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

@CovidAnalysis, March 2024, Version 23
https://c19early.org/fmmeta.html

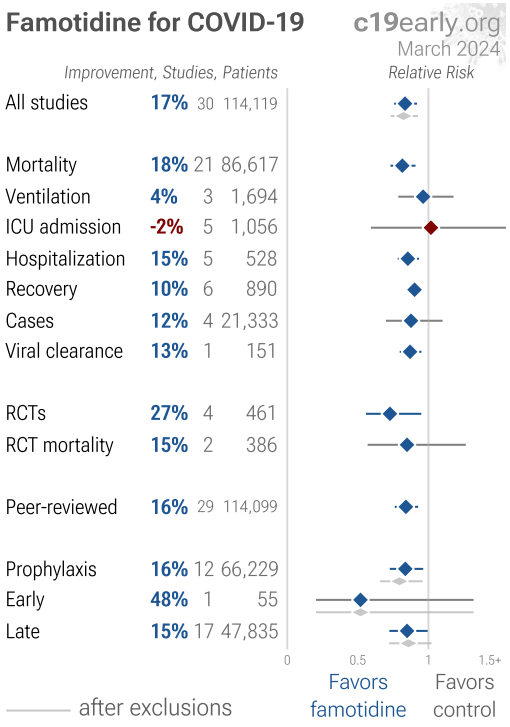
Abstract

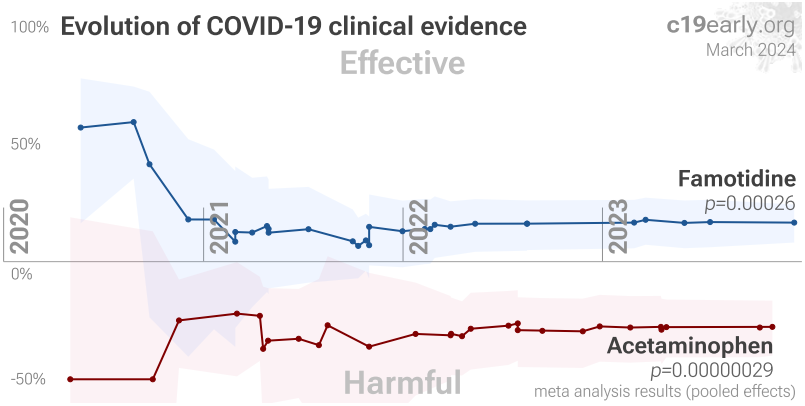
Statistically significant lower risk is seen for mortality, hospitalization, recovery, and viral clearance. 15 studies from 15 independent teams in 7 countries show statistically significant improvements.

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.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments are significantly more effective.

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





HIGHLIGHTS

Famotidine reduces risk for COVID-19 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.

Famotidine was the 26th treatment shown effective with ≥3 clinical studies in October 2021, now known with p = 0.00026 from 30 studies.

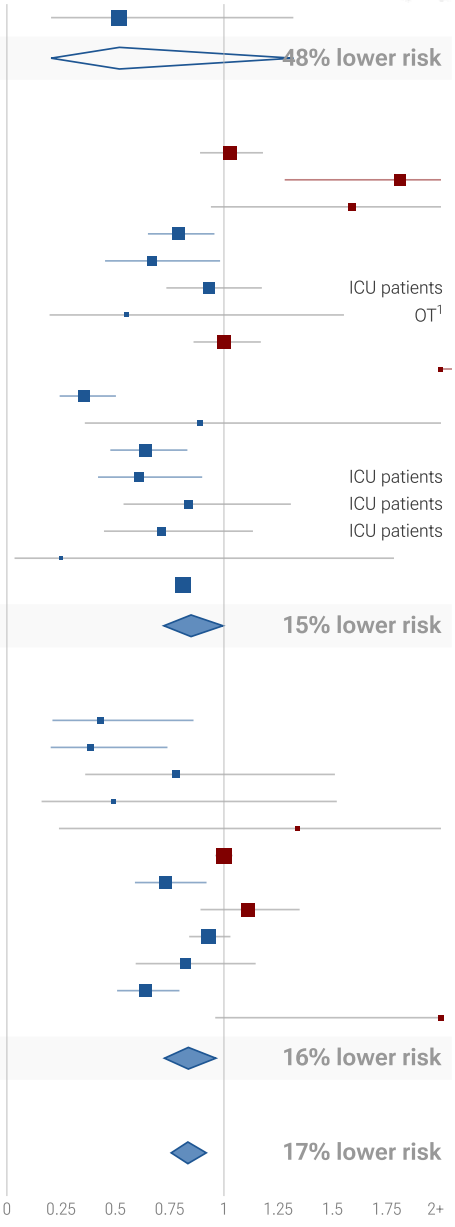
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

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

30 famotidine COVID-19 studies

c19early.org
March 2024

	Improvement	RR [CI]		Treatment	Control
Brennan (DB RCT)	48%	0.52 [0.20-1.32]	no recov.	5/27	10/28
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)	-81%	1.81 [1.28-2.58]	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 = 88.3%, p = 0.044					
	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	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 = 88.3%, p = 0.00026

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

Efficacy in COVID-19 famotidine studies (pooled effects)

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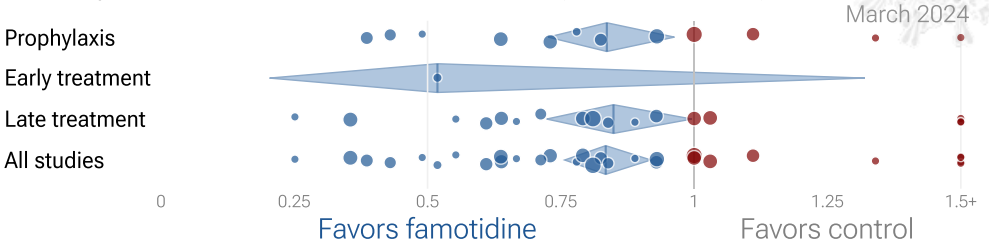
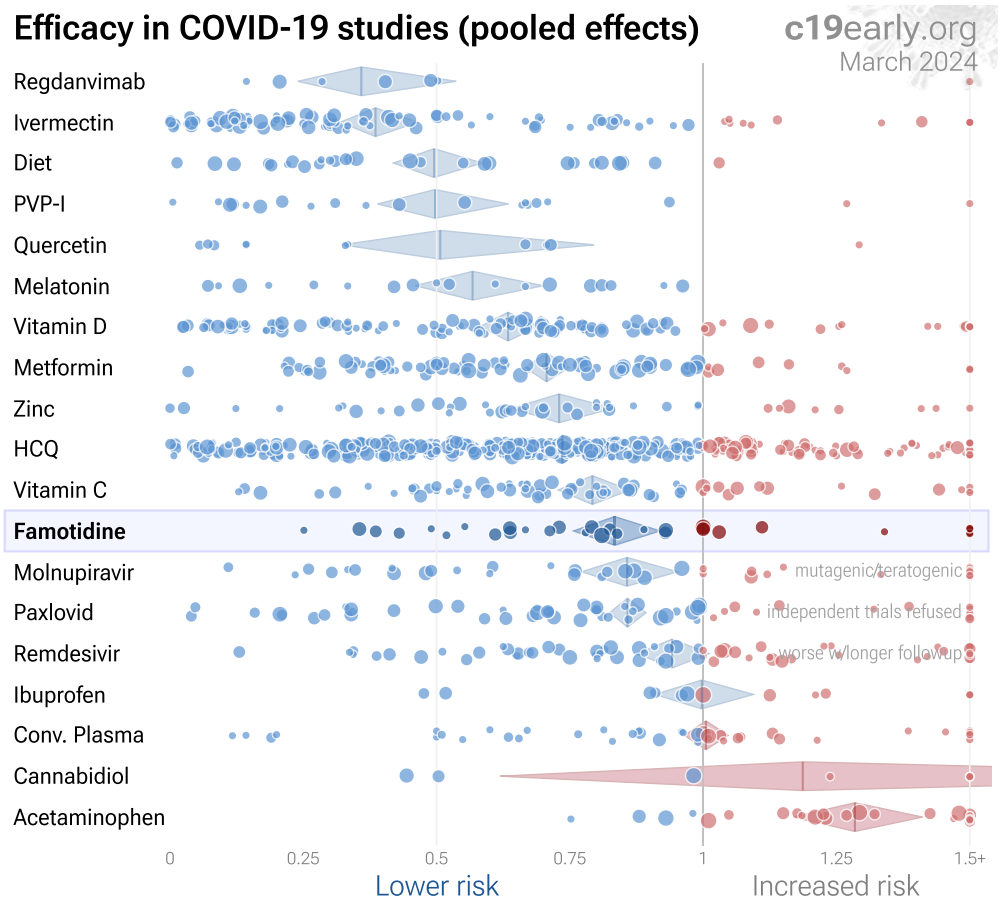




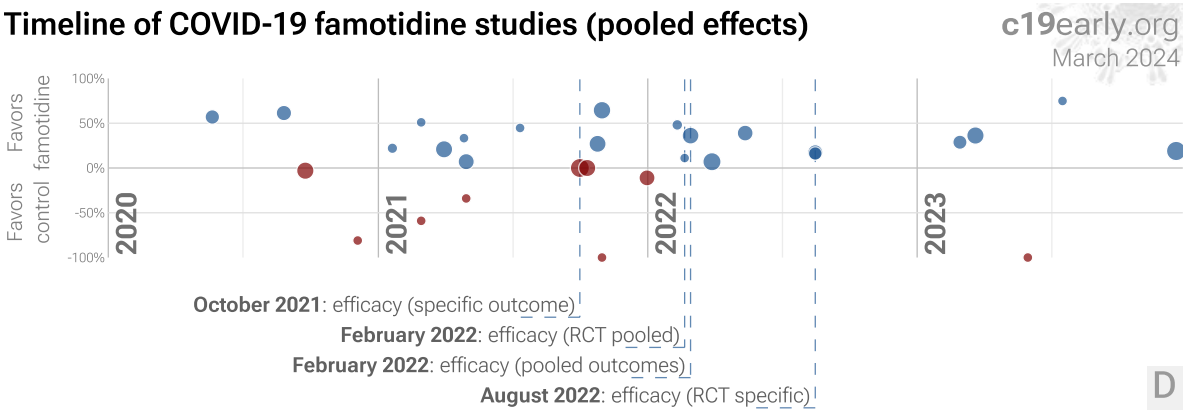


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. 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 issues *Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors *Note A, Malone, Murigneux, Lv, Lui*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk *c19early.org (B)*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Analysis. We analyze all significant controlled studies of 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 2 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

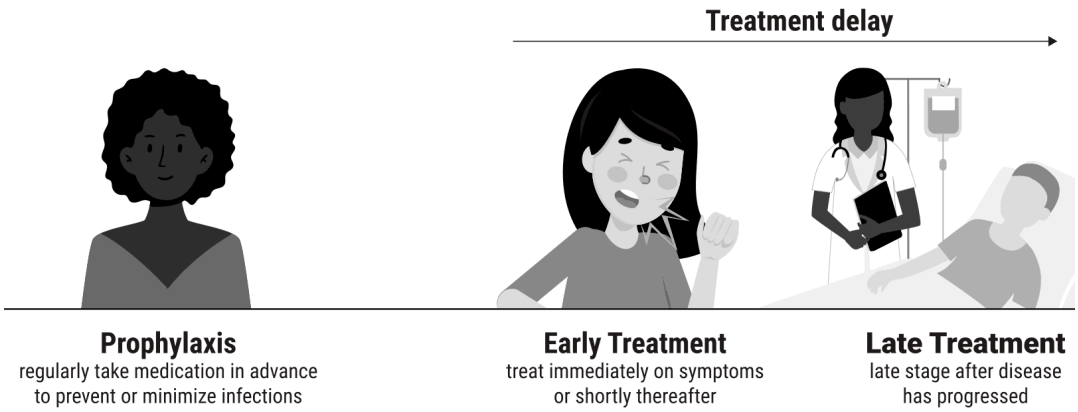


Figure 2. Treatment stages.

Preclinical Research

An *In Vitro* study supports the efficacy of famotidine *Loffredo*.

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 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 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.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**17%** [8-24%] ***	30	114,119	242
After exclusions	**18%** [7-27%] **	26	113,292	204
Peer-reviewed studies	**16%** [7-24%] ***	29	114,099	236
Randomized Controlled Trials	27% [5-44%] *	4	461	56
Mortality	**18%** [9-27%] ***	21	86,617	150
Ventilation	**4%** [-18-21%]	3	1,694	15
ICU admission	-2% [-75-41%]	5	1,056	37
Hospitalization	**15%** [7-22%] ***	5	528	38
Recovery	**10%** [5-14%] ****	6	890	68
Cases	**12%** [-10-30%]	4	21,333	28
RCT mortality	**15%** [-26-43%]	2	386	19
RCT hospitalization	**17%** [12-22%] ****	3	349	25

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 percentage improvement with treatment and the 95% confidence interval. * p<0.05 ** p<0.01 *** p<0.001 **** p<0.0001.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	48% [-32-80%]	**15%** [0-28%] *	**16%** [4-27%] *
After exclusions	48% [-32-80%]	**14%** [-2-28%]	21% [4-34%] *
Peer-reviewed studies	48% [-32-80%]	**14%** [-2-27%]	**16%** [4-27%] *
Randomized Controlled Trials	48% [-32-80%]	25% [1-43%] *	
Mortality		**20%** [6-31%] **	**15%** [-4-29%]
Ventilation		**4%** [-18-21%]	
ICU admission		-2% [-75-41%]	
Hospitalization		**17%** [13-21%] ****	**6%** [3-9%] ***
Recovery	48% [-32-80%]	**10%** [5-14%] ****	37% [-54-74%]
Cases			**12%** [-10-30%]
RCT mortality		**15%** [-26-43%]	
RCT hospitalization		**17%** [12-22%] ****	

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * p<0.05 ** p<0.01 *** p<0.001 **** p<0.0001.

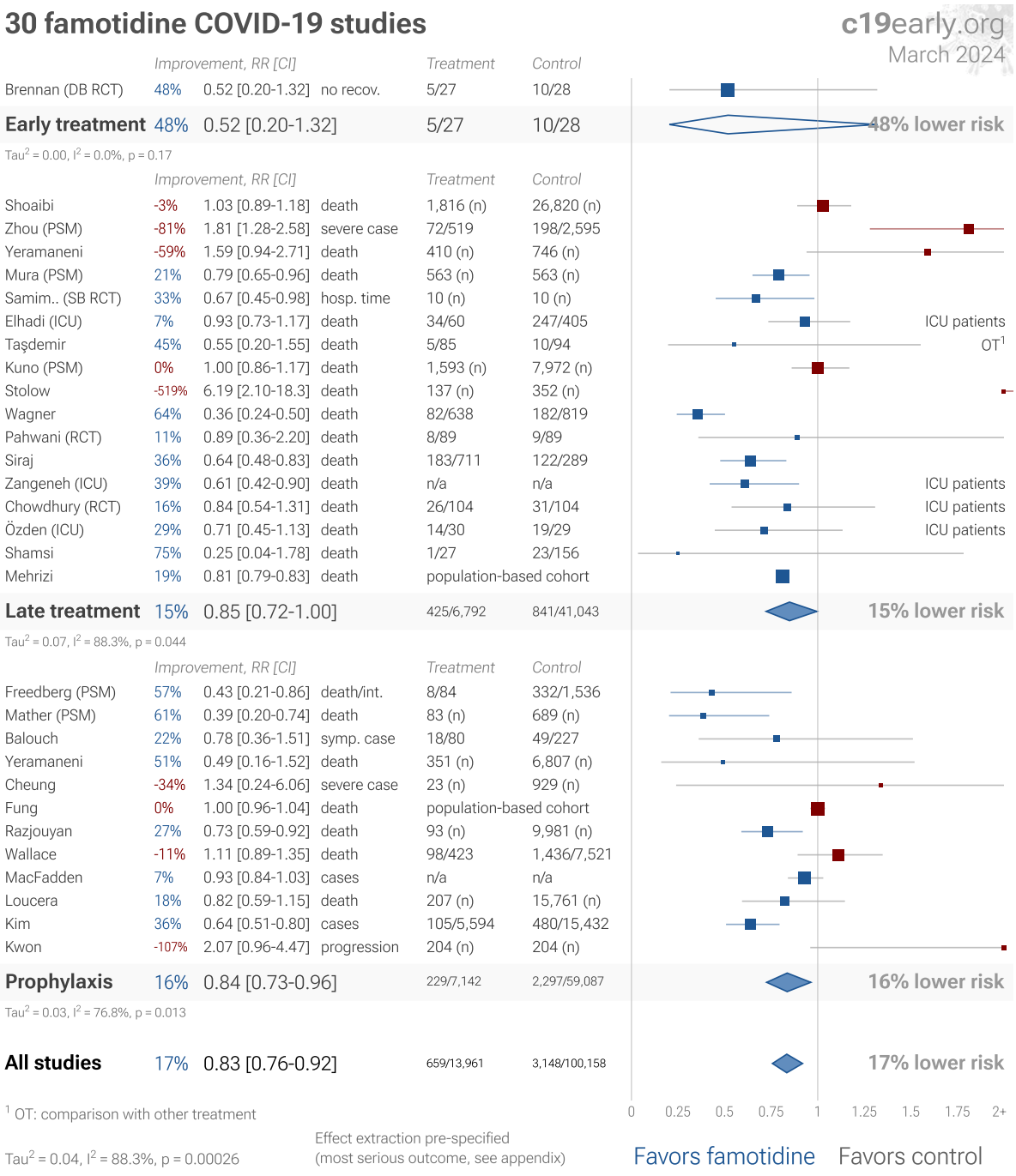


Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

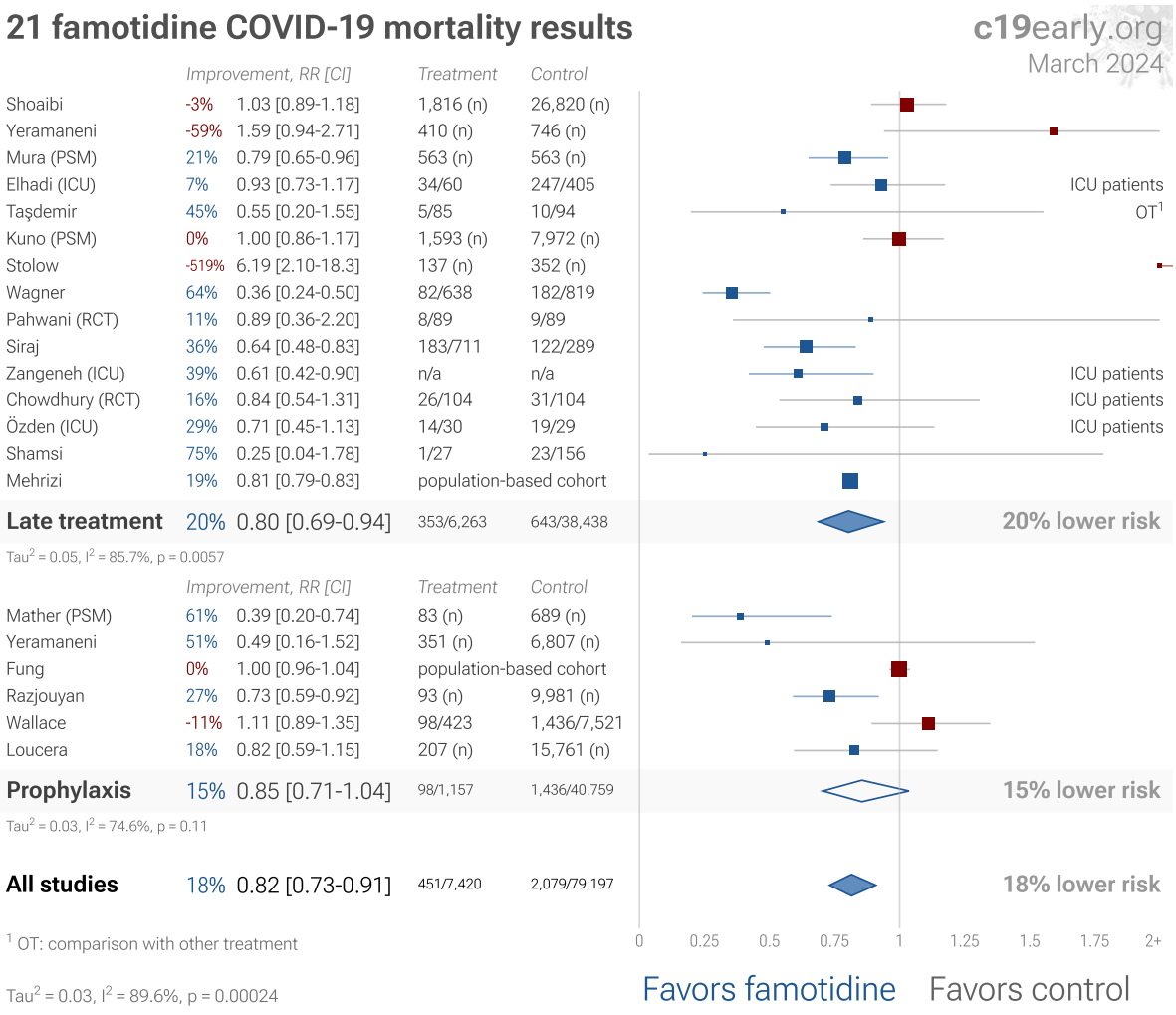


Figure 4. Random effects meta-analysis for mortality results.

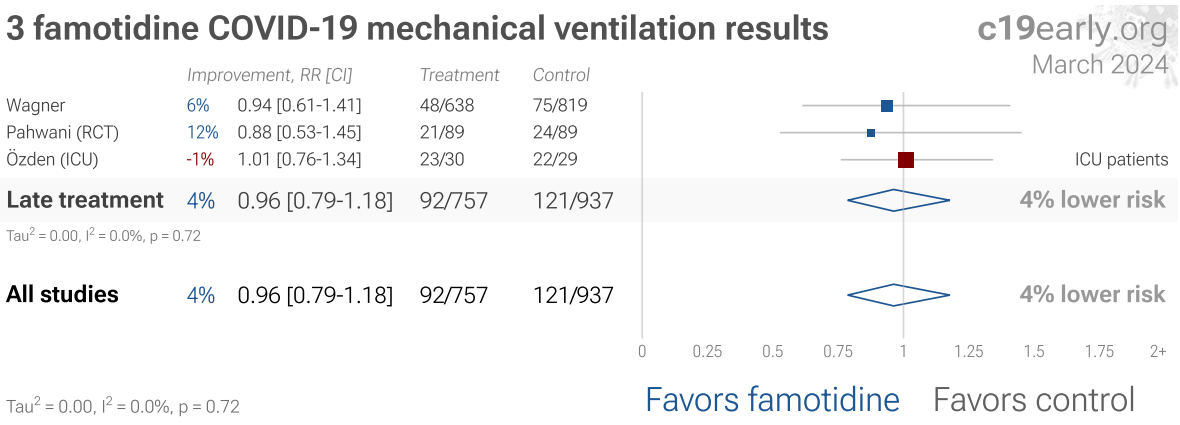


Figure 5. Random effects meta-analysis for ventilation.

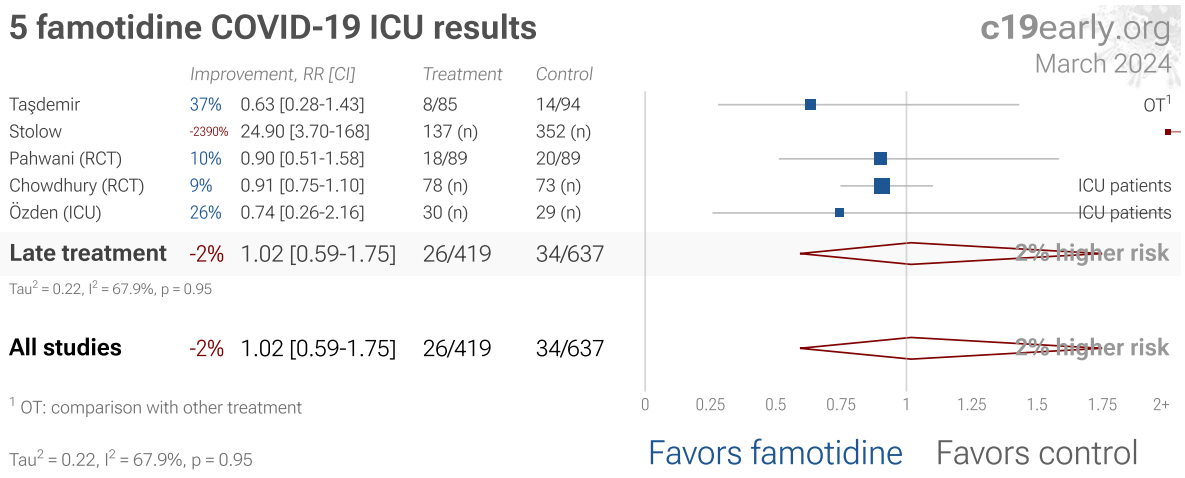


Figure 6. Random effects meta-analysis for ICU admission.

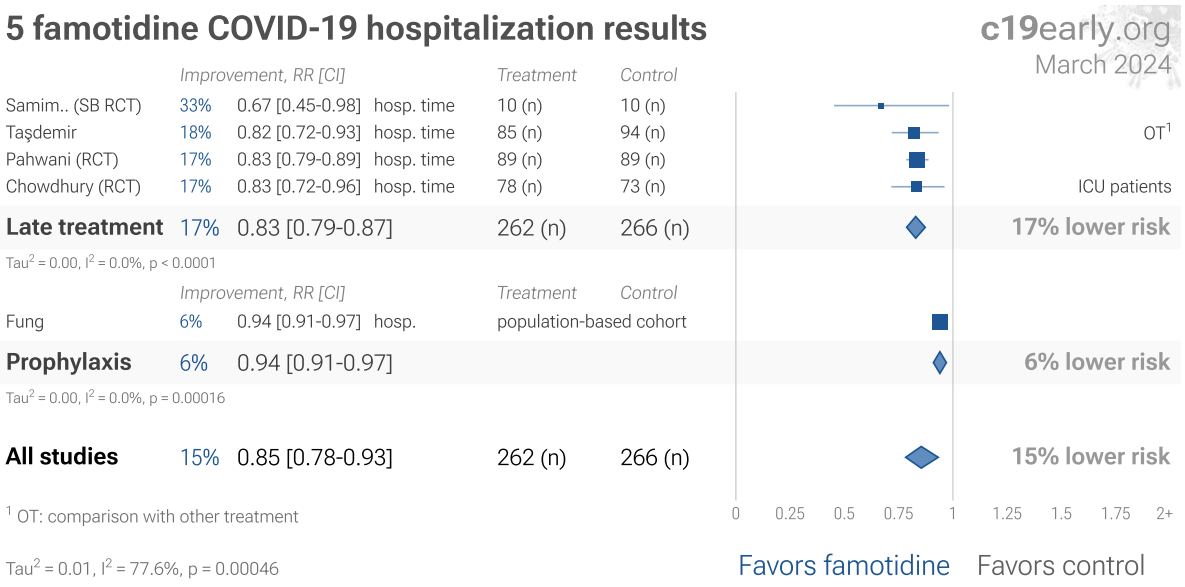


Figure 7. Random effects meta-analysis for hospitalization.

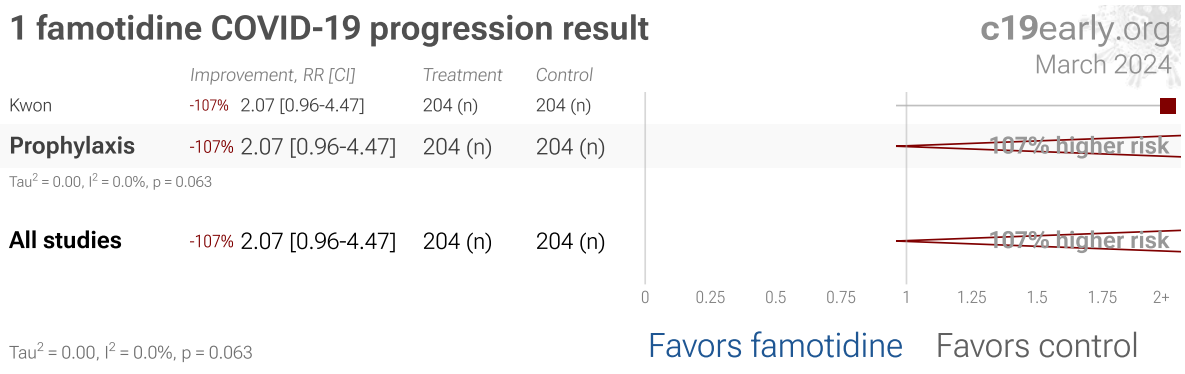


Figure 8. Random effects meta-analysis for progression.

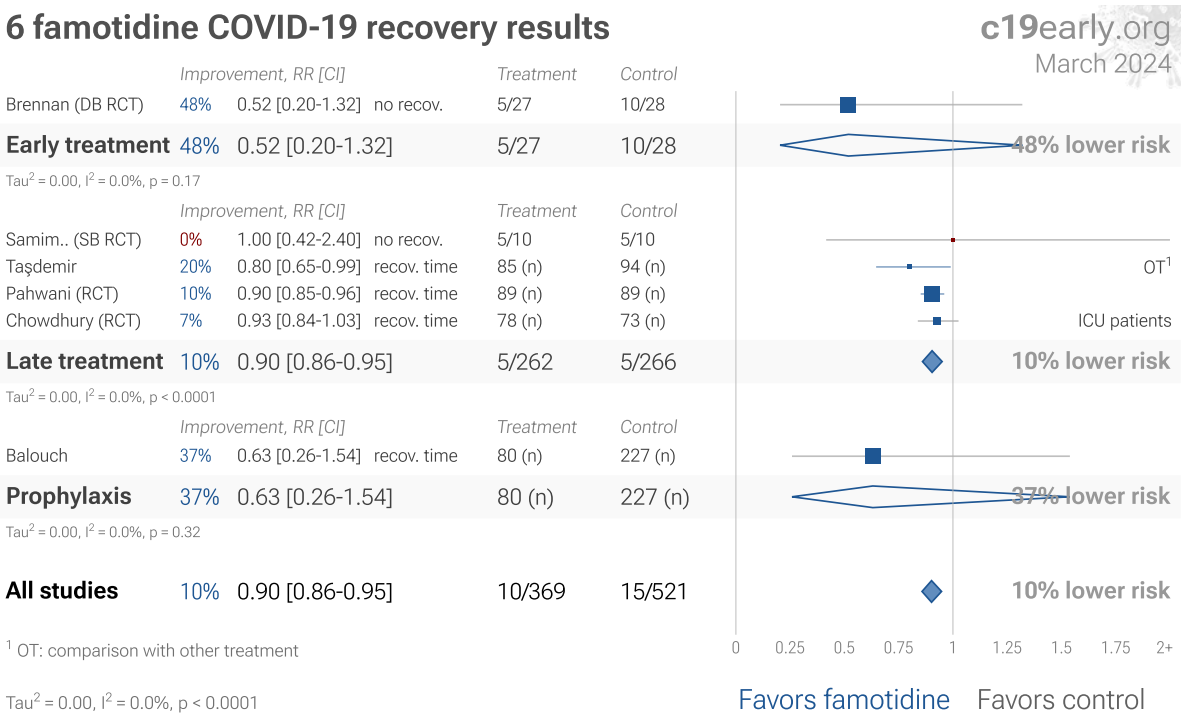


Figure 9. Random effects meta-analysis for recovery.

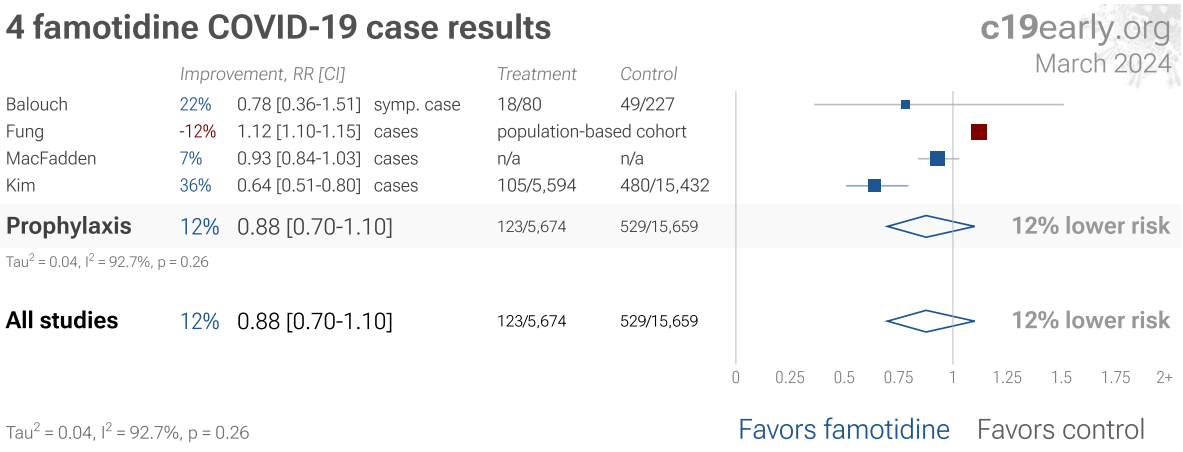


Figure 10. Random effects meta-analysis for cases.

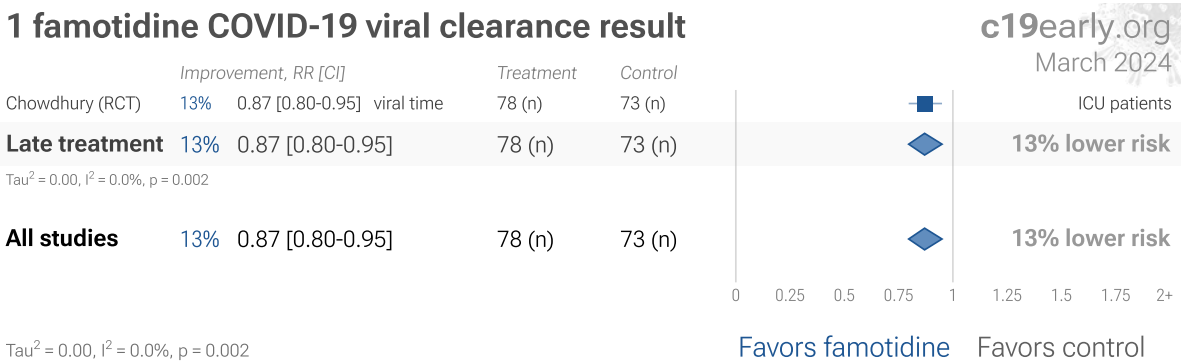


Figure 11. Random effects meta-analysis for viral clearance.

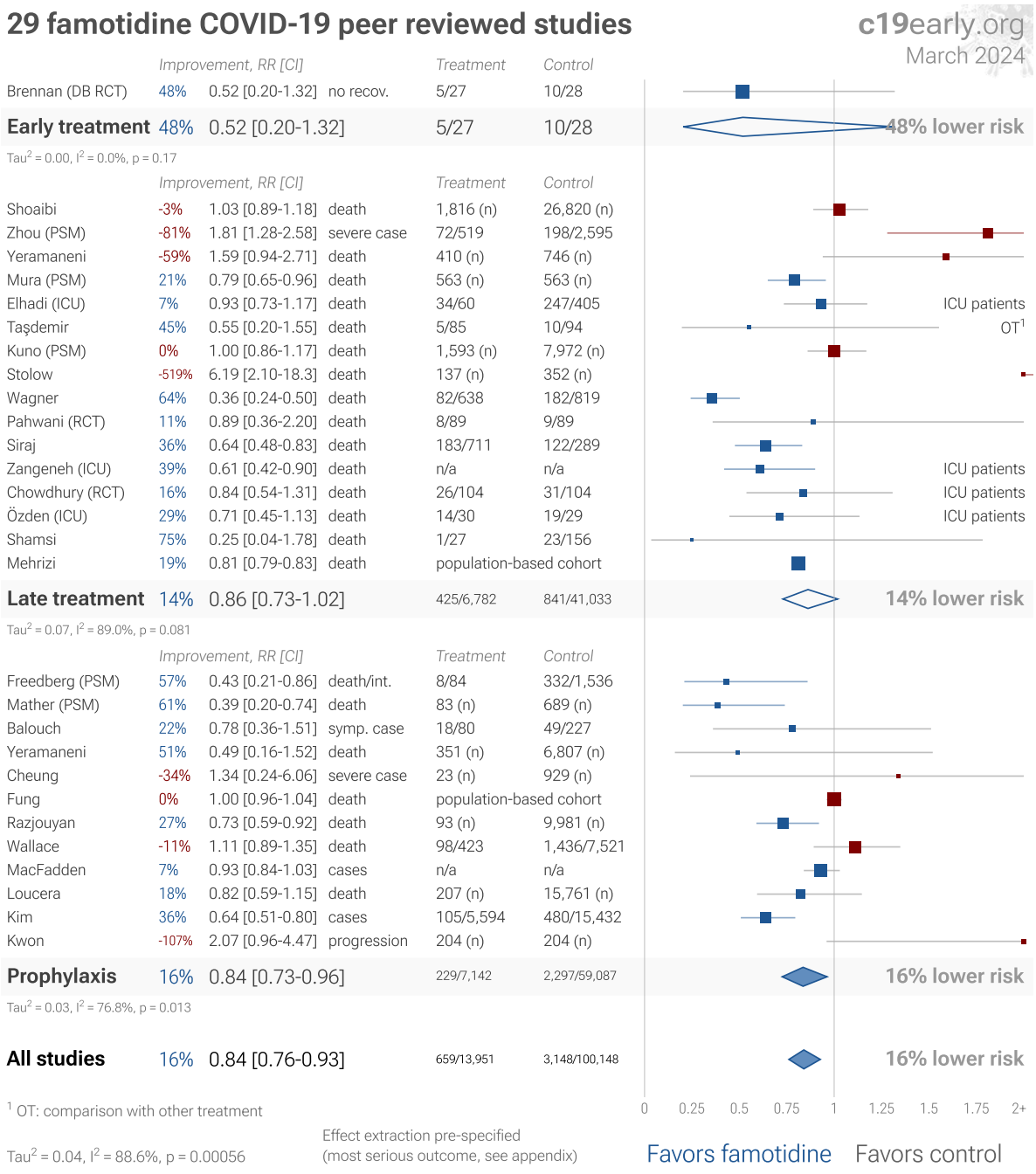


Figure 12. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 13 shows a comparison of results for RCTs and non-RCT studies. The median effect size for RCTs is 25% improvement, compared to 20% for other studies. Figure 14, 15, and 16 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.

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

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

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 66 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments (they may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration).

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

Using all studies identifies efficacy 5.7+ months faster for COVID-19. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

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

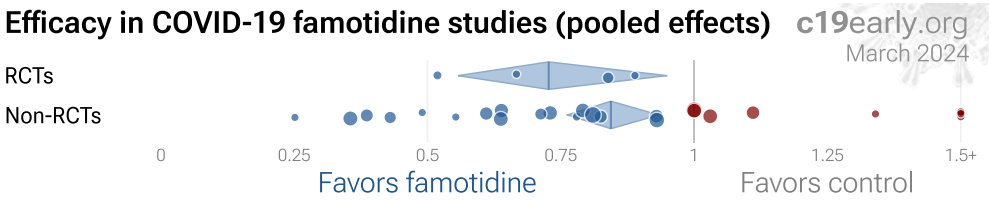


Figure 13. Results for RCTs and non-RCT studies.

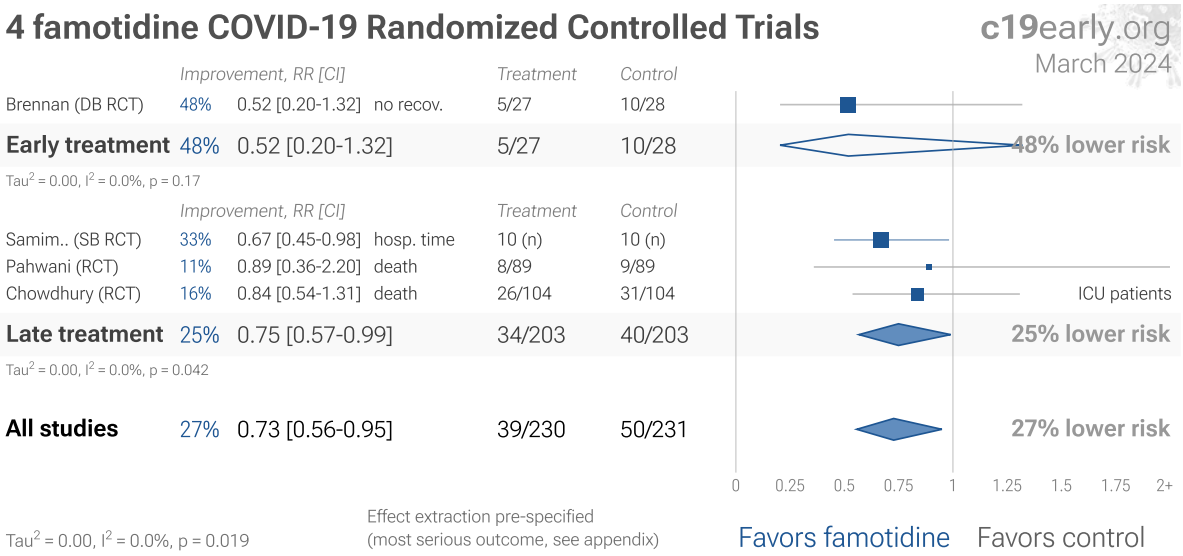


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

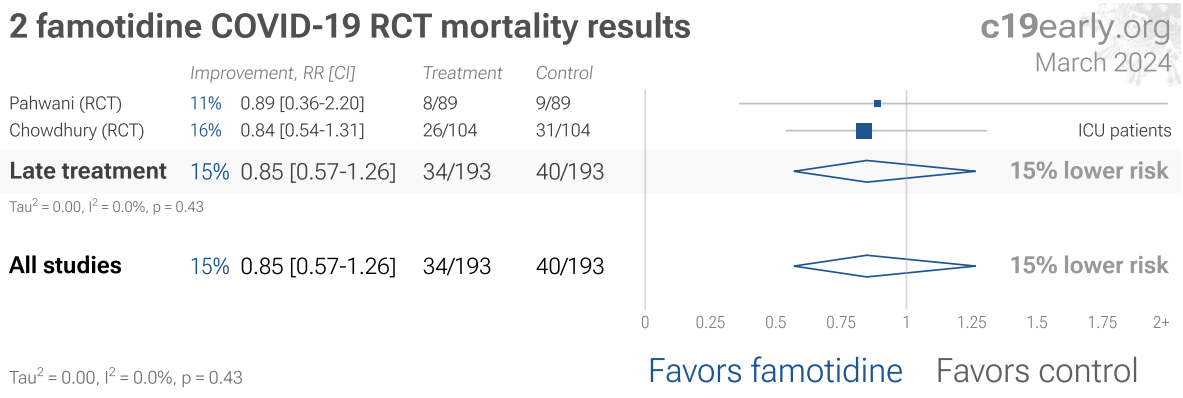


Figure 15. Random effects meta-analysis for RCT mortality results.

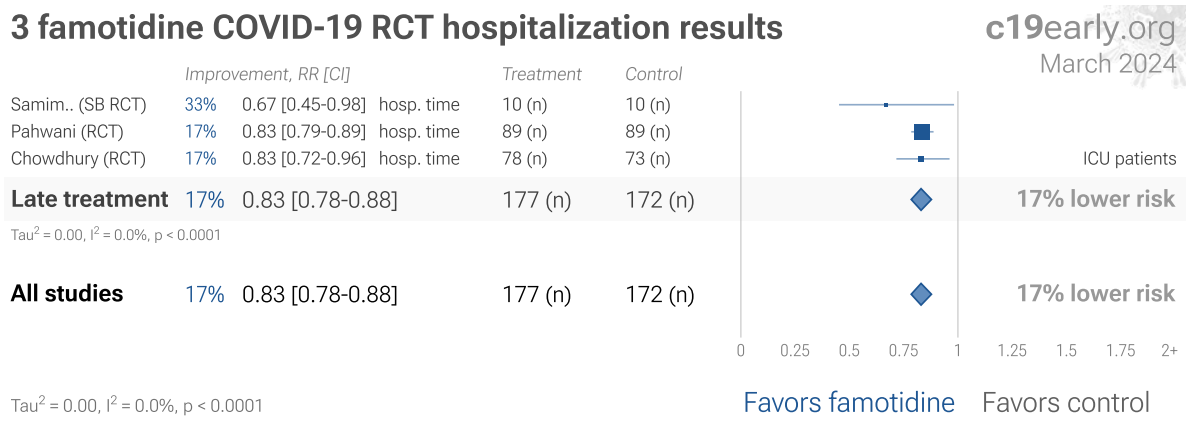


Figure 16. Random effects meta-analysis for RCT hospitalization results.

Exclusions

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

The studies excluded are as below. Figure 17 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.

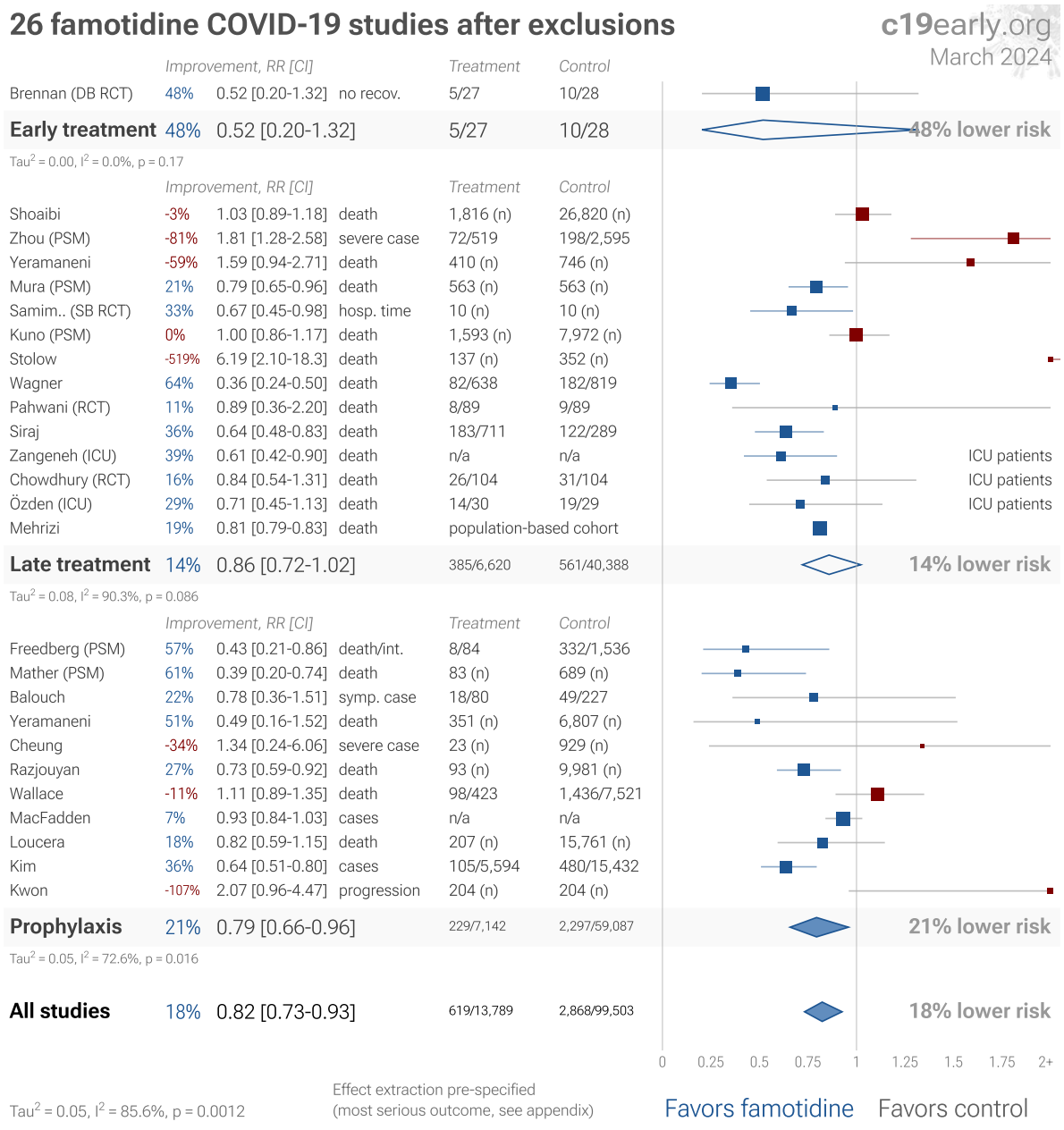


Figure 17. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Heterogeneity

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

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours *McLean, Treanor*. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post exposure prophylaxis	86% fewer cases *Ikematsu*
<24 hours	-33 hours symptoms *Hayden*
24-48 hours	-13 hours symptoms *Hayden*
Inpatients	-2.5 hours to improvement *Kumar*

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

Figure 18 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

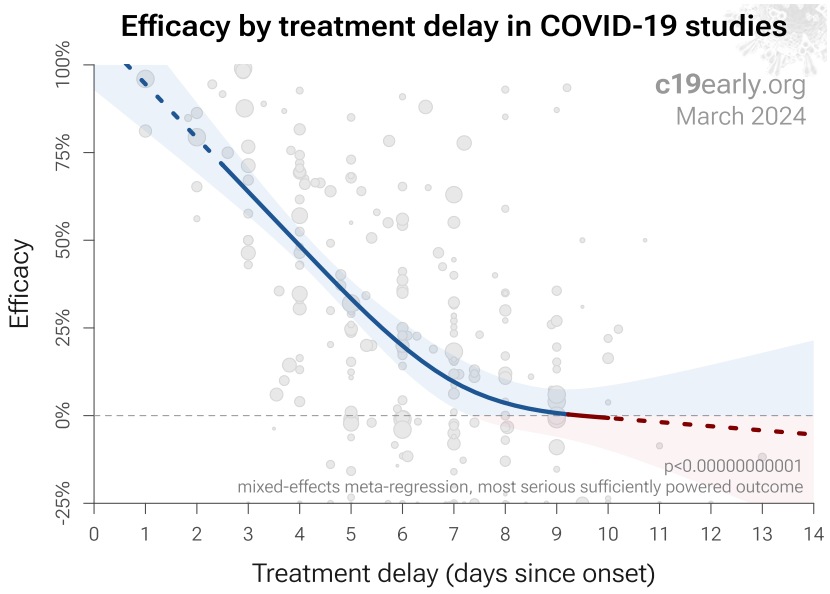


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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

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

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

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

Other treatments. The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

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

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

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

Pooled outcomes identify efficacy faster. Currently, 44 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 treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

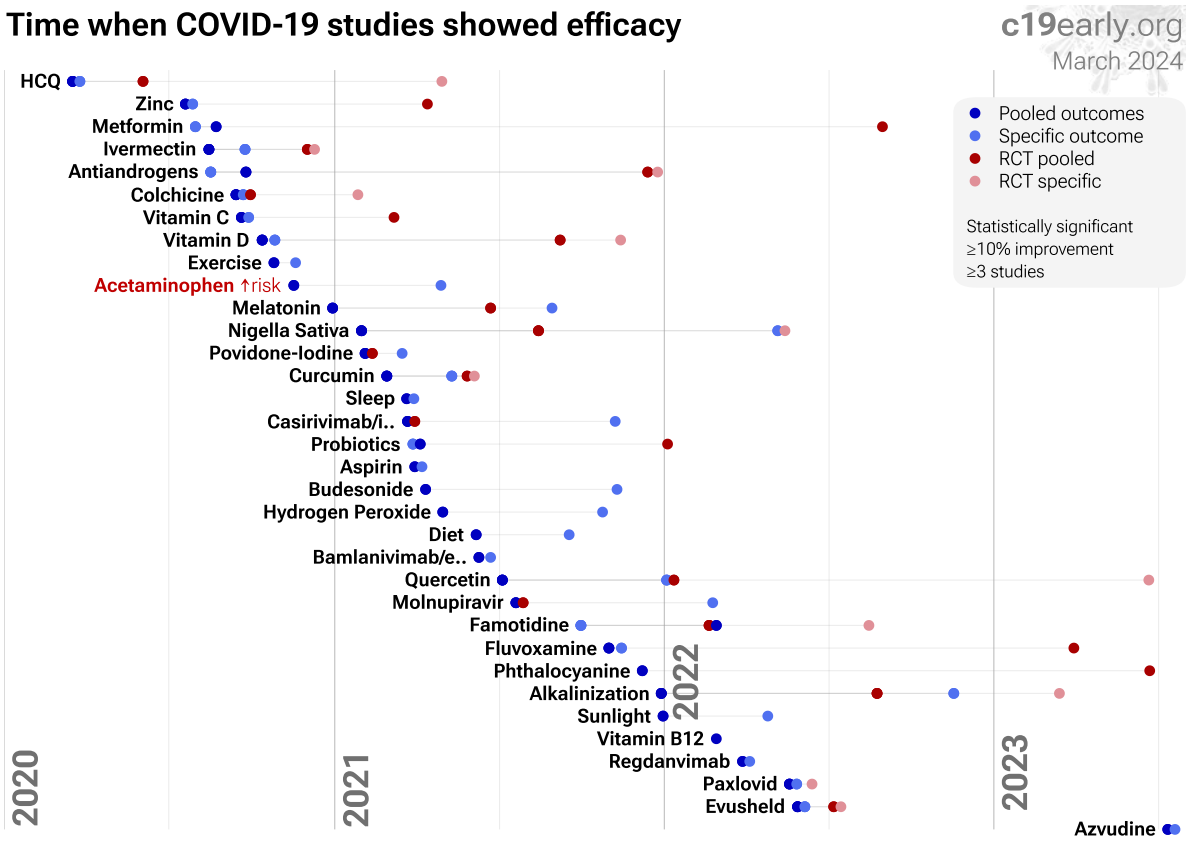


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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

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

Discussion

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

incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results [Boulware, Meeus, Meneguesso]. For 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 20 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.

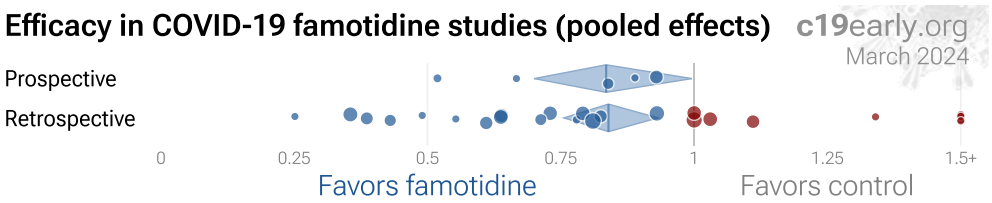


Figure 20. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 21 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ [Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

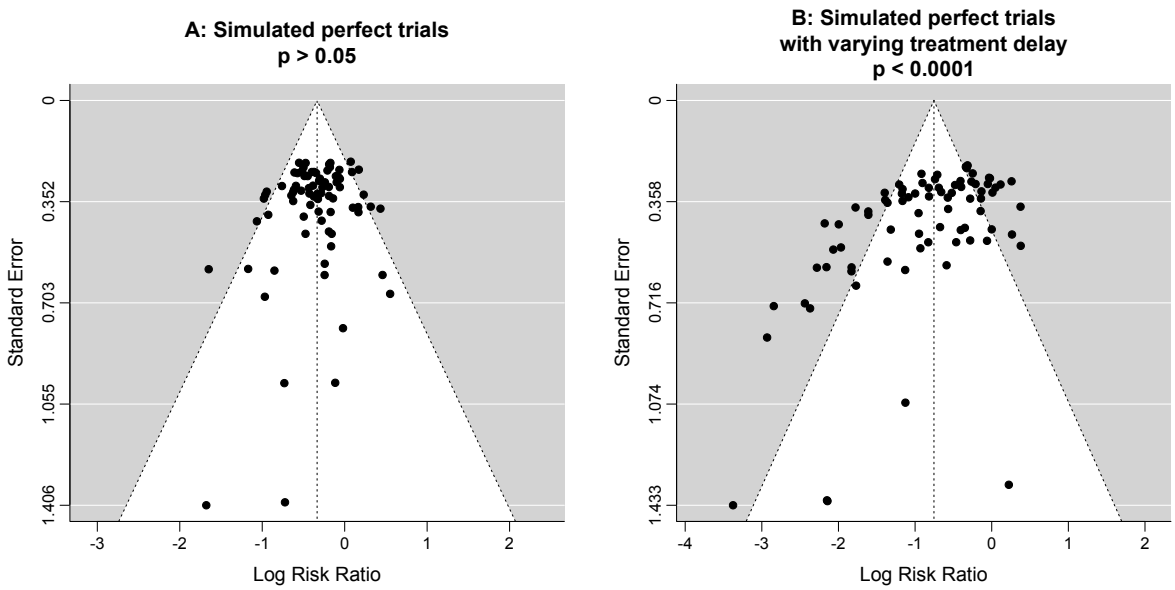


Figure 21. Example funnel plot analysis for simulated perfect trials.

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 by specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

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

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

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

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

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

treatments.

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

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

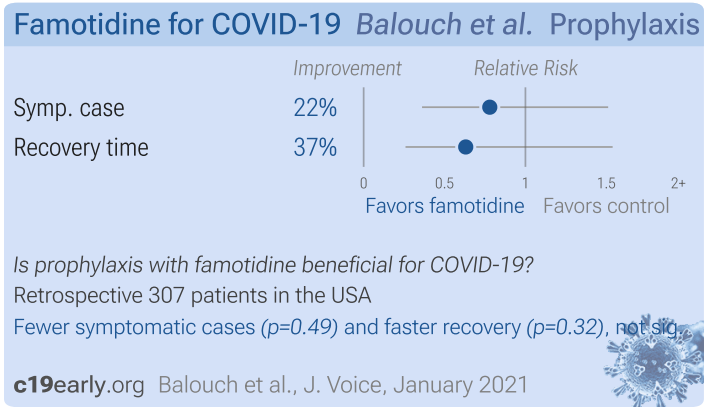
Notes. 1 of the 30 studies compare against other treatments, which may reduce the effect seen.

Conclusion

Famotidine is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, recovery, and viral clearance. 15 studies from 15 independent teams in 7 countries show statistically significant improvements. 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.

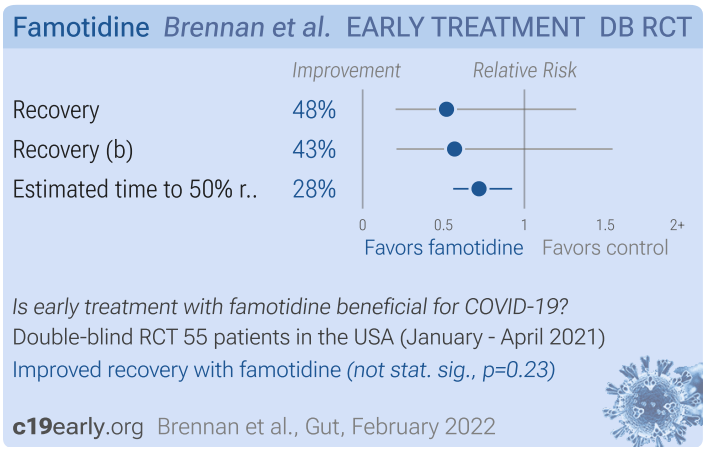
Study Notes

Balouch



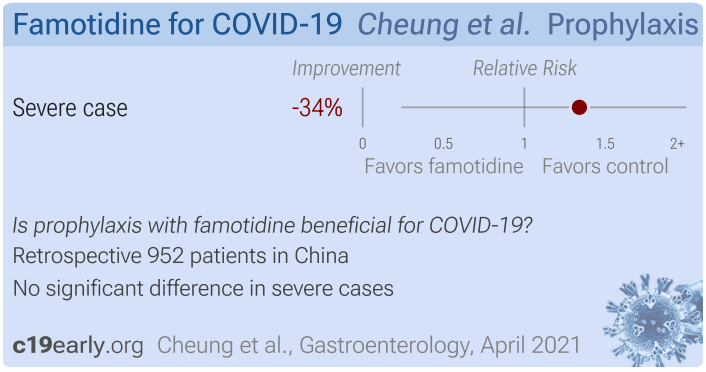
Balouch: Survey of 307 patients in the USA, showing no significant difference in COVID-19 cases with famotidine use.

Brennan



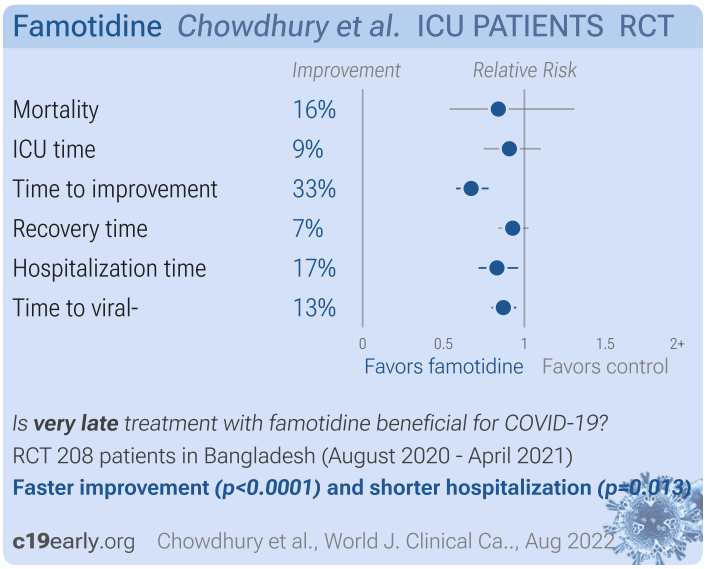
Brennan: Small RCT with 27 famotidine and 28 placebo patients, showing improved recovery with treatment. Recovery was faster with treatment for 14 of 16 symptoms. There was no mortality or hospitalization. NCT04724720.

Cheung



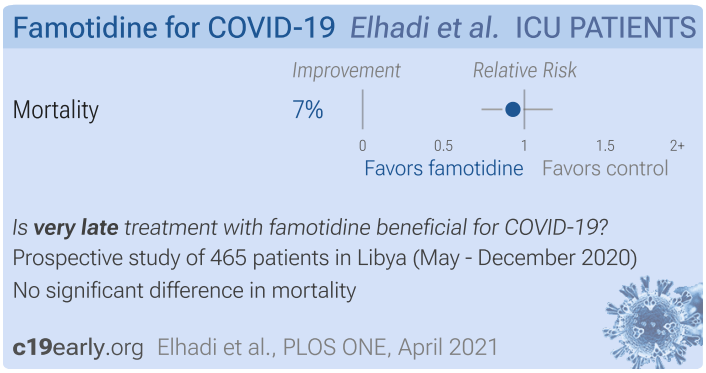
Cheung: Retrospective 952 COVID-19 patients in Hong Kong, showing no significant difference in severe disease with famotidine use.

Chowdhury



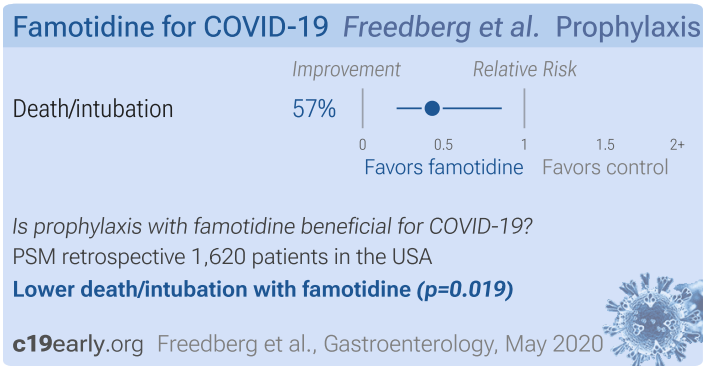
Chowdhury: RCT 208 ICU patients in Bangladesh, showing improved recovery with famotidine. Famotidine 40mg (<60kg) or 60mg every 8 hours.

Elhadi



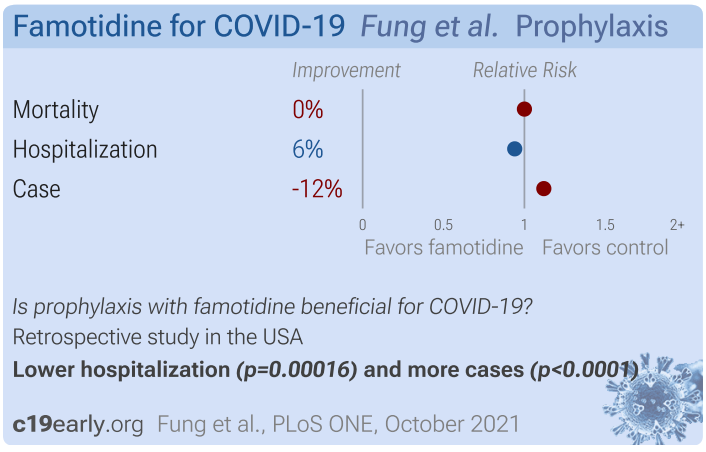
Elhadi: Prospective study of 465 COVID-19 ICU patients in Libya showing no significant differences with treatment.

Freedberg



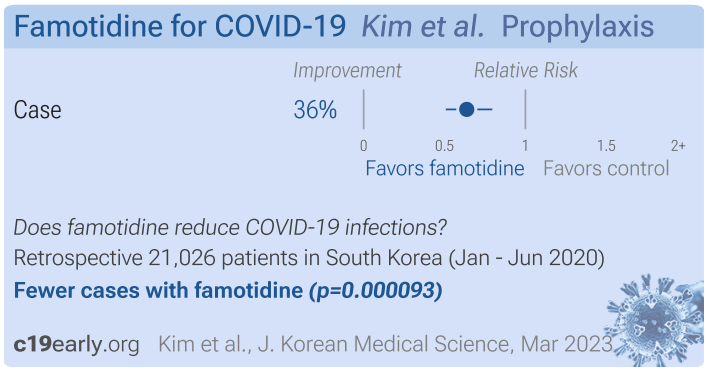
Freedberg: PSM retrospective 1,620 hospitalized patients in the USA, 84 with existing famotidine use, showing lower risk of combined death/intubation with treatment.

Fung



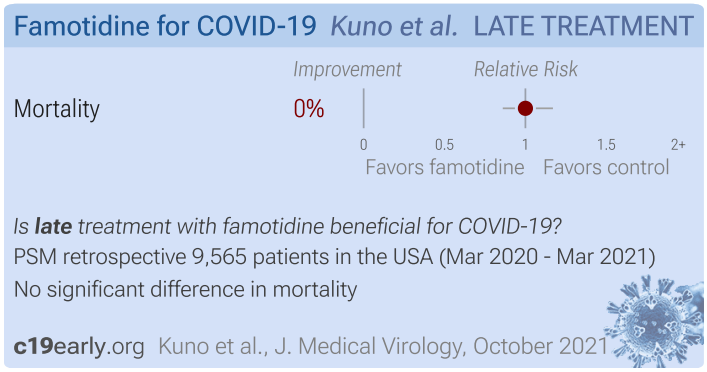
Fung: Retrospective database analysis of 374,229 patients in the USA, showing higher cases, lower hospitalizations, and no change in mortality with famotidine use.

Kim



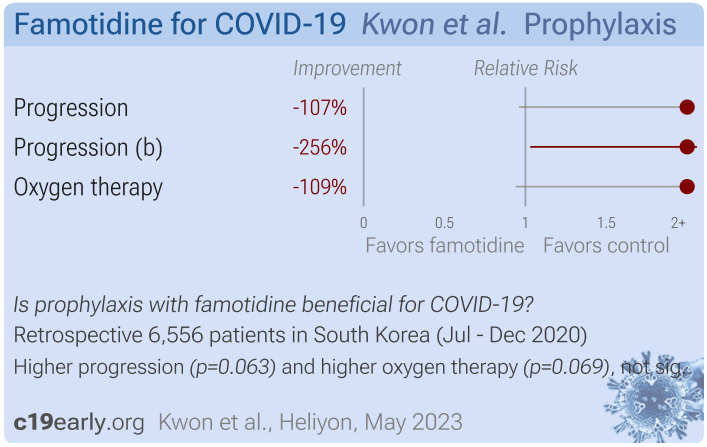
Kim: PSM retrospective in South Korea, showing lower risk of COVID-19 cases with H2RA (including famotidine) and PPA use, but no significant difference in severe outcomes (few events, results provided for the combined groups only).

Kuno



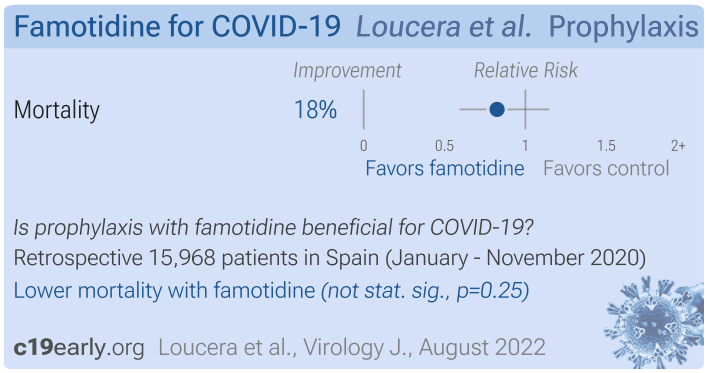
Kuno: PSM retrospective 9,565 COVID-19 hospitalized patients in the USA, 1,593 receiving famotidine, showing no significant difference in mortality.

Kwon



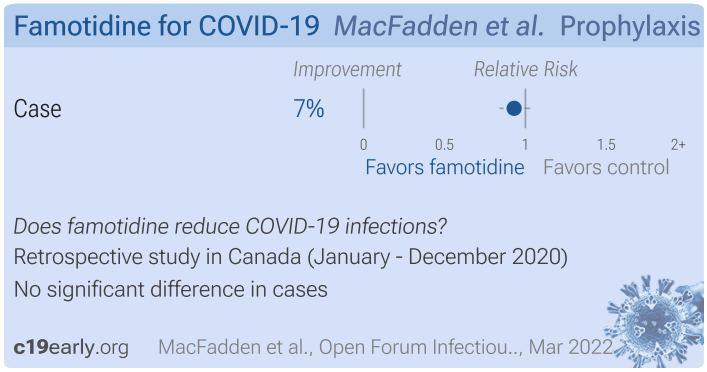
Kwon: PSM retrospective 6,556 COVID-19 patients in South Korea, showing higher risk of poor outcomes with famotidine vs. other H2-blocker use.

Loucera



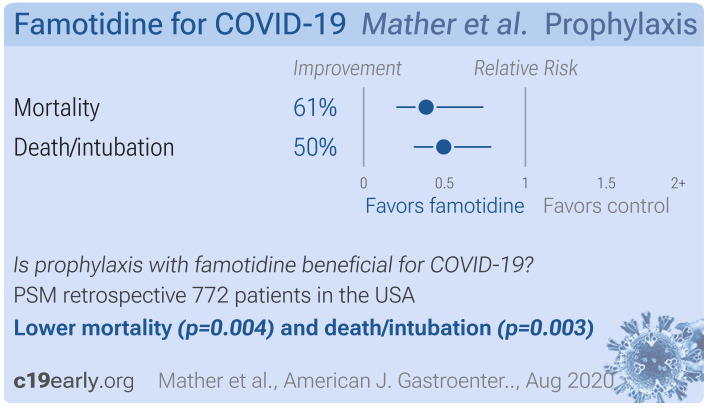
Loucera: Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different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

MacFadden



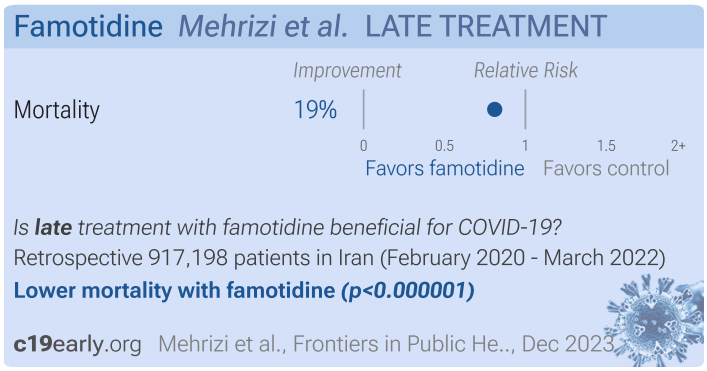
MacFadden: Retrospective 26,121 cases and 2,369,020 controls ≥65yo in Canada, showing no significant difference in cases with chronic use of famotidine.

Mather



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

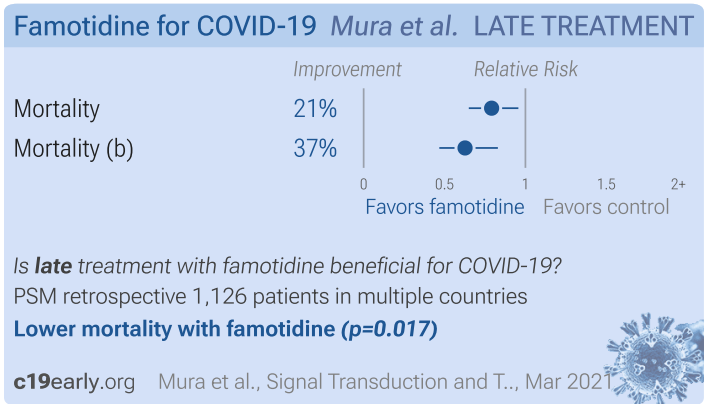
Mehrizi



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

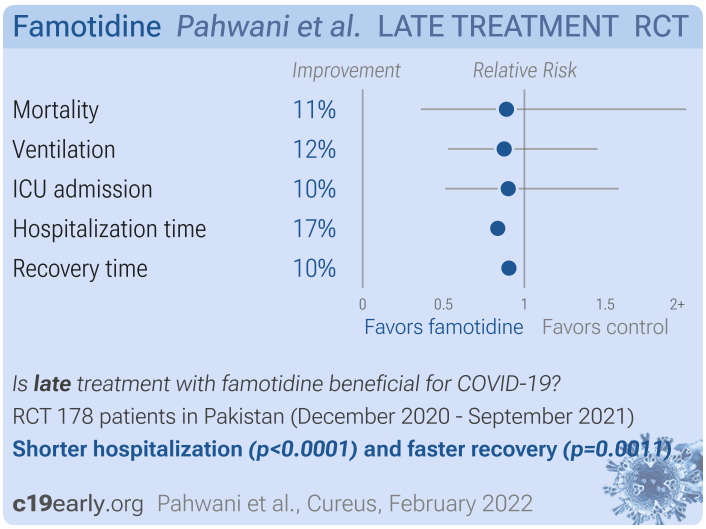
Confounding by indication is likely to be significant for many medications. Authors adjustments have very limited severity information (admission type refers to ward vs. ER department on initial arrival). We can estimate the impact of confounding from typical usage patterns, the prescription frequency,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

Mura



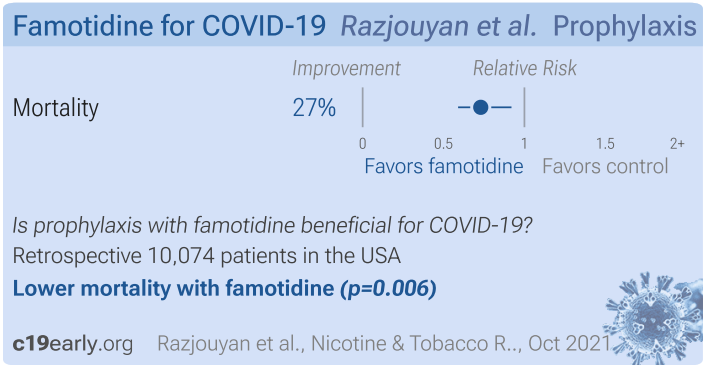
Mura: PSM retrospective TriNetX database analysis of 1,379 severe COVID-19 patients requiring respiratory support, showing lower mortality with aspirin (not reaching statistical significance) and famotidine, and improved results from the combination of both.

Pahwani



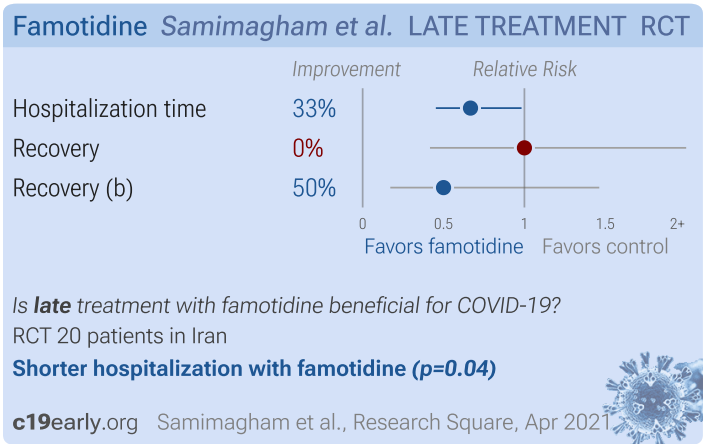
Pahwani: RCT with 89 famotidine and 89 control patients in Pakistan, showing faster recovery but no significant difference in mortality. 40mg oral famotidine daily.

Razjouyan



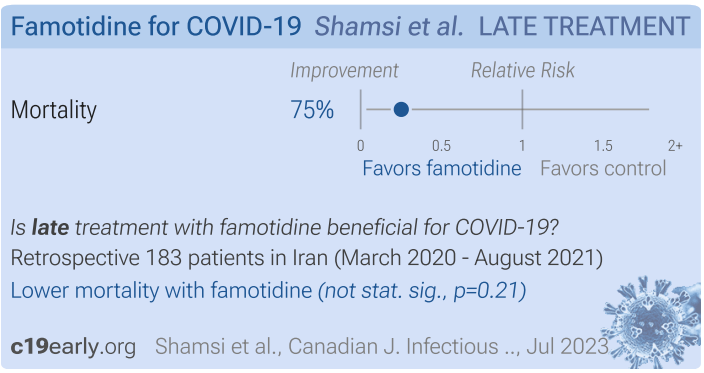
Razjouyan: Retrospective 10,074 veterens in the USA, showing lower mortality with existing famotidine use.

Samimagham



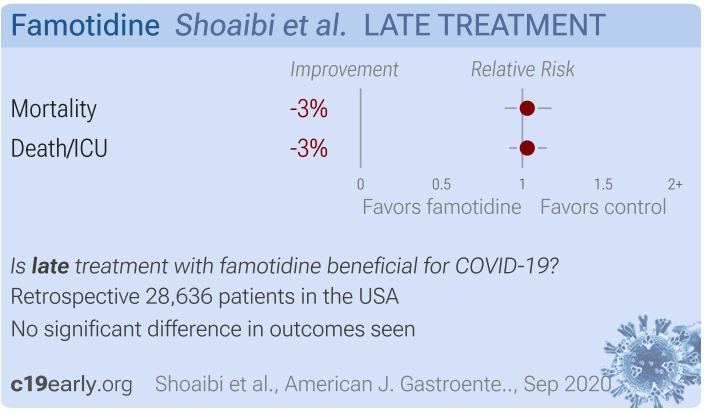
Samimagham: Very small RCT with 20 patients in Iran, showing shorter hospitalization time with famotidine treatment. There was no mortality or ICU admission. Famotidine 160mg four times a day. IRCT20200509047364N2.

Shamsi



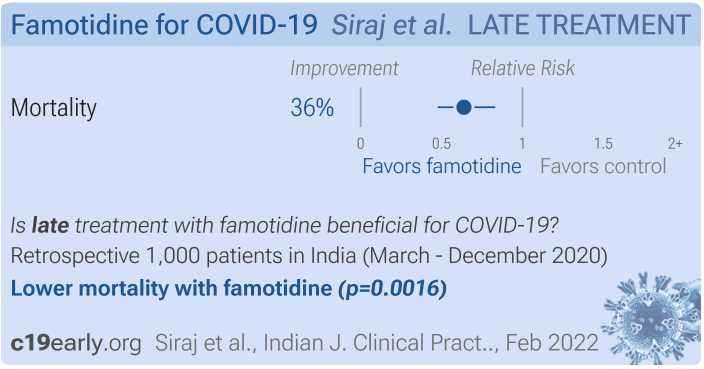
Shamsi: Retrospective 183 hospitalized pediatric COVID-19 patients in Iran, showing no significant difference in mortality with famotidine in unadjusted results.

Shoaibi



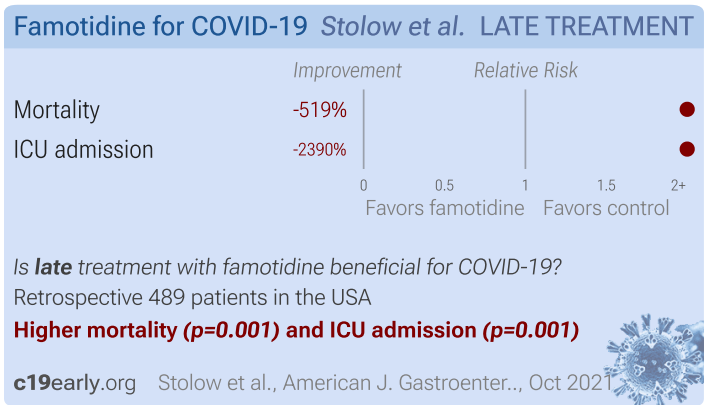
Shoaibi: Retrospective 1,816 famotidine users and 26,820 non-users hospitalized for COVID-19 in the USA, showing no significant differences with treatment.

Siraj



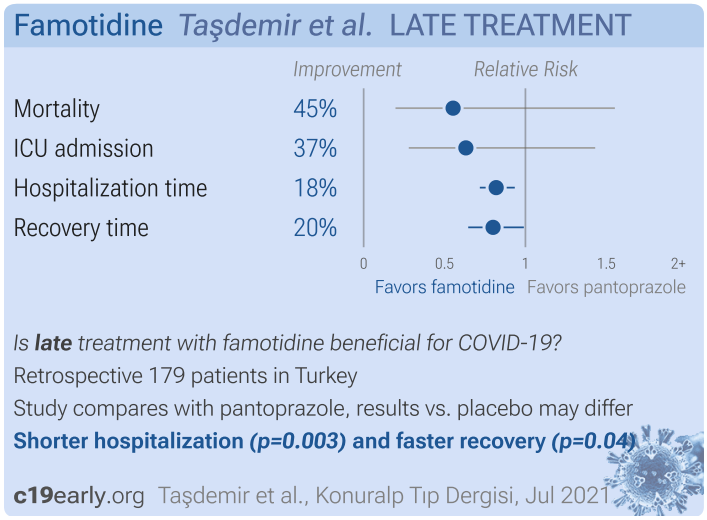
Siraj: Retrospective 1,000 COVID+ hospitalized patients in India, showing lower mortality with famotidine and remdesivir in multivariable logistic regression.

Stolow



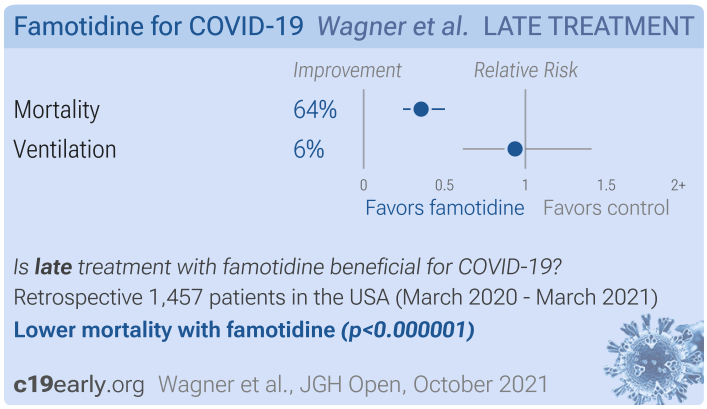
Stolow: Retrospective 489 COVID+ hospitalized patients in the USA, showing higher mortality with famotidine treatment.

Taşdemir



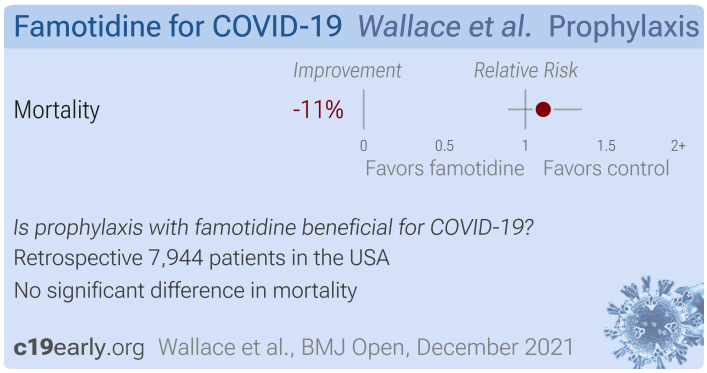
Taşdemir: Retrospective 179 hospitalized patients in Turkey, 85 treated with famotidine and 94 treated with pantoprazole, showing faster recovery with famotidine in unadjusted results.

Wagner



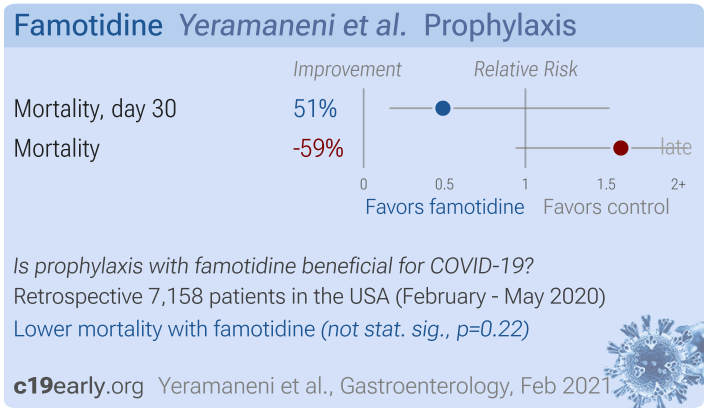
Wagner: Retrospective 2,184 hospitalized patients in the USA, 638 treated with famotidine, showing lower mortality with treatment.

Wallace



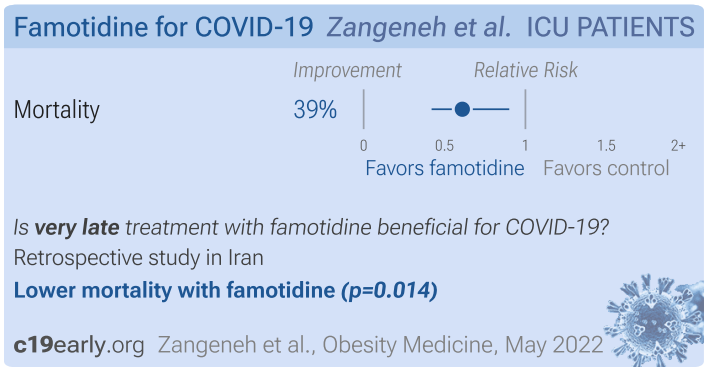
Wallace: Retrospective 9,532 hospitalized COVID+ veterans in the USA, showing no significant difference in mortality with famotidine use. The study provides results for use before, after, and before+after. Before+after should more accurately represent prophylaxis up to COVID-19 infection (and continued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

Yeramaneni



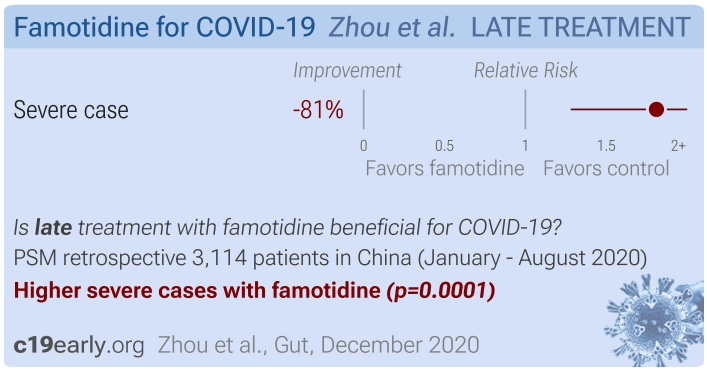
Yeramaneni: Retrospective 7,158 hospitalized COVID-19 patients in the USA, showing higher risk or mortality with in-hospital famotidine use, but lower risk when there was pre-existing at-home use, without statistical significance in both cases.

Zangeneh



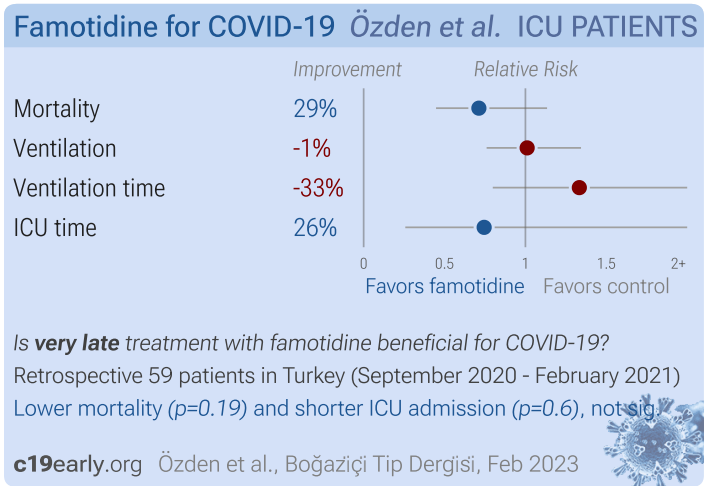
Zangeneh: Retrospective 193 ICU patients in Iran, showing lower mortality with famotidine treatment.

Zhou



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

Özden



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. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality

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

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

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

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

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

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, 81.0% higher, HR 1.81, p < 0.001, treatment 72 of 519 (13.9%), control 198 of 2,595 (7.6%), death/intubation/ICU, propensity score matching, 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, RR 0.43, p = 0.02, treatment 8 of 84 (9.5%), control 332 of 1,536 (21.6%), NNT 8.3, propensity score matching.
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, 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.

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