, Cox proportional hazards.
Razjouyan, 10/25/2021, retrospective, USA, peer-reviewed, 7 authors.	risk of death, 27.0% lower, OR 0.73, p = 0.006, treatment 93, control 9,981, adjusted per study, RR approximated with OR.
Wallace, 12/31/2021, retrospective, database analysis, USA, peer-reviewed, 6 authors.	risk of death, 11.0% higher, RR 1.11, p = 0.33, treatment 98 of 423 (23.2%), control 1,436 of 7,521 (19.1%), adjusted per study, odds ratio converted to relative risk, multivariable.
Yeramaneni, 2/28/2021, retrospective, USA, peer-reviewed, 6 authors, study period 11 February, 2020 - 8 May, 2020.	risk of death, 51.0% lower, OR 0.49, p = 0.22, treatment 351, control 6,807, adjusted per study, with home use, multivariable, day 30, 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.

References

1. **Together Trial**, *Repurposed Approved and Under Development Therapies for Patients With Early-Onset COVID-19 and Mild Symptoms*, NCT04727424, clinicaltrials.gov/study/NCT04727424.
2. **Ryu** et al., *Fibrin drives thromboinflammation and neuropathology in COVID-19*, Nature, doi:10.1038/s41586-024-07873-4.
3. **Rong** et al., *Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19*, Cell Host & Microbe, doi:10.1016/j.chom.2024.11.007.
4. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.
5. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.
6. **Hampshire** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.
7. **Duloquin** et al., *Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2*, Journal of Clinical Medicine, doi:10.3390/jcm13051397.

8. **Sodagar** et al., *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, Biomolecules, doi:10.3390/biom12070971.
9. **Sagar** et al., *COVID-19-associated cerebral microbleeds in the general population*, Brain Communications, doi:10.1093/braincomms/fcae127.
10. **Verma** et al., *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, bioRxiv, doi:10.1101/2024.06.02.596989.
11. **Panagea** et al., *Neurocognitive Impairment in Long COVID: A Systematic Review*, Archives of Clinical Neuropsychology, doi:10.1093/arclin/acae042.
12. **Ariza** et al., *COVID-19: Unveiling the Neuropsychiatric Maze—From Acute to Long-Term Manifestations*, Biomedicines, doi:10.3390/biomedicines12061147.
13. **Vashisht** et al., *Neurological Complications of COVID-19: Unraveling the Pathophysiological Underpinnings and Therapeutic Implications*, Viruses, doi:10.3390/v16081183.
14. **Ahmad** et al., *Neurological Complications and Outcomes in Critically Ill Patients With COVID-19: Results From International Neurological Study Group From the COVID-19 Critical Care Consortium*, The Neurohospitalist, doi:10.1177/19418744241292487.
15. **Wang** et al., *SARS-CoV-2 membrane protein induces neurodegeneration via affecting Golgi-mitochondria interaction*, Translational Neurodegeneration, doi:10.1186/s40035-024-00458-1.
16. **Eberhardt** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.
17. **Van Tin** et al., *Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF-κB Signaling*, Cells, doi:10.3390/cells13161331.
18. **Borka Balas** et al., *COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice*, Reviews in Cardiovascular Medicine, doi:10.31083/j.rcm2405125.
19. **AlTaweel** et al., *An In-Depth Insight into Clinical, Cellular and Molecular Factors in COVID19-Associated Cardiovascular Ailments for Identifying Novel Disease Biomarkers, Drug Targets and Clinical Management Strategies*, Archives of Microbiology & Immunology, doi:10.26502/ami.936500177.
20. **Saha** et al., *COVID-19 beyond the lungs: Unraveling its vascular impact and cardiovascular complications—mechanisms and therapeutic implications*, Science Progress, doi:10.1177/00368504251322069.
21. **Trender** et al., *Changes in memory and cognition during the SARS-CoV-2 human challenge study*, eClinicalMedicine, doi:10.1016/j.eclinm.2024.102842.
22. **Dugied** et al., *Multimodal SARS-CoV-2 interactome sketches the virus-host spatial organization*, Communications Biology, doi:10.1038/s42003-025-07933-z.
23. **Malone** et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, Nature Reviews Molecular Cell Biology, doi:10.1038/s41580-021-00432-z.
24. **Murigneux** et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.
25. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.
26. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.
27. **Niarakis** et al., *Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1282859.
28. **Katiyar** et al., *SARS-CoV-2 Assembly: Gaining Infectivity and Beyond*, Viruses, doi:10.3390/v16111648.
29. **Wu** et al., *Decoding the genome of SARS-CoV-2: a pathway to drug development through translation inhibition*, RNA Biology, doi:10.1080/15476286.2024.2433830.
30. **c19early.org**, c19early.org/treatments.html.
31. **Loffredo** et al., *The in-vitro effect of famotidine on SARS-CoV-2 proteases and virus replication*, Scientific Reports, doi:10.1038/s41598-021-84782-w.
32. **Zeraatkar** et al., *Consistency of covid-19 trial preprints with published reports and impact for decision making: retrospective review*, BMJ Medicine, doi:10.1136/bmjmed-2022-0003091.
33. **Davidson** et al., *No evidence of important difference in summary treatment effects between COVID-19 preprints and peer-reviewed publications: a meta-epidemiological study*, Journal of Clinical Epidemiology, doi:10.1016/j.jclinepi.2023.08.011.
34. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings, Second Edition*, doi:10.1002/9780470691922.
35. **Gøtzsche**, P., *Bias in double-blind trials*, Doctoral Thesis, University of Copenhagen, www.scientificfreedom.dk/2023/05/16/bias-in-double-blind-trials-doctoral-thesis/.
36. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.
37. **c19early.org (B)**, c19early.org/fmsupp.html#fig_rctobs.
38. **Concato** et al., NEJM, 342:1887-1892, doi:10.1056/NEJM200006223422507.
39. **Anglemyer** et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews 2014, Issue 4, doi:10.1002/14651858.MR000034.pub2.
40. **c19early.org (C)**, c19early.org/rctobs.html.
41. **Lee** et al., *Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines*, Arch Intern Med., 2011, 171:1, 18-22, doi:10.1001/archinternmed.2010.482.
42. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.

43. **Nichol** et al., *Challenging issues in randomised controlled trials*, Injury, 2010, doi: 10.1016/j.injury.2010.03.033, www.injuryjournal.com/article/S0020-1383(10)00233-0/fulltext.

44. **Elhadi** et al., *Epidemiology, outcomes, and utilization of intensive care unit resources for critically ill COVID-19 patients in Libya: A prospective multi-center cohort study*, PLOS ONE, doi:10.1371/journal.pone.0251085.

45. **Fung** et al., *Effect of common maintenance drugs on the risk and severity of COVID-19 in elderly patients*, PLoS ONE, doi:10.1371/journal.pone.0266922.

46. **Shamsi** et al., *Survival and Mortality in Hospitalized Children with COVID-19: A Referral Center Experience in Yazd, Iran*, Canadian Journal of Infectious Diseases and Medical Microbiology, doi:10.1155/2023/5205188.

47. **Taşdemir** et al., *Famotidine in COVID-19 treatment*, Konuralp Tıp Dergisi, doi:10.18521/ktd.935888.

48. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.

49. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.

50. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.

51. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.

52. **Kumar** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, The Lancet Infectious Diseases, doi:10.1016/S1473-3099(21)00469-2.

53. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.3071.

54. **Korves** et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, medRxiv, doi:10.1101/2024.03.08.24303818.

55. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.

56. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.

57. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, medRxiv, doi:10.1101/2021.08.27.21262754.

58. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, Research Square, doi:10.21203/rs.3.rs-910467/v1.

59. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.

60. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.

61. **Williams**, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.

62. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, Rapid Communications in Mass Spectrometry, doi:10.1002/rcm.9358.

63. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.

64. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.

65. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.

66. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.

67. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.

68. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.

69. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.

70. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.

71. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.

72. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.

73. **Xing** et al., *Published anti-SARS-CoV-2 in vitro hits share common mechanisms of action that synergize with antivirals*, Briefings in Bioinformatics, doi:10.1093/bib/bbab249.

74. **Chen** et al., *Synergistic Inhibition of SARS-CoV-2 Replication Using Disulfiram/Ebselen and Remdesivir*, ACS Pharmacology & Translational Science, doi:10.1021/acsptsci.1c00022.

75. **Hempel** et al., *Synergistic inhibition of SARS-CoV-2 cell entry by otamixaban and covalent protease inhibitors: pre-clinical assessment of pharmacological and molecular properties*, Chemical Science, doi:10.1039/D1SC01494C.

76. **Schultz** et al., *Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2*, Nature, doi:10.1038/s41586-022-04482-x.

77. **Ohashi** et al., *Potential anti-COVID-19 agents, cepharanthine and nelfinavir, and their usage for combination treatment*, iScience, doi:10.1016/j.isci.2021.102367.

78. **Al Krad** et al., *The protease inhibitor Nirmatrelvir synergizes with inhibitors of GRP78 to suppress SARS-CoV-2 replication*, bioRxiv, doi:10.1101/2025.03.09.642200.

79. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.

80. **Singh** et al., *The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis*, Journal of Antimicrobial Chemotherapy, doi:10.1093/jac/dkae045.

81. **Meneguesso**, A., *Médica defende tratamento precoce da Covid-19*, www.youtube.com/watch?v=X5FCrIm_19U.

82. **Boulware**, D., *Comments regarding paper rejection*, twitter.com/boulware_dr/status/1311331372884205570.

83. **Meeus**, G., *Online Comment*, twitter.com/gertmeeus_MD/status/1386636373889781761.

84. **twitter.com**, twitter.com/KashPrime/status/1768487878454124914.

85. **Rothstein**, H., *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*, www.wiley.com/en-ae/Publication+Bias+in+Meta+Analysis:+Prevention,+Assessment+and+Adjustments-p-9780470870143.

86. **Stanley** et al., *Meta-regression approximations to reduce publication selection bias*, Research Synthesis Methods, doi:10.1002/jrsm.1095.

87. **Rücker** et al., *Arcsine test for publication bias in meta-analyses with binary outcomes*, Statistics in Medicine, doi:10.1002/sim.2971.

88. **Peters**, J., *Comparison of Two Methods to Detect Publication Bias in Meta-analysis*, JAMA, doi:10.1001/jama.295.6.676.

89. **Moreno** et al., *Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study*, BMC Medical Research Methodology, doi:10.1186/1471-2288-9-2.

90. **Macaskill** et al., *A comparison of methods to detect publication bias in meta-analysis*, Statistics in Medicine, doi:10.1002/sim.698.

91. **Egger** et al., *Bias in meta-analysis detected by a simple, graphical test*, BMJ, doi:10.1136/bmj.315.7109.629.

92. **Harbord** et al., *A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints*, Statistics in Medicine, doi:10.1002/sim.2380.

93. **Enyeji** et al., *Effective Treatment of COVID-19 Infection with Repurposed Drugs: Case Reports*, Viral Immunology, doi:10.1089/vim.2024.0034.

94. **Malone (B)** et al., *COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms*, Frontiers in Pharmacology, doi:10.3389/fphar.2021.633680.

95. **Brennan** et al., *Oral famotidine versus placebo in non-hospitalised patients with COVID-19: a randomised, double-blind, data-intense, phase 2 clinical trial*, Gut, doi:10.1136/gutjnl-2022-326952.

96. **Mehrizi** et al., *Drug prescription patterns and their association with mortality and hospitalization duration in COVID-19 patients: insights from big data*, Frontiers in Public Health, doi:10.3389/fpubh.2023.1280434.

97. **Files** et al., *Report of the first seven agents in the I-SPY COVID trial: a phase 2, open label, adaptive platform randomised controlled trial*, eClinicalMedicine, doi:10.1016/j.eclinm.2023.101889.

98. **Özden** et al., *Effects of Famotidine on COVID-19 Patients in Intensive Care Unit: A Retrospective Clinical Trial*, Boğaziçi Tip Dergisi, doi:10.14744/bmj.2023.77044.

99. **Chowdhury** et al., *Role of H2 receptor blocker famotidine over the clinical recovery of COVID-19 patients: A randomized controlled trial*, World Journal of Clinical Cases, doi:10.12998/wjcc.v10.i23.8170.

100. **Zangeneh** et al., *Survival analysis based on body mass index in patients with Covid-19 admitted to the intensive care unit of Amir Al-Momenin Hospital in Arak – 2021*, Obesity Medicine, doi:10.1016/j.obmed.2022.100420.

101. **Siraj** et al., *Efficacy of Various Treatment Modalities on Patient-related Outcome in Hospitalized COVID-19 Patients – A Retrospective Study*, Indian Journal of Clinical Practice, 32:9, ijcp.in/Admin/CMS/PDF/6.%20OriginalResearch_IJCP_Feb2022.pdf.

102. **Pahwani** et al., *Efficacy of Oral Famotidine in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2*, Cureus, doi:10.7759/cureus.22404.

103. **Wagner** et al., *A retrospective analysis of clinical outcomes between hospitalized patients with COVID-19 who received famotidine or pantoprazole*, JGH Open, doi:10.1002/jgh3.12905.

104. **Stolow** et al., *A Retrospective Review: Famotidine Use Is Not Associated With Improved Outcomes in Hospitalized Patients With COVID-19*, American Journal of Gastroenterology, doi:10.14309/01.ajg.0000778736.01714.cd.

105. **Kuno** et al., *The association between famotidine and in-hospital mortality of patients with COVID-19*, Journal of Medical Virology, doi:10.1002/jmv.27375.

106. **Samimagham** et al., *The Efficacy of Famotidine in improvement of outcomes in Hospitalized COVID-19 Patients: A phase III randomised clinical trial*, Research Square, doi:10.21203/rs.3.rs-462937/v1.

107. **Mura** et al., *Real-world evidence for improved outcomes with histamine antagonists and aspirin in 22,560 COVID-19 patients*, Signal Transduction and Targeted Therapy, doi:10.1038/s41392-021-00689-y.

108. **Yeramaneni** et al., *Famotidine Use Is Not Associated With 30-day Mortality: A Coarsened Exact Match Study in 7158 Hospitalized Patients With Coronavirus Disease 2019 From a Large Healthcare System*, Gastroenterology, doi:10.1053/j.gastro.2020.10.011.

109. **Zhou** et al., *Proton pump inhibitor or famotidine use and severe COVID-19 disease: a propensity score-matched territory-wide study*, Gut, doi:10.1136/gutjnl-2020-323668.

110. **Shoaibi** et al., *Comparative Effectiveness of Famotidine in Hospitalized COVID-19 Patients*, American Journal of Gastroenterology, doi:10.14309/ajg.0000000000001153.

111. **Kwon** et al., *Effectiveness of famotidine on the risk of poor prognosis in patients with COVID-19: A nationwide cohort study in Korea*, Heliyon, doi:10.1016/j.heliyon.2023.e16171.

112. **Kim** et al., *Histamine-2 Receptor Antagonists and Proton Pump Inhibitors Are Associated With Reduced Risk of SARS-CoV-2 Infection Without Comorbidities Including Diabetes, Hypertension, and Dyslipidemia: A Propensity Score-Matched Nationwide Cohort Study*, Journal of Korean Medical Science, doi:10.3346/jkms.2023.38.e99.

113. **Loucera** et al., *Real-world evidence with a retrospective cohort of 15,968 COVID-19 hospitalized patients suggests 21 new effective treatments*, Virology Journal, doi:10.1186/s12985-023-02195-9.

114. **MacFadden** et al., *Screening Large Population Health Databases for Potential COVID-19 Therapeutics: A Pharmacopeia-Wide Association Study (PWAS) of Commonly Prescribed Medications*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofac156.

115. **Wallace** et al., *Association of the patterns of use of medications with mortality of COVID-19 infection: a hospital-based observational study*, BMJ Open, doi:10.1136/bmjopen-2021-050051.

116. **Razjouyan** et al., *Smoking Status and Factors associated with COVID-19 In-Hospital Mortality among US Veterans*, Nicotine & Tobacco Research, doi:10.1093/ntr/ntab223.

117. **Cheung** et al., *Association Between Famotidine Use and COVID-19 Severity in Hong Kong: A Territory-wide Study*, Gastroenterology, doi:10.1053/j.gastro.2020.05.098.

118. **Balouch** et al., *Role of Famotidine and Other Acid Reflux Medications for SARS-CoV-2: A Pilot Study*, Journal of Voice, doi:10.1016/j.jvoice.2021.01.007.

119. **Mather** et al., *Impact of Famotidine Use on Clinical Outcomes of Hospitalized Patients With COVID-19*, American Journal of Gastroenterology, doi:10.14309/ajg.0000000000000832.

120. **Freedberg** et al., *Famotidine Use Is Associated With Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study*, Gastroenterology, doi:10.1053/j.gastro.2020.05.053.

121. **Malone (C)**, R., *More Than Just Heartburn: Does Famotidine Effectively Treat Patients with COVID-19?*, Digestive Diseases and Sciences, doi:10.1007/s10620-021-06875-w.

122. **Mura (B)** et al., *Real-world Evidence for Improved Outcomes with Histamine Antagonists and Aspirin in 22,560 COVID-19 Patients*, Research Square, doi:10.21203/rs.3.rs-369927/v1.

123. **Tomera** et al., *Famotidine with Celecoxib Adjuvant Therapy on Hospitalized COVID-19 Patients: A Case Series*, SSRN Electronic Journal, doi:10.2139/ssrn.3646583.

124. **Malone (D)** et al., *Famotidine and Celecoxib COVID-19 Treatment Without and With Dexamethasone; Retrospective Comparison of Sequential Continuous Cohorts*, Research Square, doi:10.21203/rs.3.rs-526394/v1.

125. **Chenchula** et al., *Famotidine Repurposing for Novel Corona Virus Disease of 2019: A Systematic Review*, Drug Research, doi:10.1055/a-1397-6763.

126. **Saini** et al., *The Potential of Drug Repurposing as a Rapid Response Strategy in COVID-19 Therapeutics*, Journal of Advances in Medical and Pharmaceutical Sciences, doi:10.9734/jamps/2024/v26i12728.

127. **Tachoua** et al., *Highlights in TMPRSS2 inhibition mechanism with guanidine derivatives approved drugs for COVID-19 treatment*, Journal of Biomolecular Structure and Dynamics, doi:10.1080/07391102.2023.2169762.

128. **Masoudi-Sobhanzadeh** et al., *Structure-based drug repurposing against COVID-19 and emerging infectious diseases: methods, resources and discoveries*, Briefings in Bioinformatics, doi:10.1093/bib/bbab113.

129. **Calleja** et al., *Inhibitors of SARS-CoV-2 PLpro*, Frontiers in Chemistry, doi:10.3389/fchem.2022.876212.

130. **Wu (B)** et al., *Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods*, Acta Pharmaceutica Sinica B, doi:10.1016/j.apsb.2020.02.008.

131. **Ponnampalli** et al., *COVID-19: Vaccines and therapeutics*, Bioorganic & Medicinal Chemistry Letters, doi:10.1016/j.bmcl.2022.128987.

132. **Pandit** et al., *e-Pharmacophore modeling and in silico study of CD147 receptor against SARS-CoV-2 drugs*, Genomics & Informatics, doi:10.5808/gi.23005.

133. **Oliver** et al., *Different drug approaches to COVID-19 treatment worldwide: an update of new drugs and drugs repositioning to fight against the novel coronavirus*, Therapeutic Advances in Vaccines and Immunotherapy, doi:10.1177/25151355221144845.

134. **Pati** et al., *Drug discovery through Covid-19 genome sequencing with siamese graph convolutional neural network*, Multimedia Tools and Applications, doi:10.1007/s11042-023-15270-8.

135. **Islam** et al., *Molecular-evaluated and explainable drug repurposing for COVID-19 using ensemble knowledge graph embedding*, Scientific Reports, doi:10.1038/s41598-023-30095-z.

136. **Esam** et al., *In silico investigation of the therapeutic and prophylactic potential of medicinal substances bearing guanidine moieties against COVID-19*, Chemical Papers, doi:10.1007/s11696-022-02528-y.

137. **Sperry** et al., *Target-agnostic drug prediction integrated with medical record analysis uncovers differential associations of statins with increased survival in COVID-19 patients*, PLOS Computational Biology, doi:10.1371/journal.pcbi.1011050.

138. **c19early.org (D)**, c19early.org/timeline.html.

139. **Mateja** et al., *The choice of viral load endpoint in early phase trials of COVID-19 treatments aiming to reduce 28-day hospitalization and/or death*, The Journal of Infectious Diseases, doi:10.1093/infdis/jiaf282.

140. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.

141. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.

142. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.

143. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.

144. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.