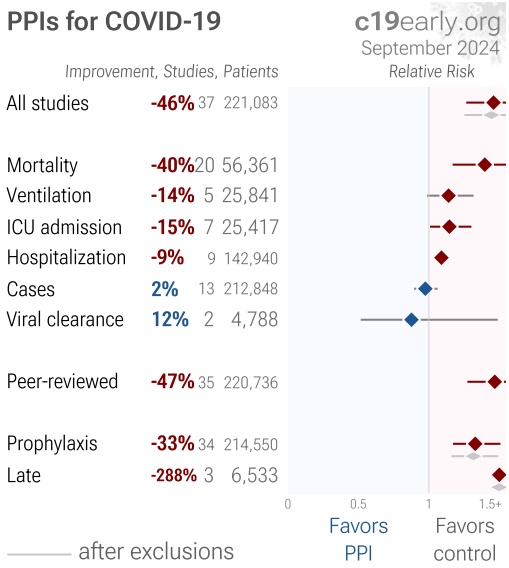
PPIs for COVID-19: real-time meta analysis of 37 studies

@CovidAnalysis, September 2024, Version 24
https://c19early.org/ppimeta.html

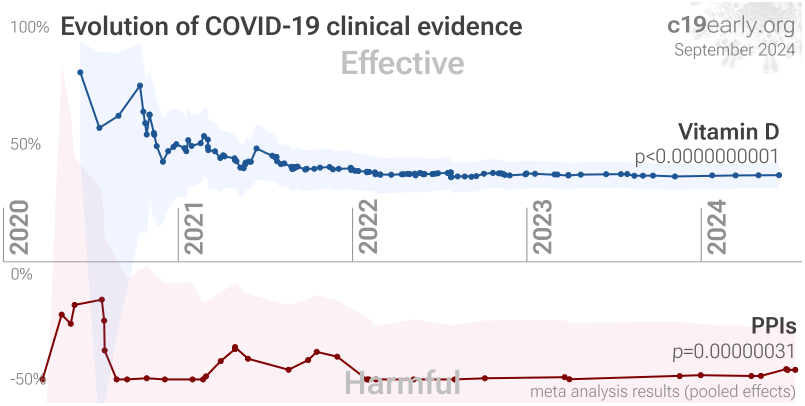
Abstract

Meta analysis shows 40% [17-67%] higher mortality, and pooled analysis using the most serious outcome reported shows 46% [27-68%] higher risk.

Potential mechanisms of harm include increased expression of ACE2, impaired immune responses due to gut microbiome changes, reduced antibacterial activity of neutrophils, easier passage of SARS-CoV-2 through the gastrointestinal tract due to reduced stomach acid, increased risk of secondary bacterial infections, degraded cellular defense mechanisms due to impaired lysosomal function, reduced absorption of nutrients critical for the immune system, potential interactions with COVID-19 medications, lung microbiome alterations, increased oxidative stress, impact on vitamin C and iron levels, potential effects on interferon responses, changes in coagulation factors, hypochlorhydria-induced hypergastrinemia, potential increased vulnerability to gastrointestinal pathogens, and delayed gastric emptying which may impair pharmacokinetics of COVID-19 medications.



All data to reproduce this paper and sources are in the appendix. 8 other meta analyses show significant harm with PPIs for mortality [1-3], severity [1,2,4-8], and cases [2].



PPIS FOR COVID-19 — HIGHLIGHTS

1st treatment shown harmful with ≥3 clinical studies in September 2020, now with p = 0.00000031 from 37 studies.

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

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 92 treatments.

37 PPI COVID-19 studies

c19early.org
September 2024

	Improvement, RR [CI]		Treatment	Control
Zhou (PSM)	-165%	2.65 [1.75-4.00] severe case	151/524	173/2,620
Yao	-600%	7.00 [4.57-10.7] severe case	694 (n)	2,330 (n)
Liwang	-204%	3.04 [1.22-7.60] death	216 (n)	149 (n)
Late treatment	-288%	3.88 [1.87-8.04]	151/1,434	173/5,099
$Tau^2 = 0.34$, $I^2 = 87.9\%$, $p = 0.00029$				
	Improvement, RR [CI]		Treatment	Control
Yan	-240%	3.40 [2.00-5.79] severe case	16/32	20/136
Blanc	56%	0.44 [0.23-0.82] cases	63 (n)	116 (n)
Freedberg (PSM)	-34%	1.34 [1.06-1.69] death/int.	8/84	332/1,536
Argenziano	1%	0.99 [0.73-1.34] ICU	38/163	198/837
Vila-Corcoles	-9%	1.09 [0.80-1.50] cases	11,807 (n)	23,129 (n)
Lee (PSM)	-79%	1.79 [1.30-3.10] severe case	267 (n)	267 (n)
Luxenburger	-248%	3.48 [1.29-9.39] death	12/62	5/90
Almario	-179%	2.79 [1.65-4.70] cases		
García-Menaya	-228%	3.28 [1.22-9.94] death	15/54	5/59
Mas Romero	26%	0.74 [0.38-1.45] death	11/82	21/116
Fan (PSM)	-17%	1.17 [0.65-2.90] death	n/a	n/a
McKeigue	-44%	1.44 [1.31-1.58] severe case	case control	
Zhang (PSM)	-11%	1.11 [0.92-1.33] hosp. time	29 (n)	29 (n)
Elmunzer	13%	0.87 [0.66-1.14] death	417 (n)	1,429 (n)
Morán Blanco	31%	0.69 [0.36-1.33] symp. case	12/48	13/36
Cheung	25%	0.75 [0.07-6.00] severe case	4 (n)	948 (n)
Liu	-127%	2.27 [1.64-3.13] death	68/227	53/459
Jimenez	-124%	2.24 [1.80-2.80] death	1,357 (all patients)	
Israelsen (PSM)	5%	0.95 [0.74-1.22] death	166/3,955	189/3,955
Shah	3%	0.97 [0.85-1.10] death	6,262 (n)	8,696 (n)
Ramachandran	-92%	1.92 [1.11-2.99] death	16/46	40/249
Shafrir (PSM)	-47%	1.47 [0.77-2.80] severe case	22/655	15/655
Wu (PSW)	-197%	2.97 [1.63-5.42] death	1,046 (n)	3,588 (n)
Shupp	19%	0.81 [0.54-1.22] death	448 (n)	2,048 (n)
Kodvanj	7%	0.93 [0.85-1.02] death		
Kim (PSM)	-28%	1.28 [0.48-3.37] death	9/437	7/437
Shokri	-81%	1.81 [1.01-3.25] severe case	121 (n)	549 (n)
Elkanzi	-17%	1.17 [0.76-1.81] death	36/159	29/150
Patil	-48%	1.48 [1.32-1.66] death	4,566 (n)	15,349 (n)
Gramont (PSW)	-59%	1.59 [1.18-2.14] severe case	424 (n)	410 (n)
Cheung	-49%	1.49 [1.13-1.98] death	population-based cohort	
Hirsch	15%	0.85 [0.64-1.13] hosp.	116,209 (all patients)	
Al-Momani	-100%	2.00 [0.46-8.71] death	3/69	4/184
Zeng	-46%	1.46 [1.05-2.03] death	population-based cohort	
Prophylaxis	-33%	1.33 [1.17-1.51]	432/31,527	931/65,457
$Tau^2 = 0.09$, $I^2 = 84.6\%$, $p < 0.0001$				
All studies	-46%	1.46 [1.27-1.68]	583/32,961	1,104/70,556

288% higher risk

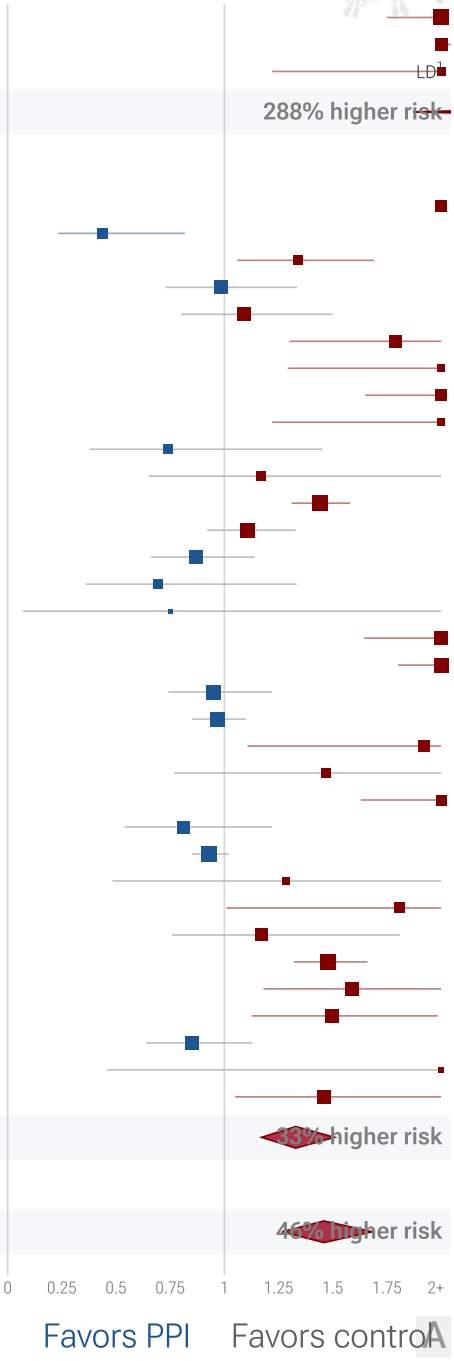
33% higher risk

46% higher risk

[1] LD: comparison with low dose treatment

$Tau^2 = 0.14$, $I^2 = 89.3\%$, $p < 0.0001$

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



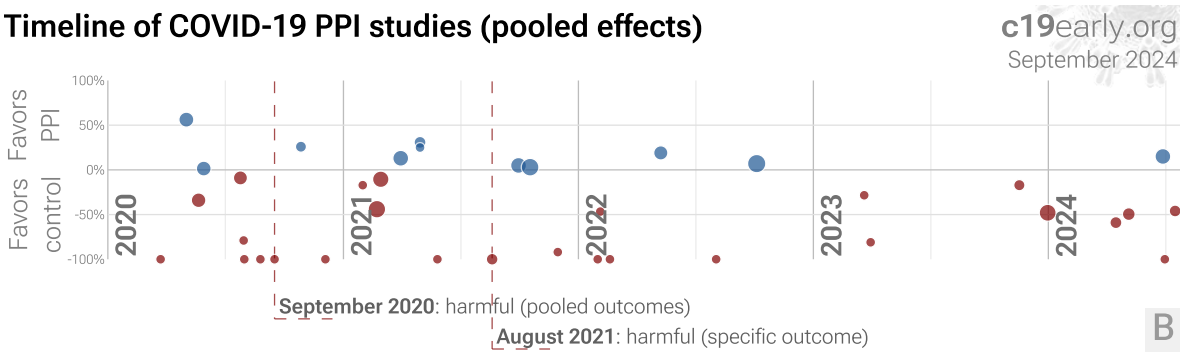


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in PPI studies.** The marked dates indicate the time when a harmful effect was identified with statistical significance from ≥3 studies for pooled outcomes and one or more specific outcome. Harm based on specific outcomes was delayed by 11.1 months, compared to using pooled outcomes.

Introduction

Potential mechanisms of harm include increased expression of ACE2, impaired immune responses due to gut microbiome changes, reduced antibacterial activity of neutrophils, easier passage of SARS-CoV-2 through the gastrointestinal tract due to reduced stomach acid, increased risk of secondary bacterial infections, degraded cellular defense mechanisms due to impaired lysosomal function, reduced absorption of nutrients critical for the immune system, potential interactions with COVID-19 medications, lung microbiome alterations, increased oxidative stress, impact on vitamin C and iron levels, potential effects on interferon responses, changes in coagulation factors, hypochlorhydria-induced hypergastrinemia, potential increased vulnerability to gastrointestinal pathogens, and delayed gastric emptying which may impair pharmacokinetics of COVID-19 medications.

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

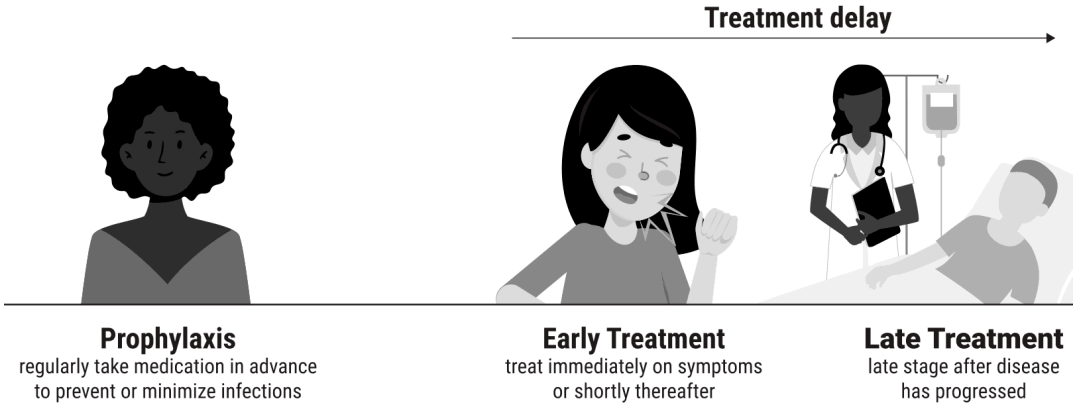


Figure 2. Treatment stages.

Results

Table 1 summarizes the results for all stages combined, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 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	**-46%** [-68--27%] ****	37	221,083	526
After exclusions	**-44%** [-67--25%] ****	36	220,413	520
Peer-reviewed studies	**-47%** [-69--27%] ****	35	220,736	487
Mortality	**-40%** [-67--17%] ***	20	56,361	310
Ventilation	**-14%** [-32-1%]	5	25,841	157
ICU admission	**-15%** [-30--1%] *	7	25,417	94
Hospitalization	**-9%** [-15--3%] **	9	142,940	105
Cases	**2%** [-6-10%]	13	212,848	134
Viral	**12%** [-49-48%]	2	4,788	14

Table 1. **Random effects meta-analysis for all stages combined, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Late treatment	*Prophylaxis*
All studies	**-288%** [-704--87%] ***	**-33%** [-51--17%] ****
After exclusions	**-288%** [-704--87%] ***	**-32%** [-49--16%] ****
Peer-reviewed studies	**-288%** [-704--87%] ***	**-33%** [-50--17%] ****
Mortality	**-204%** [-660--22%] *	**-37%** [-64--14%] ***
Ventilation		**-14%** [-32-1%]
ICU admission		**-15%** [-30--1%] *
Hospitalization		**-9%** [-15--3%] **
Cases		**2%** [-6-10%]
Viral		**12%** [-49-48%]

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. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

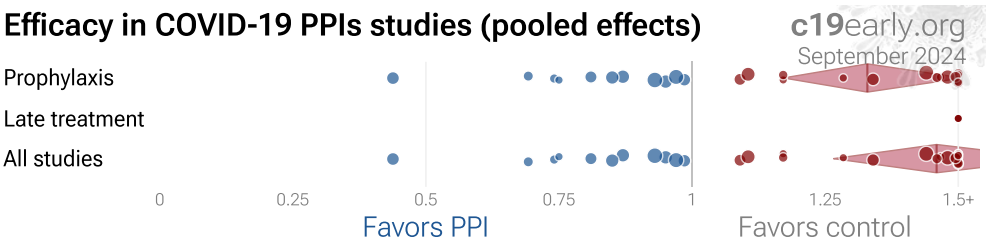


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

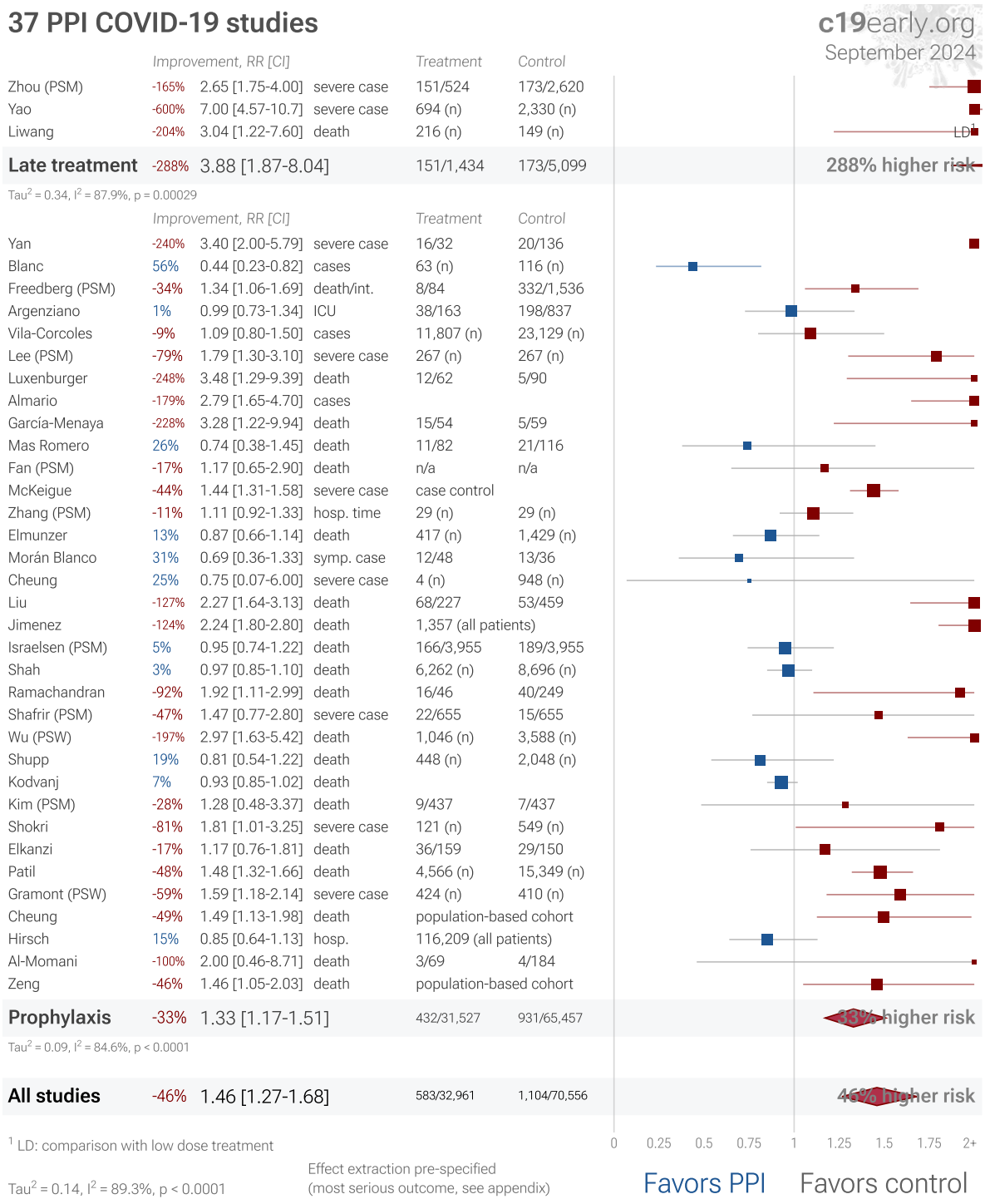


Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

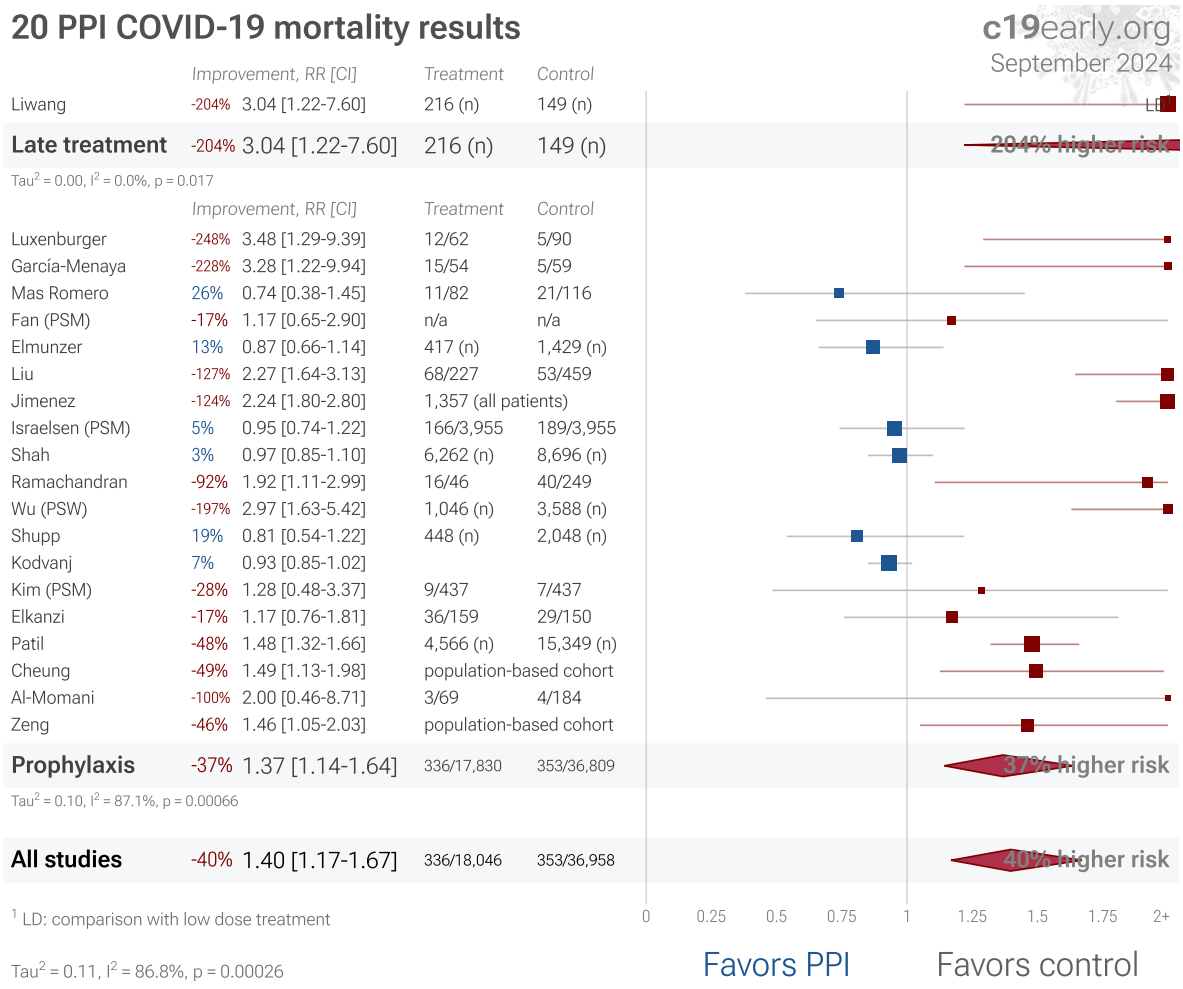


Figure 5. Random effects meta-analysis for mortality results.

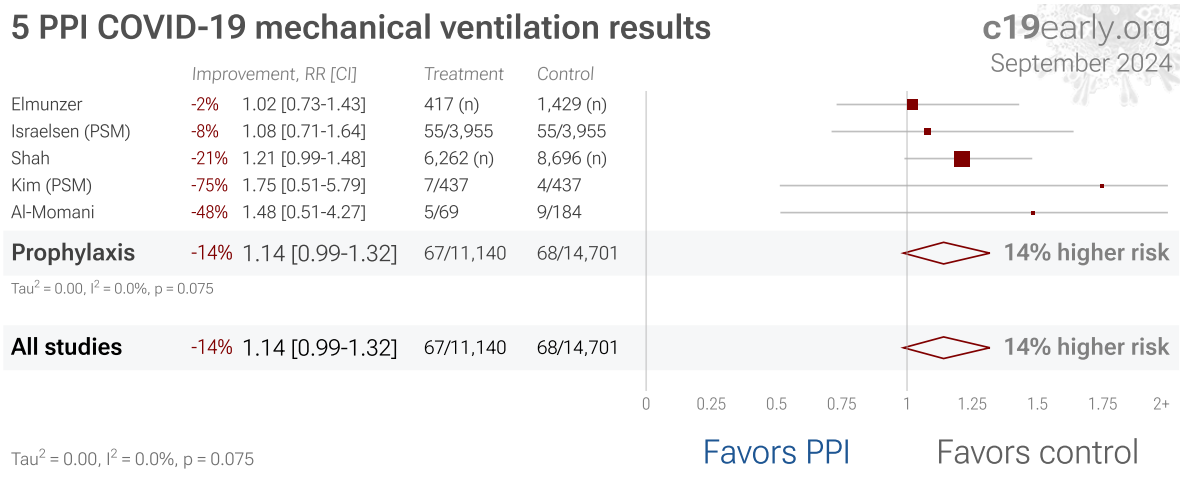


Figure 6. Random effects meta-analysis for ventilation.

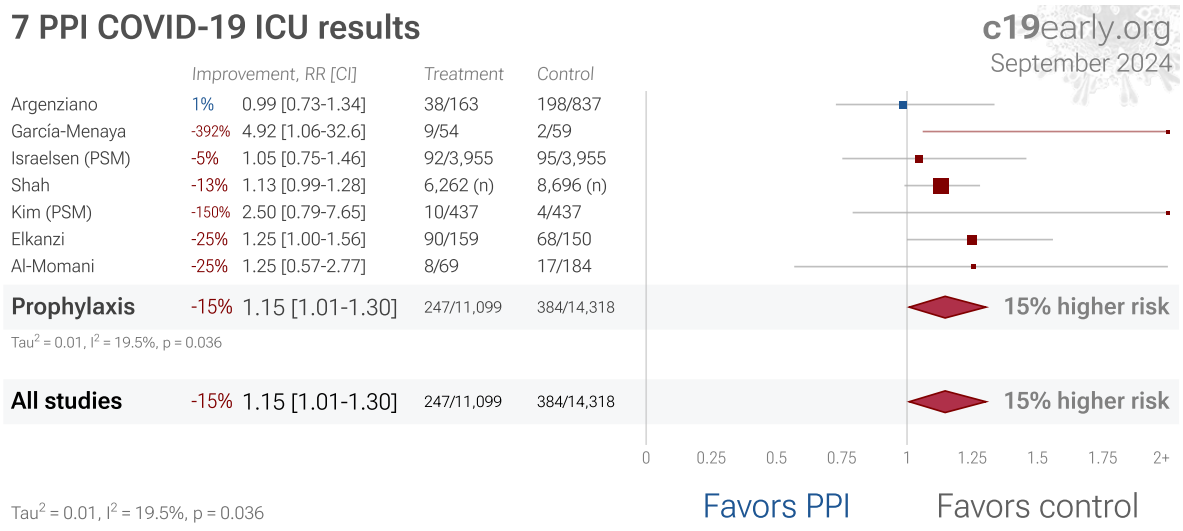


Figure 7. Random effects meta-analysis for ICU admission.

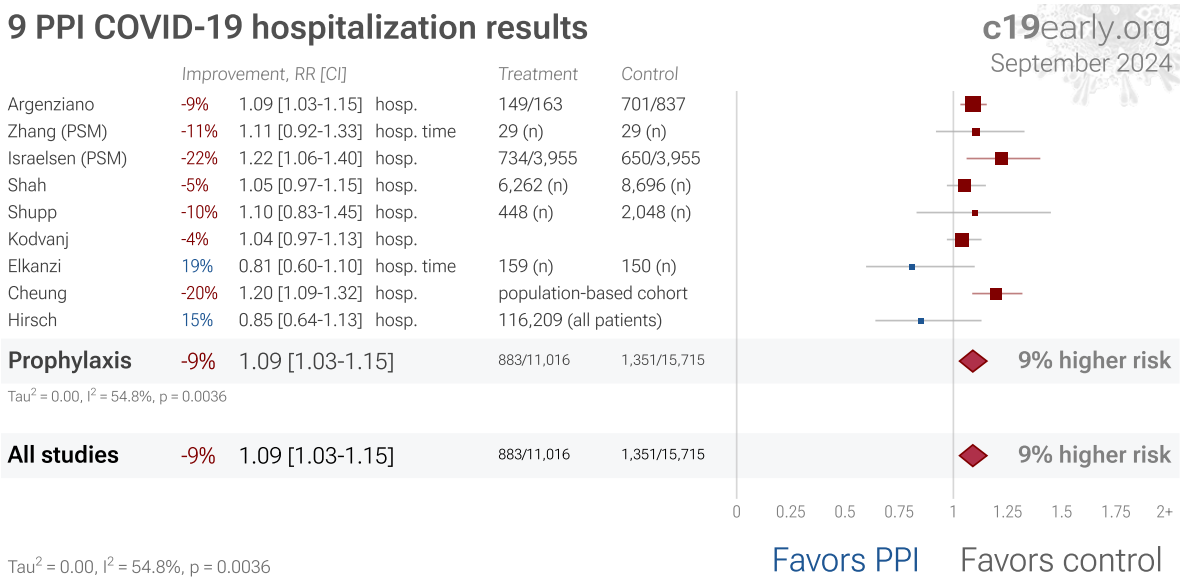


Figure 8. Random effects meta-analysis for hospitalization.

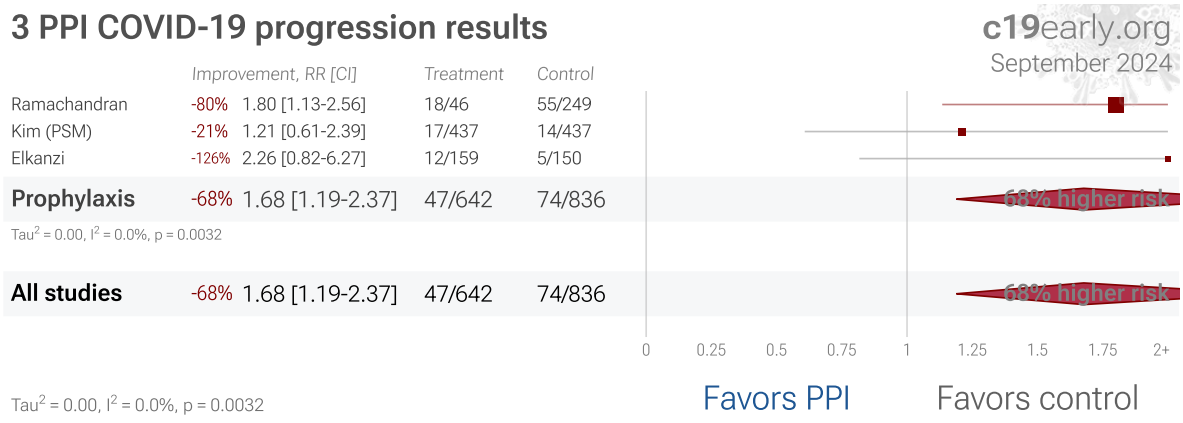


Figure 9. Random effects meta-analysis for progression.

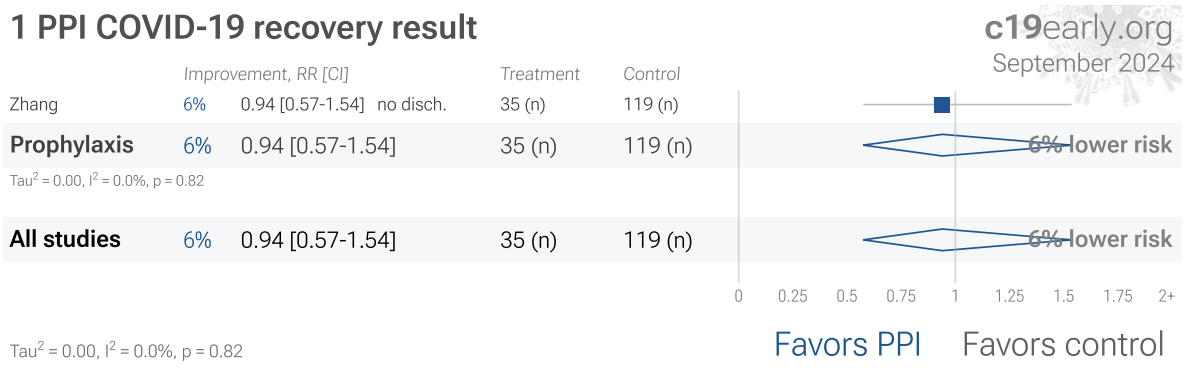


Figure 10. Random effects meta-analysis for recovery.

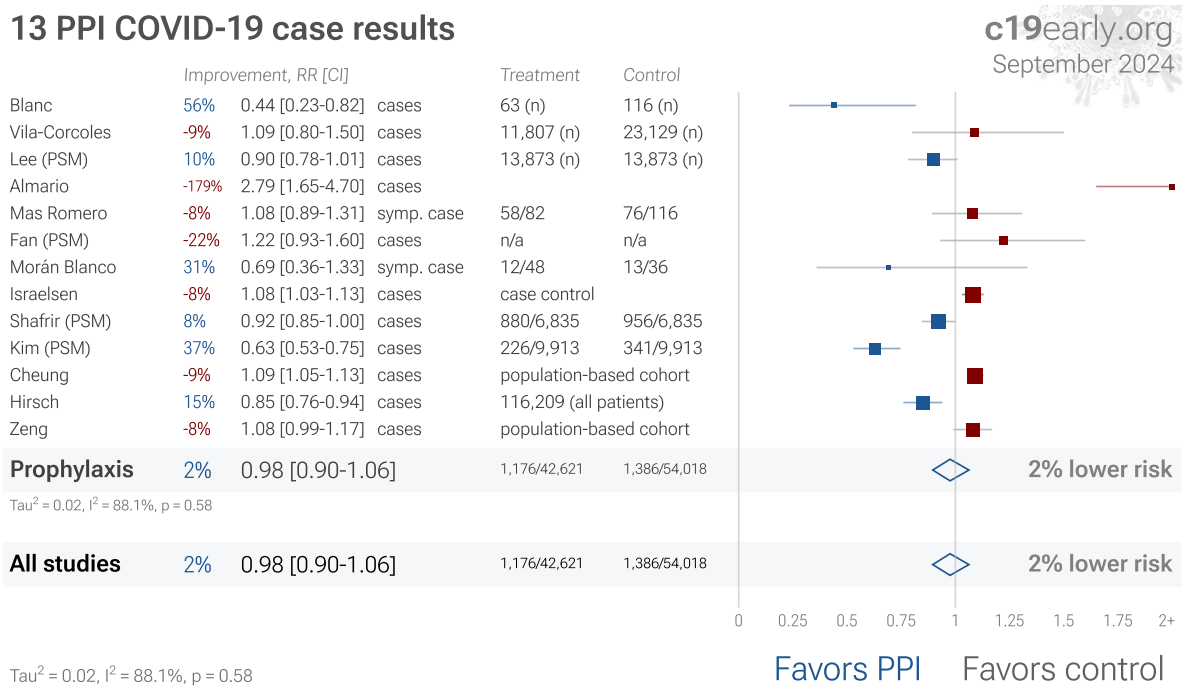


Figure 11. Random effects meta-analysis for cases.

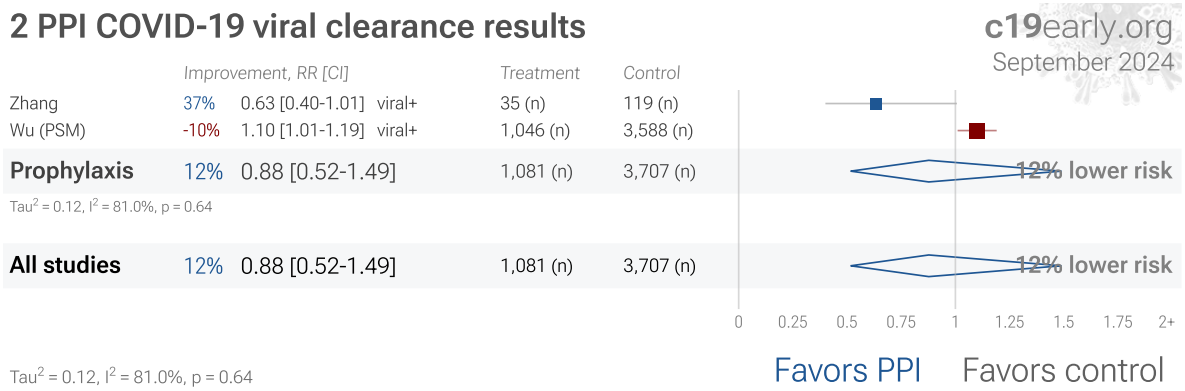


Figure 12. Random effects meta-analysis for viral clearance.

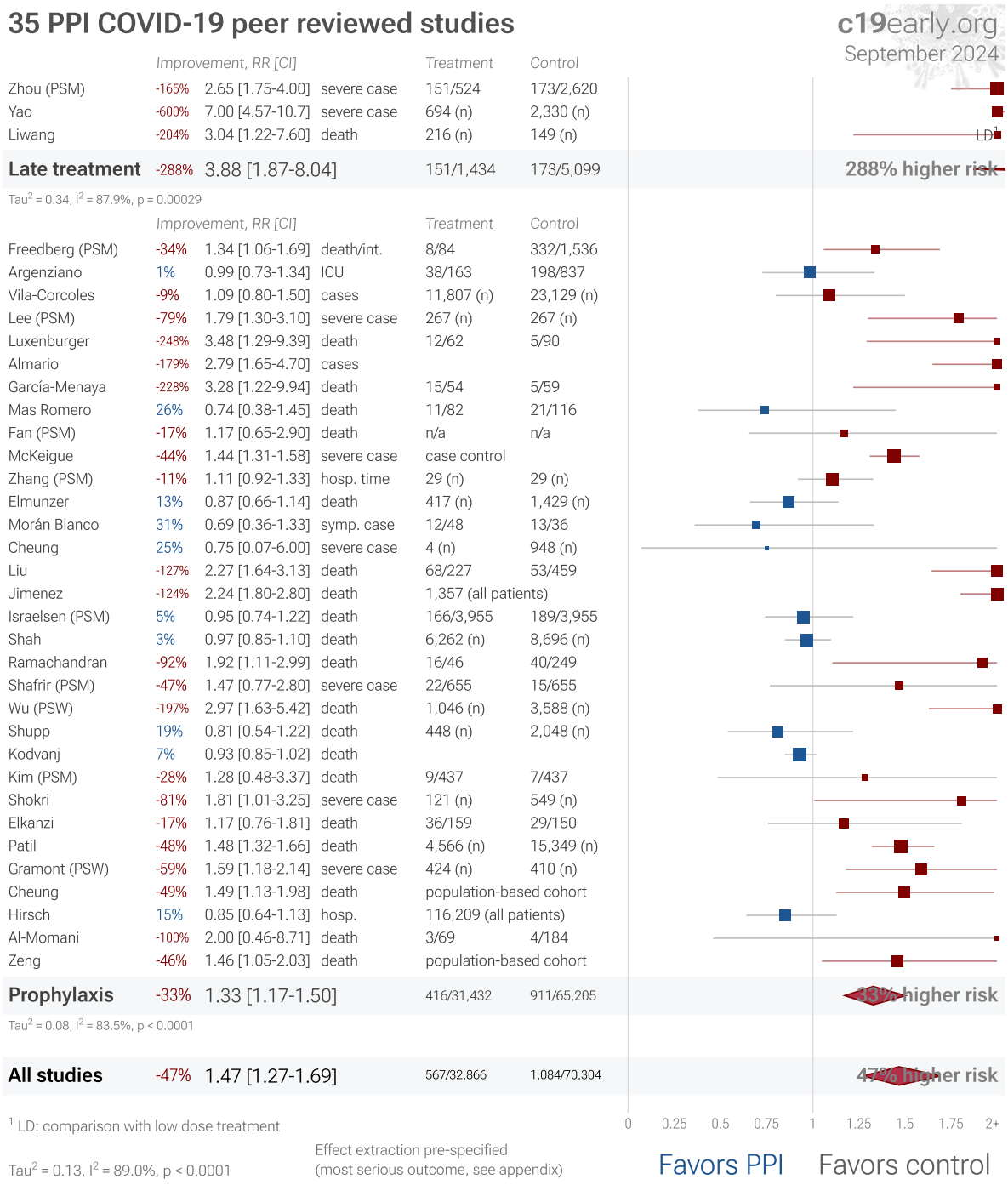


Figure 13. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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.

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

Luxenburger, unadjusted differences between groups. Excluded results: death, ARDS.

Shokri, potential data issue.

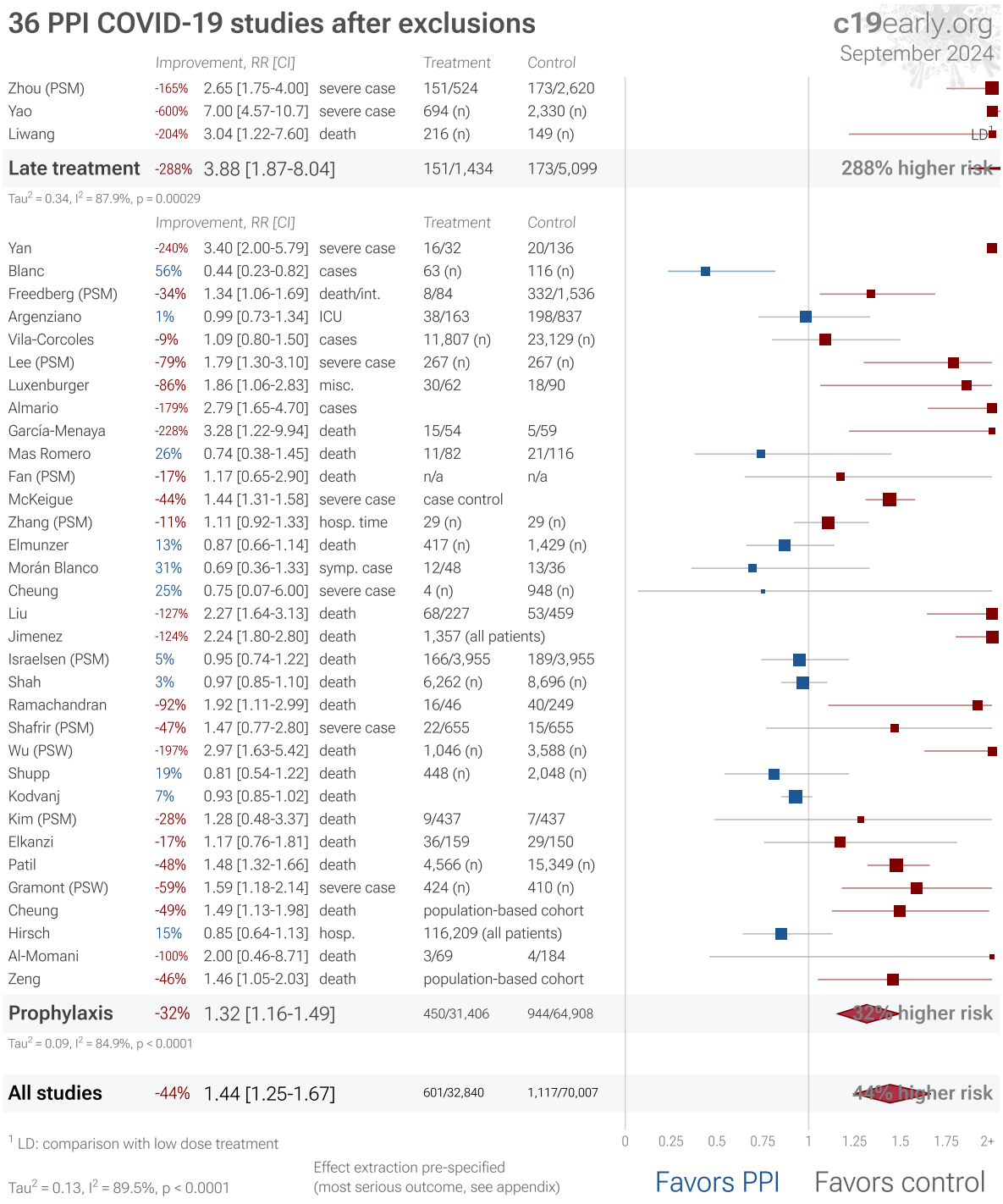


Figure 14. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome 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 [13,14]. 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 [15]
<24 hours	-33 hours symptoms [16]
24-48 hours	-13 hours symptoms [16]
Inpatients	-2.5 hours to improvement [17]

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

Figure 15 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 92 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

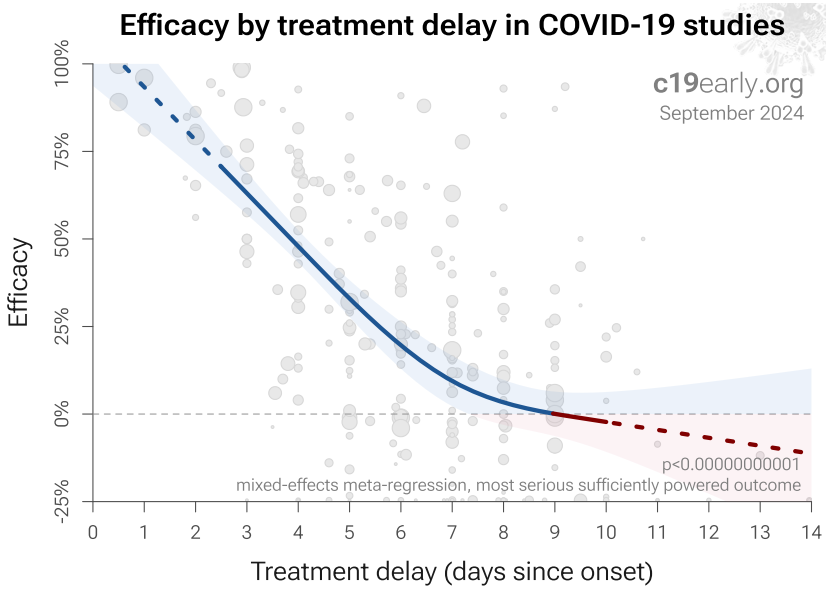


Figure 15. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 92 treatments.

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

Variants. Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [19], for example the Gamma variant shows significantly different characteristics [20-23]. 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 [24,25].

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

Other treatments. The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic[26-36], therefore efficacy may depend strongly on combined treatments.

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

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

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

Pooled Effects

Pooled effects are no longer required to show harm as of August 2021. This section validates the use of pooled effects for COVID-19, which enables earlier detection of harm, however note that pooled effects are no longer required for PPIs as of August 2021. Harm is now known based on specific outcomes. Harm based on specific outcomes was delayed by 11.1 months, compared to using pooled outcomes.

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

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

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

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

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

Validating pooled outcome analysis for COVID-19. Analysis of the the association between different outcomes across studies from all 92 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 16 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 17 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 18 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 $p = 0.0000013$ to $p = 0.000000015$.

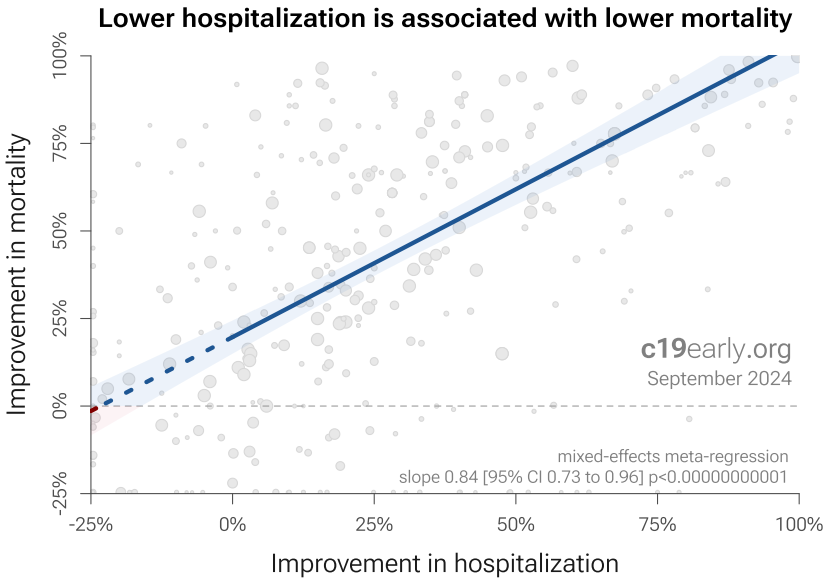


Figure 16. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

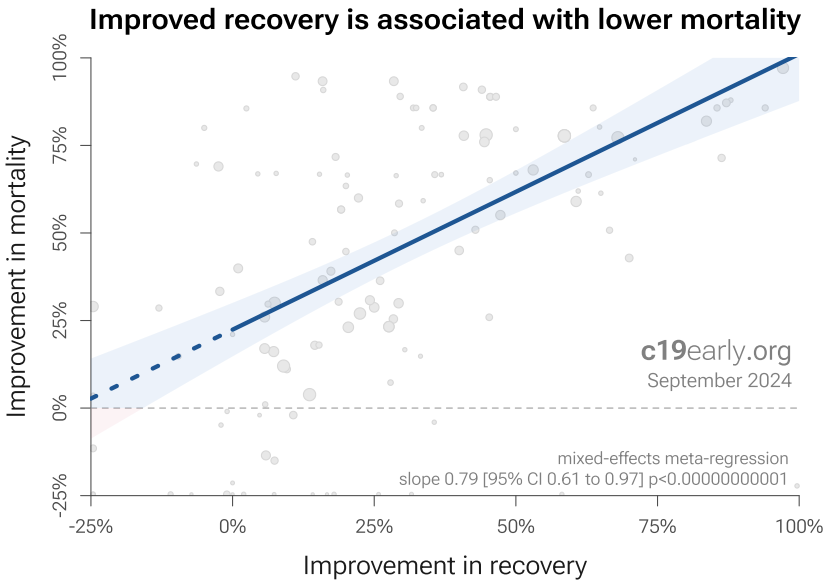


Figure 17. **Improved recovery is associated with lower mortality, supporting pooled outcome analysis.**

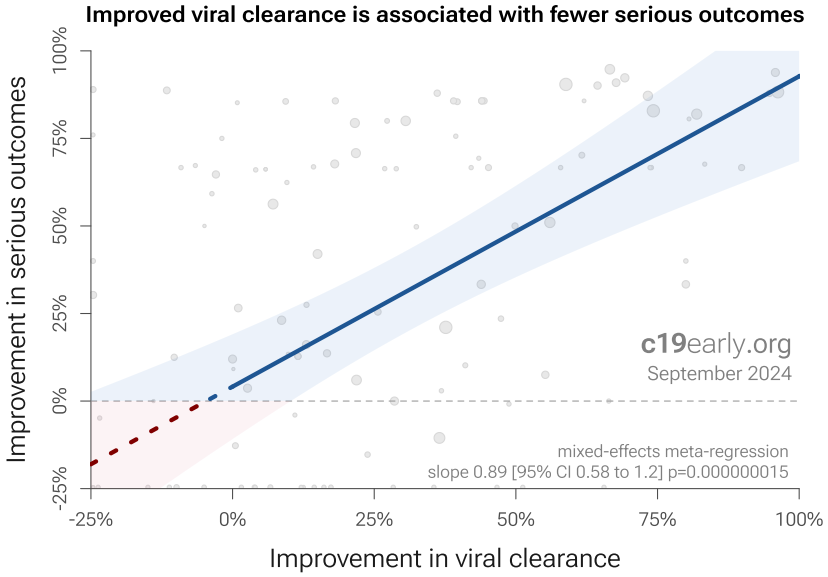


Figure 16. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (6 months for RCTs). Currently, 48 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 89% of these have been confirmed with one or more specific outcomes, with a mean delay of 5.1 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.4 months. Figure 19 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

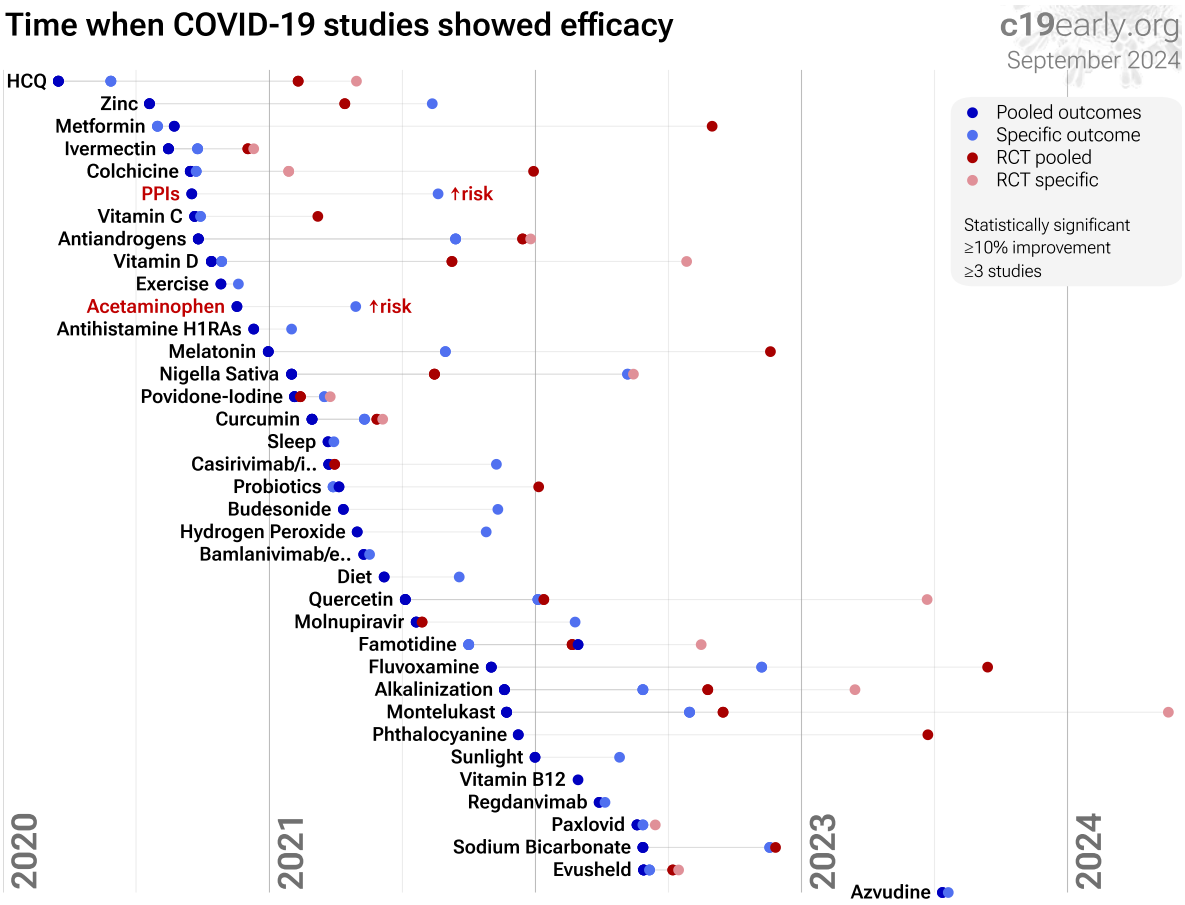


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting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

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 [40-43]. For PPI, there is currently not enough data to evaluate publication bias with high confidence.

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 20 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 $p < 0.05$[44-51]. 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.

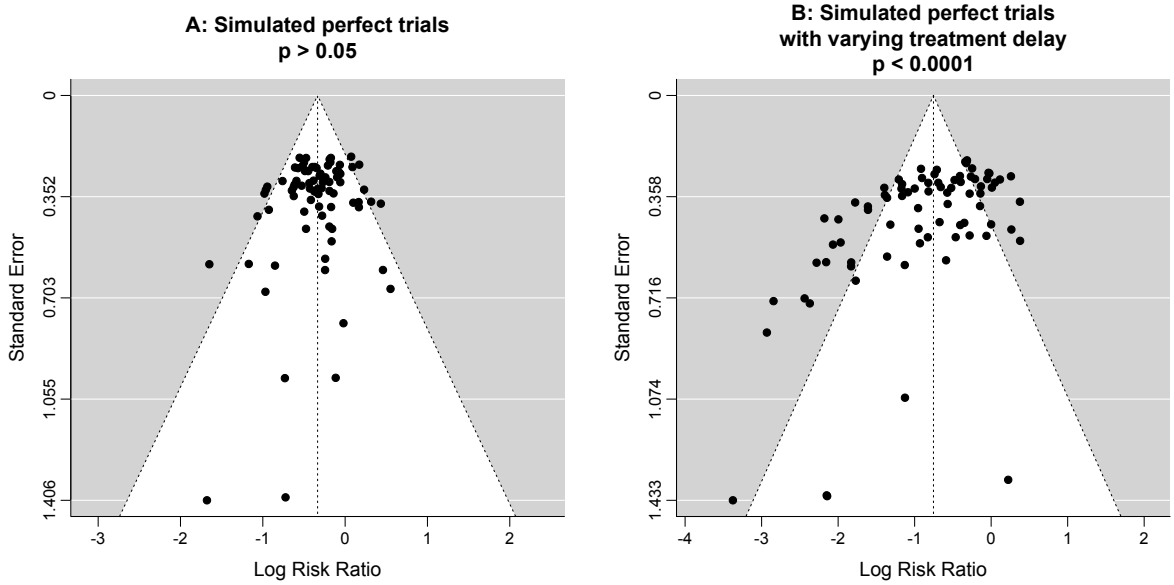


Figure 20. **Example funnel plot analysis for simulated perfect trials.**

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. PPI for COVID-19 lack this because they are generally inexpensive and widely available.

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[26-36]. 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. 8 other meta analyses show significant harm with PPIs for mortality[1-3], severity[1,2,4-8], and cases[2].

Perspective

Results compared with other treatments. SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors[52-56], providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk[57], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 21 shows an overview of the results for PPIs in the context of multiple COVID-19 treatments, and Figure 22 shows a plot of efficacy vs. cost for COVID-19 treatments.

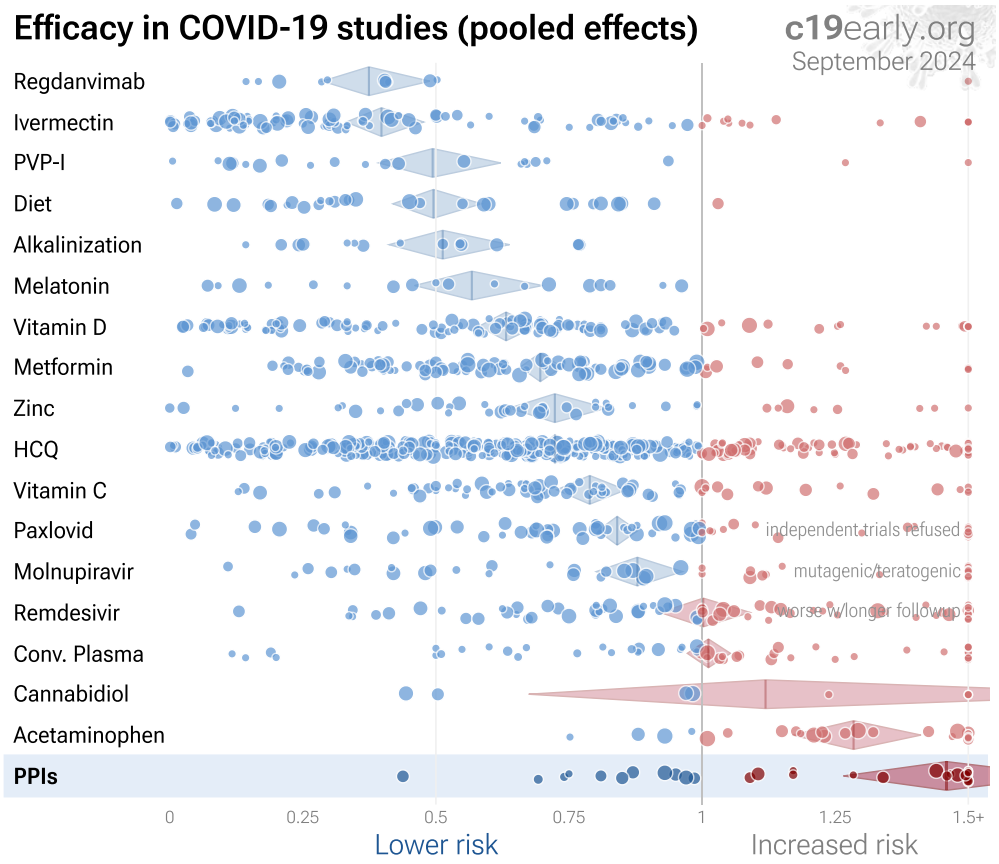


***Figure 21.* Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy[58].

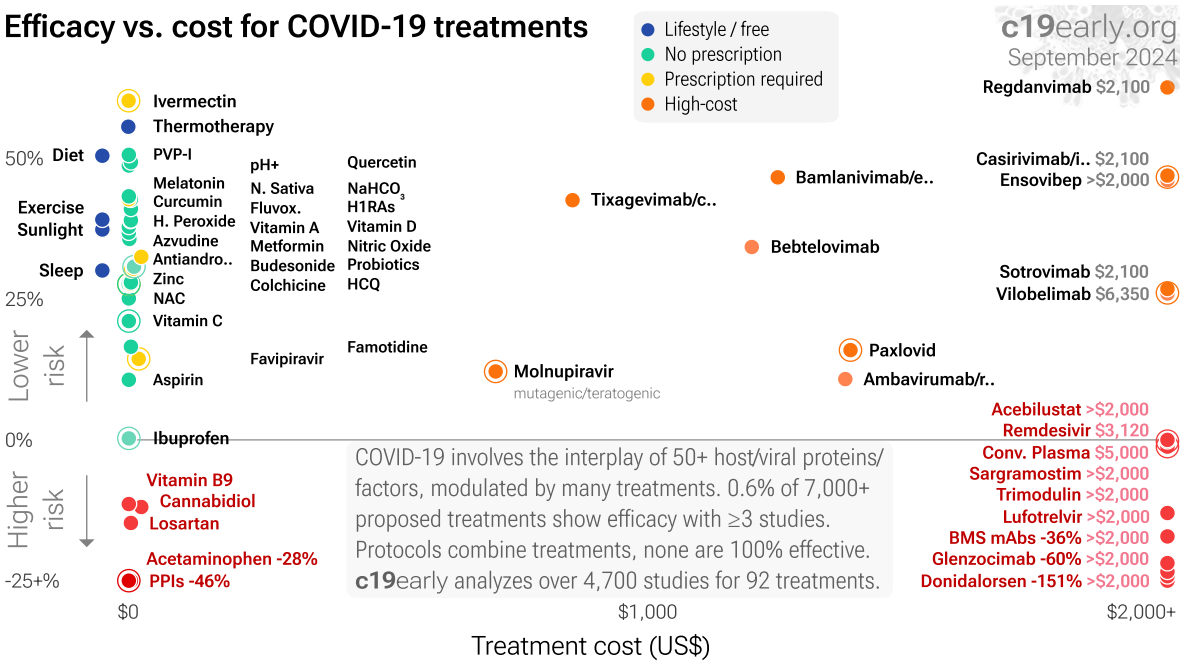


Figure 22. **Efficacy vs. cost for COVID-19 treatments.**

Conclusion

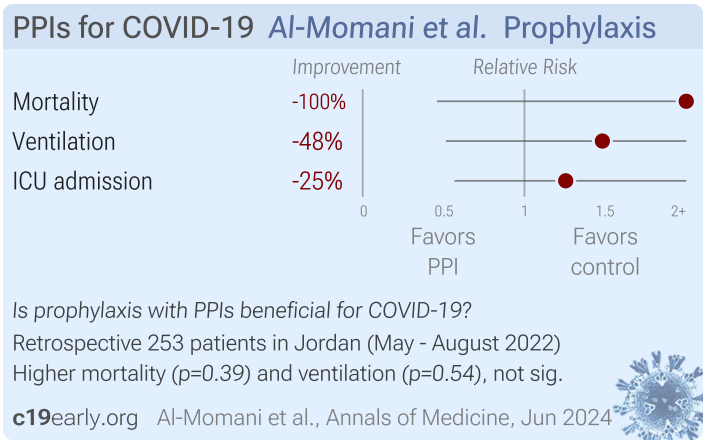
Meta analysis shows 40% [17-67%] higher mortality, and pooled analysis using the most serious outcome reported shows 46% [27-68%] higher risk.

Potential mechanisms of harm include increased expression of ACE2, impaired immune responses due to gut microbiome changes, reduced antibacterial activity of neutrophils, easier passage of SARS-CoV-2 through the gastrointestinal tract due to reduced stomach acid, increased risk of secondary bacterial infections, degraded cellular defense mechanisms due to impaired lysosomal function, reduced absorption of nutrients critical for the immune system, potential interactions with COVID-19 medications, lung microbiome alterations, increased oxidative stress, impact on vitamin C and iron levels, potential effects on interferon responses, changes in coagulation factors, hypochlorhydria-induced hypergastrinemia, potential increased vulnerability to gastrointestinal pathogens, and delayed gastric emptying which may impair pharmacokinetics of COVID-19 medications.

8 other meta analyses show significant harm with PPIs for mortality [1-3], severity [1,2,4-8], and cases [2].

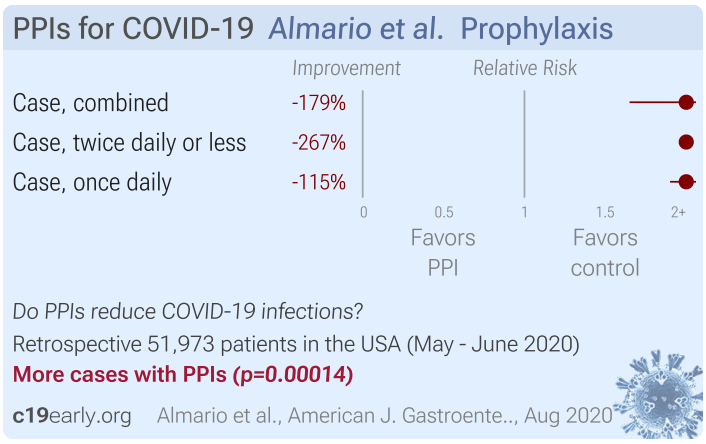
Study Notes

Al-Momani



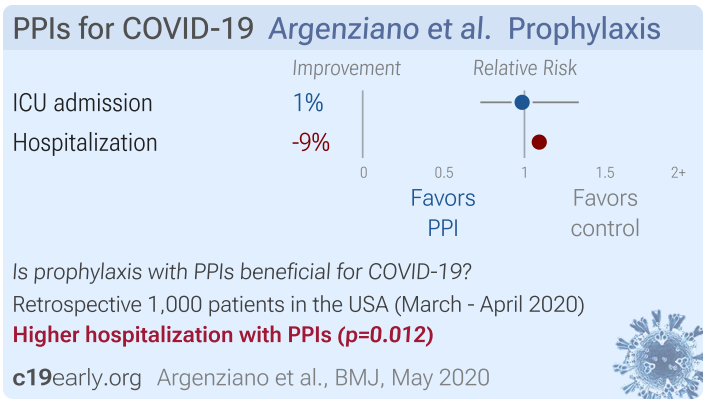
Al-Momani: Retrospective 254 hospitalized COVID-19 patients in Jordan showing higher rates of gastrointestinal symptoms such as abdominal pain and diarrhea with proton pump inhibitor (PPI) use. There were no significant differences for mortality, ventilation, and ICU admission. Authors hypothesize that PPIs may facilitate SARS-CoV-2 survival and invasion in the gastrointestinal tract.

Almario



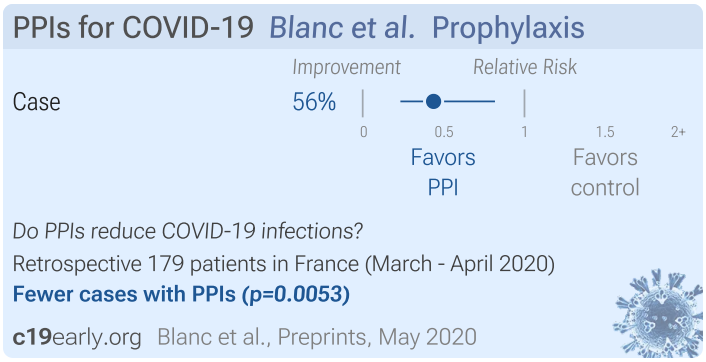
Almario: Survey of 53,130 individuals with a history of GI symptoms showing increased risk of COVID-19 positivity with proton pump inhibitor (PPI) use, especially twice-daily PPI use. There was a dose-response relationship between PPI use and COVID-19 risk. Those taking PPIs twice daily had 3.67 times higher odds of testing positive compared to those not taking PPIs. The authors hypothesize that PPI-induced hypochlorhydria may impair the body's defense against ingested pathogens like SARS-CoV-2.

Argenziano



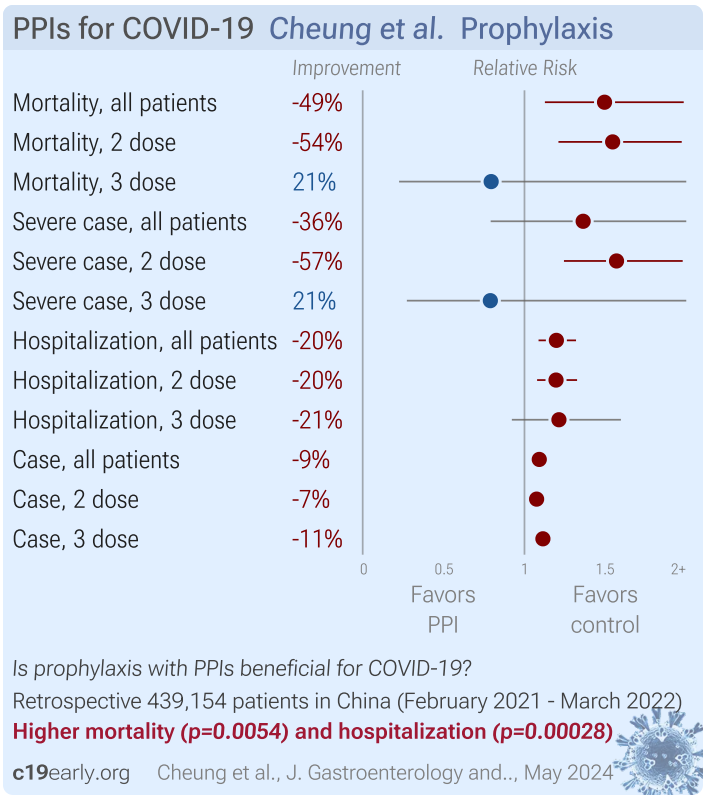
Argenziano: Retrospective 1,000 hospitalized COVID-19 patients in New York City showing high rates of acute kidney injury, inpatient dialysis, prolonged intubation times, and length of stay compared to previous cohorts.

Blanc



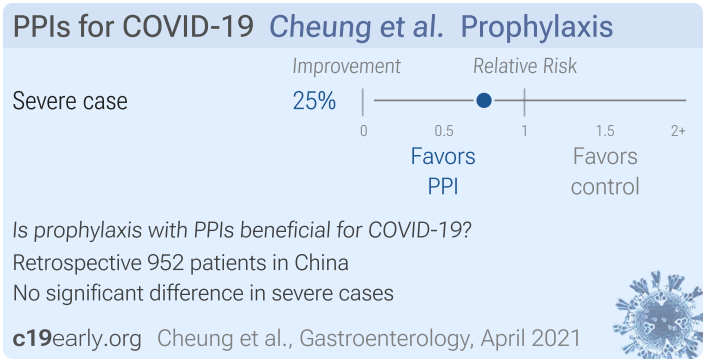
Blanc: Retrospective 179 elderly patients in France, showing higher risk of COVID-19 cases with acetaminophen use, without statistical significance.

Cheung



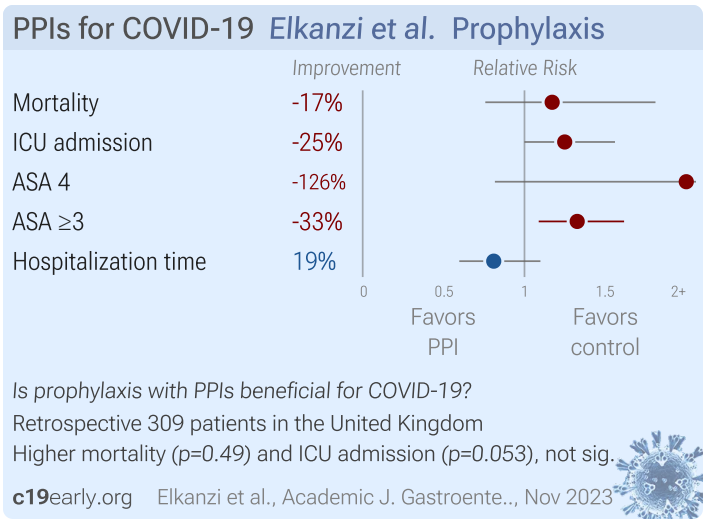
Cheung: Retrospective 627,514 patients in Hong Kong showing slightly higher risk of COVID-19 with pre-vaccination proton pump inhibitor (PPI) use in two-dose or three-dose vaccine recipients, and higher risk of hospitalization and severe outcomes only in two-dose recipients.

Cheung



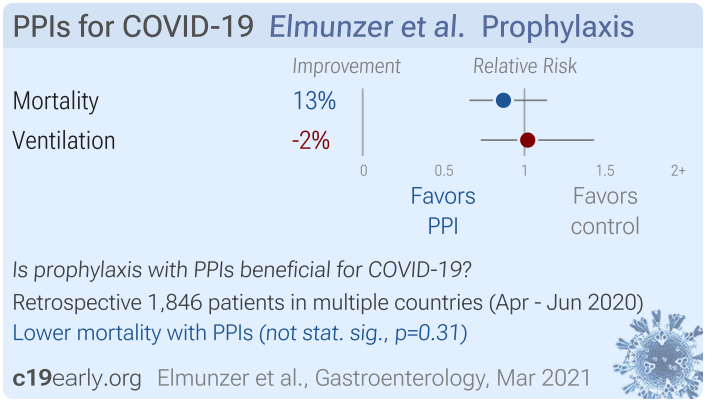
Cheung (B): Retrospective 952 COVID-19 patients in Hong Kong, showing no significant difference in severe disease with famotidine use or PPI use.

Elkanzi



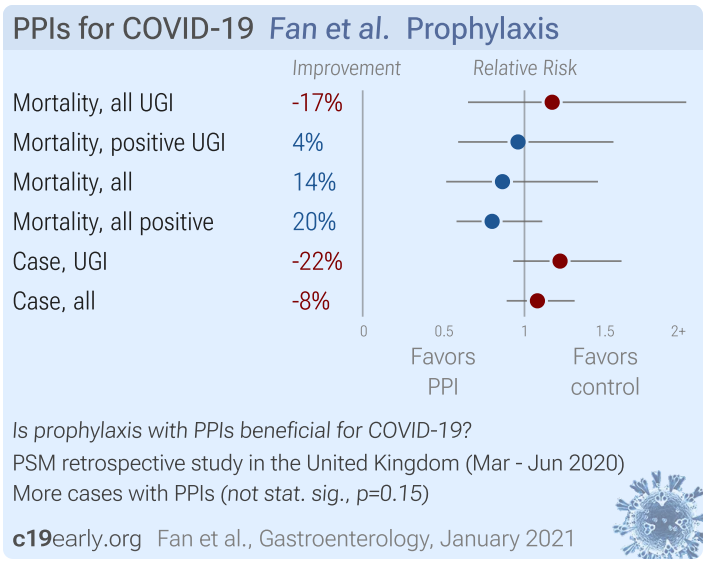
Elkanzi: Retrospective 309 hospitalized patients showing higher risk of severe cases (ASA≥3) with PPI use.

Elmunzer



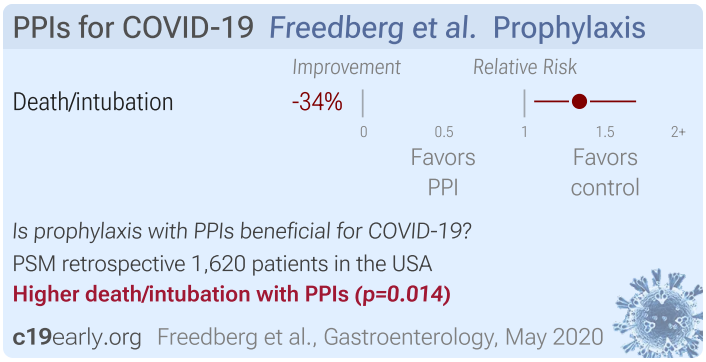
Elmunzer: Retrospective 1,846 hospitalized COVID-19 patients in North America showing no significant association between preadmission proton pump inhibitor (PPI) use and mechanical ventilation or mortality. Results do not account for the risk of hospitalization based on PPI use.

Fan



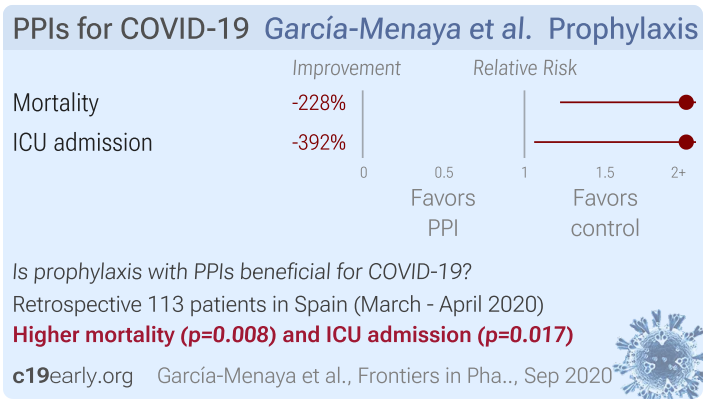
Fan: PSM retrospective 9,469 UK Biobank participants tested for COVID-19, showing no significant association between proton pump inhibitor (PPI) or histamine-2 receptor antagonist (H2RA) use and risk of SARS-CoV-2 infection or COVID-19 mortality. Omeprazole was associated with higher risk of cases in patients with upper gastrointestinal diseases. The results for patients with upper gastrointestinal diseases should be more accurate due to reduced confounding and more accurate ascertainment of current use.

Freedberg



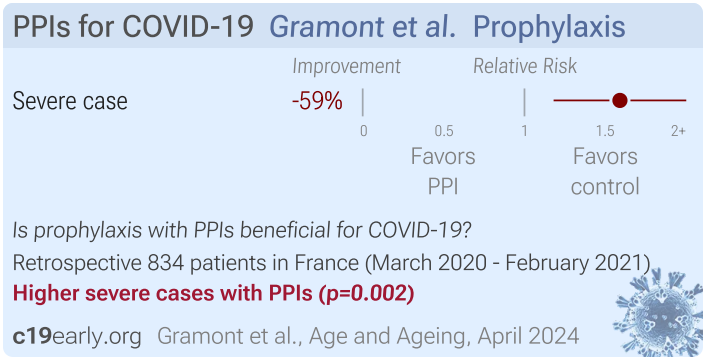
Freedberg: PSM retrospective 1,620 hospitalized patients in the USA, showing higher risk of combined death/intubation with PPI treatment.

García-Menaya



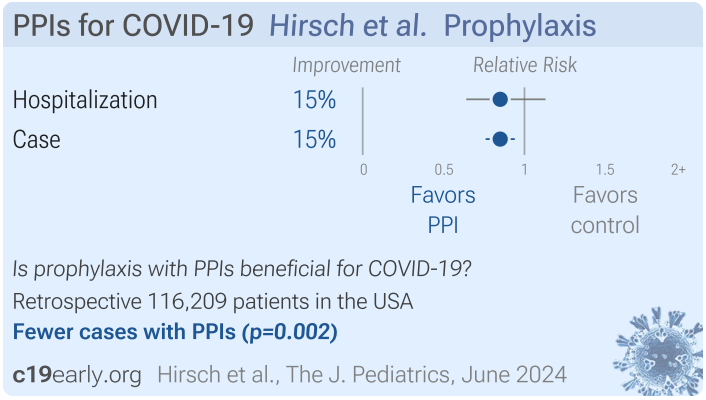
García-Menaya: Retrospective 113 hospitalized COVID-19 patients in Spain showing higher mortality and ICU admission with PPI use.

Gramont



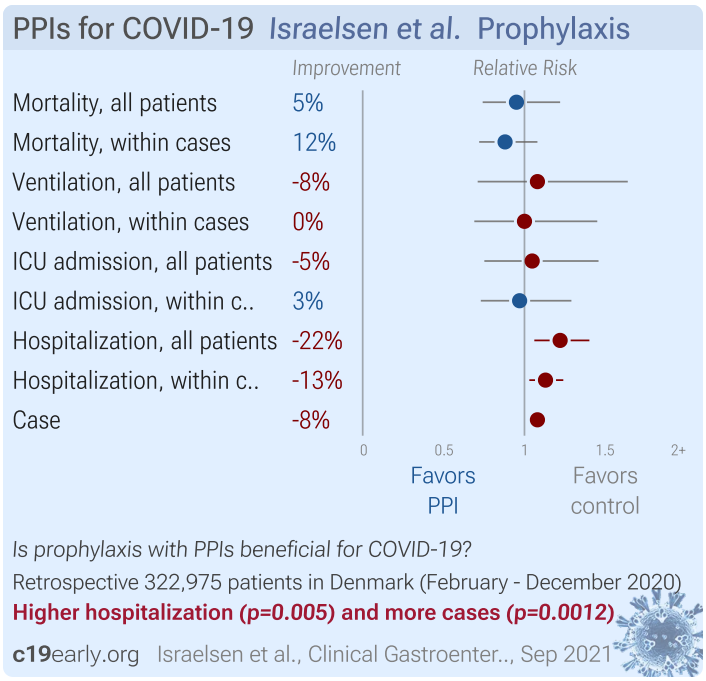
Gramont: Retrospective 834 elderly patients in France showing higher risk of severe COVID-19 with PPI use, and increasing risk with increasing dosage.

Hirsch



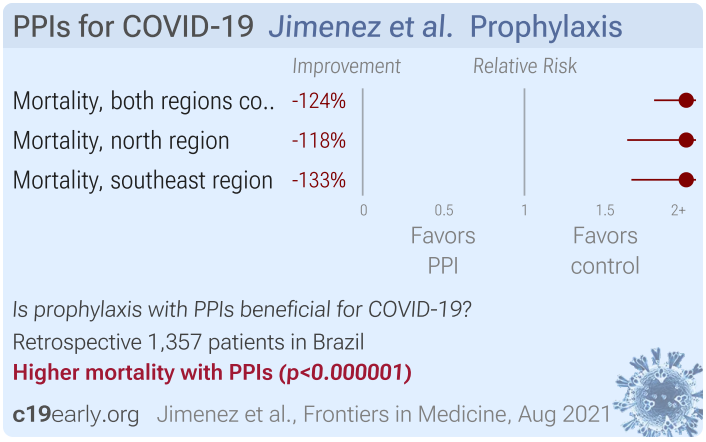
Hirsch: Retrospective 116,209 pediatric patients showing lower risk of COVID-19 with PPI use. There was no significant difference for hospitalization.

Israelsen



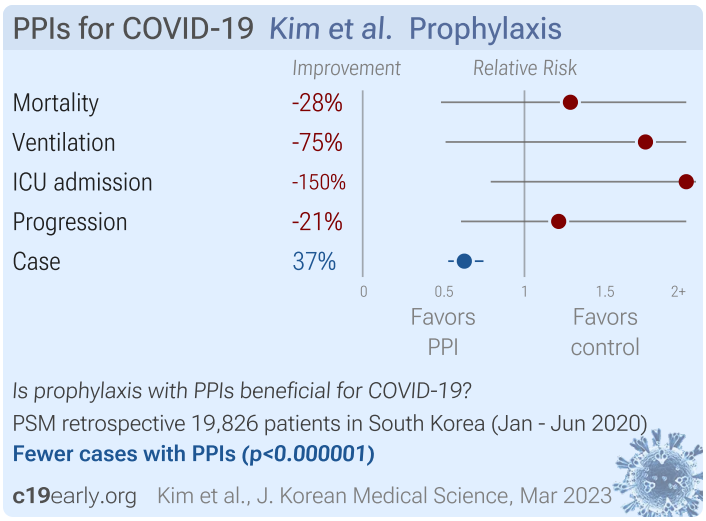
Israelsen: Retrospective 83,224 SARS-CoV-2 cases and 332,799 controls in Denmark showing increased risk of infection and hospital admission with proton pump inhibitor (PPI) use, but no significant association with ICU admission or mortality.

Jimenez



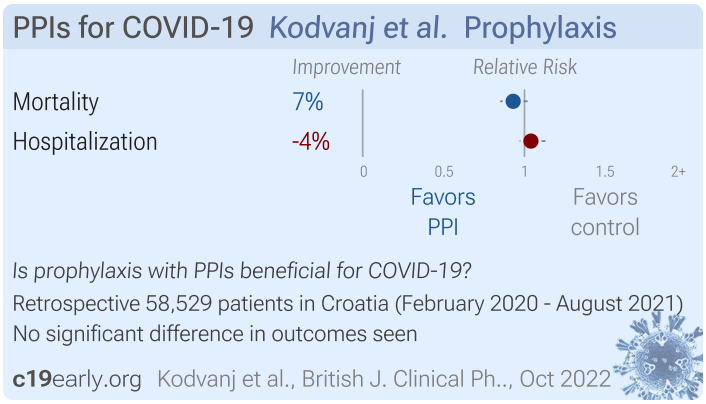
Jimenez: In Vitro study showing lower pH increased ACE2 expression and viral load on SARS-CoV-2 infection, and retrospective study showing proton pump inhibitor use, which is correlated with low gastric pH-related diseases, was associated with higher mortality.

Kim



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).

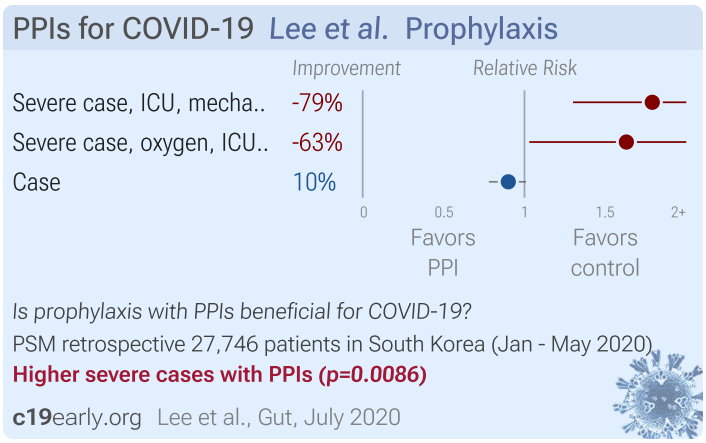
Kodvanj



Kodvanj: Retrospective 433,609 COVID-19 patients in Croatia showing no significant difference in mortality or hospitalization risk with proton-pump inhibitor (PPI) use before COVID-19 diagnosis compared to matched controls with PPI-requiring morbidities but no PPI prescriptions. There was significantly higher hospitalization for users with 1-3 prescriptions which authors do not comment on.

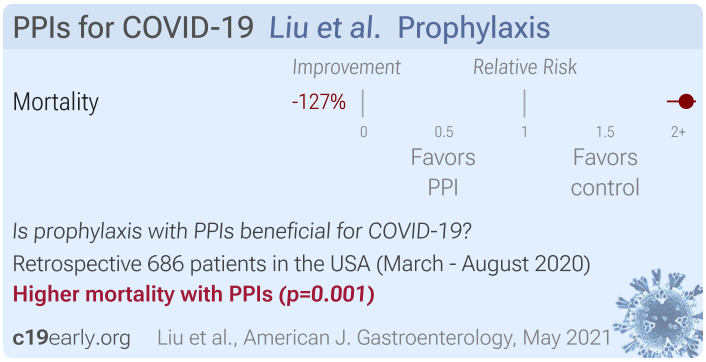
The classification of users and possible users may introduce confounding. Users required a PPI prescription, while possible users includes those with ≥3 NSAID prescriptions. Possible users may be OTC PPI users, and may differ significantly in NSAID use. NSAID use per group is not reported, and was not used in adjustments.

Lee



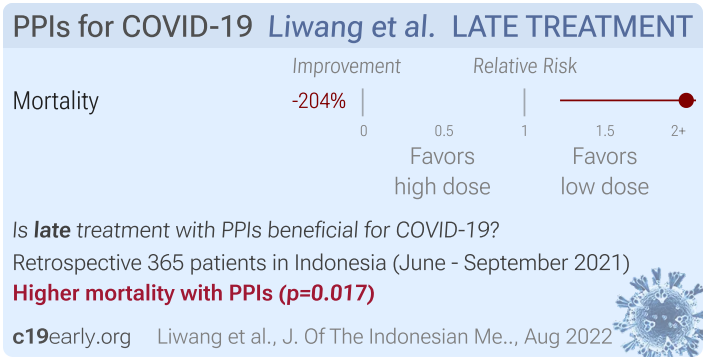
Lee: PSM retrospective 132,316 patients in South Korea, showing significantly higher risk of severe COVID-19 with PPI use, but no significant difference in cases.

Liu



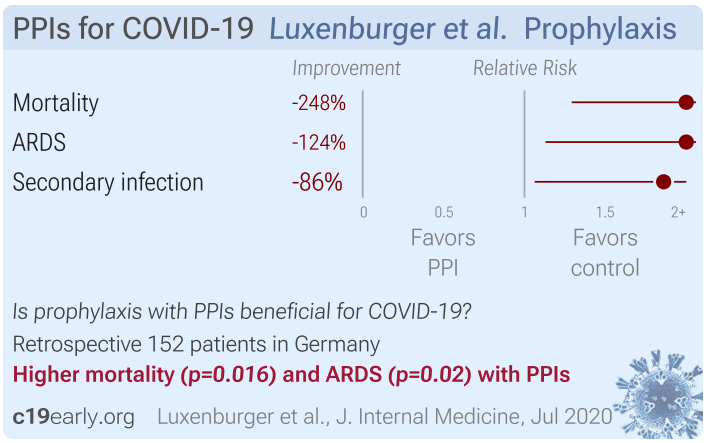
Liu: Prospective study showing COVID- PPI users had higher salivary ACE2 expression, and retrospective analysis of 694 hospitalized COVID-19 patients, showing higher mortality with PPI use.

Liwang



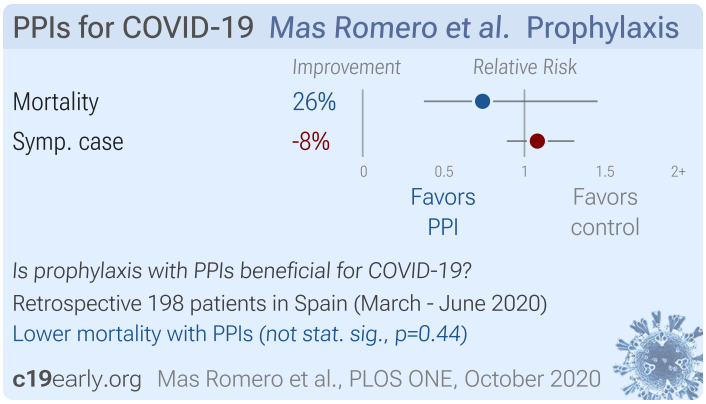
Liwang: Retrospective hospitalized COVID-19 patients in Indonesia showing higher mortality with high dose proton pump inhibitor (PPI) use compared to low dose.

Luxenburger



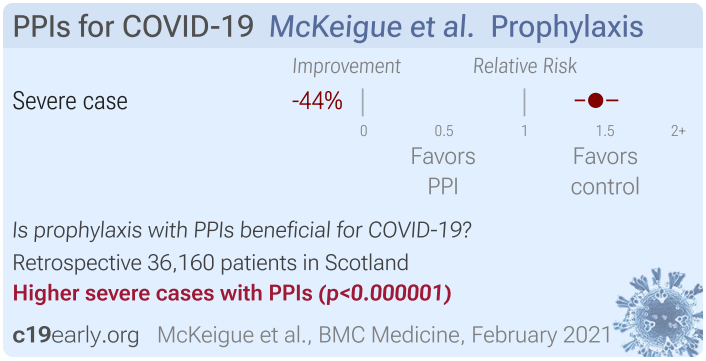
Luxenburger: Retrospective 152 hospitalized COVID-19 patients showing increased risk of secondary infections, ARDS, and mortality with proton pump inhibitor (PPI) use. Authors hypothesize that reduced gastric acid production from PPIs leads to bacterial overgrowth and microaspiration, increasing the risk of secondary lung infections. PPIs may also have immunomodulatory effects.

Mas Romero



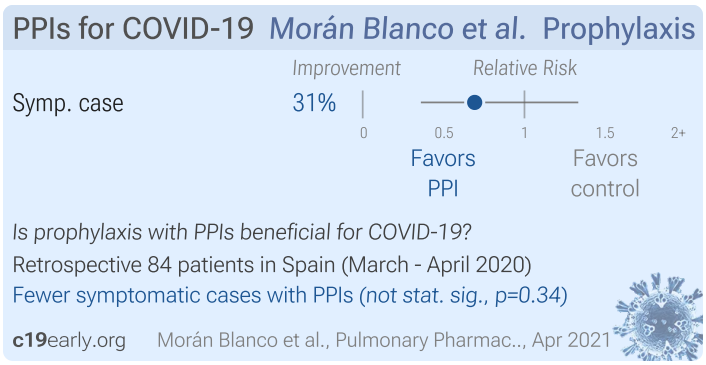
Mas Romero: Retrospective 1,084 residents from 6 long-term care facilities in Spain showing no signficant difference in cases and mortality with PPI use in unadjusted results.

McKeigue



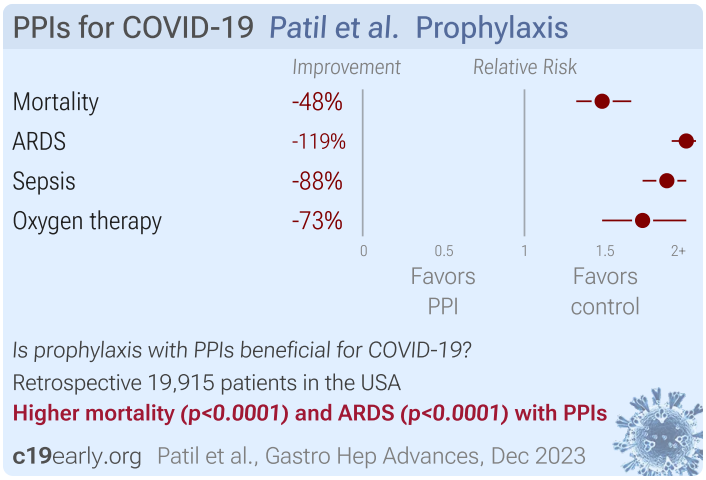
McKeigue: Retrospective 4,251 severe COVID-19 cases and 36,738 matched controls in Scotland showing increased risk of severe COVID-19 with PPI use and antihistamine H1RA use. Adjusted results are only provided for the patients not in care homes (2,357 cases and 33,803 controls).

Morán Blanco



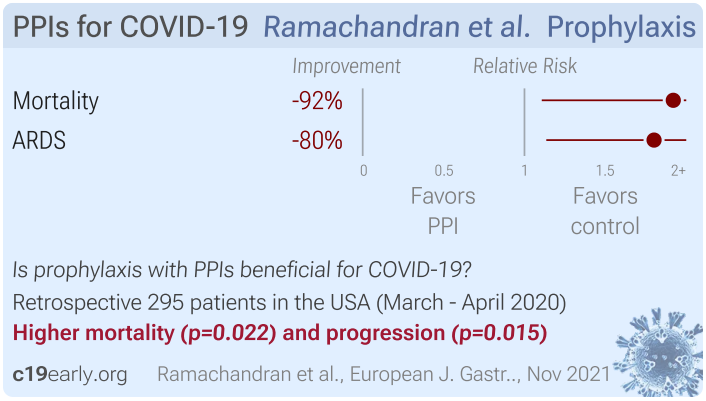
Morán Blanco: Retrospective 84 elderly nursing home residents in Spain showing no mortality, hospitalization, or ICU admission with early treatment with antihistamines alone or in combination with azithromycin.

Patil



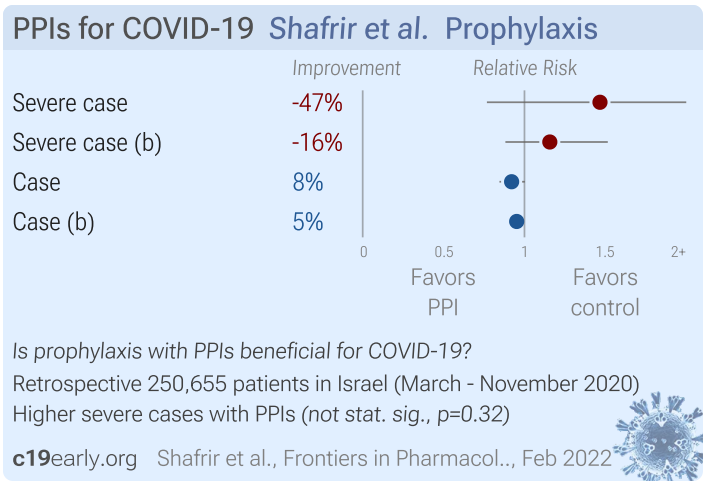
Patil: Retrospective 19,915 hospitalized COVID-19 patients with gastrointestinal symptoms, showing that use of proton pump inhibitors or H2 receptor antagonists was associated with higher mortality, ARDS, sepsis, and ventilator or oxygen requirement among patients

Ramachandran



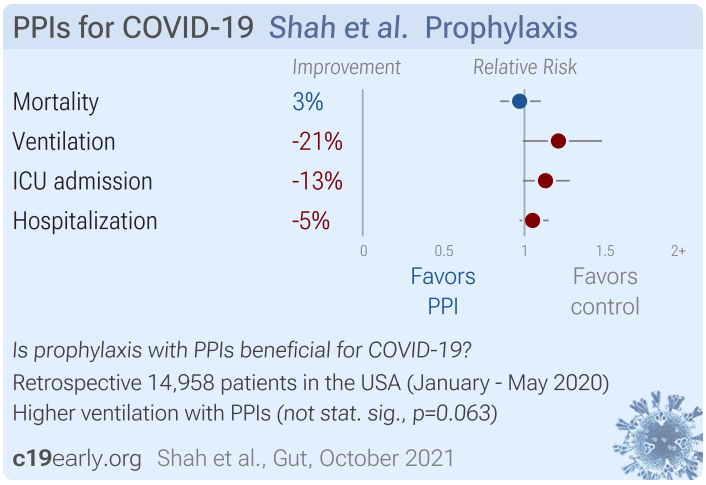
Ramachandran: Retrospective 295 hospitalized COVID-19 patients showing higher mortality and acute respiratory distress syndrome (ARDS) with pre-hospitalization proton pump inhibitor (PPI) use. Authors hypothesize that hypochlorhydria caused by PPIs may allow SARS-CoV-2 to more easily infect the gastrointestinal tract.

Shafrir



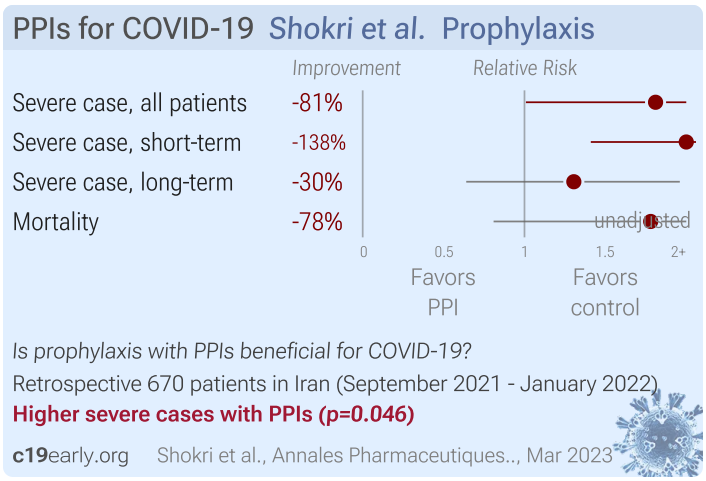
Shafrir: Retrospective 255,355 adults in Israel showing no significant association between proton pump inhibitor (PPI) use and SARS-CoV-2 positivity or COVID-19 severity.

Shah



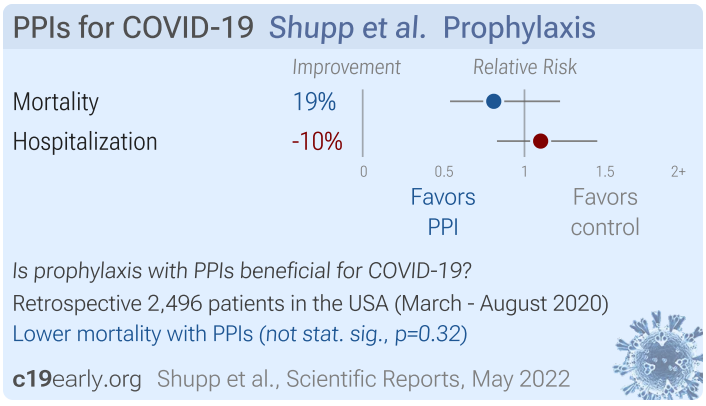
Shah: Retrospective 14,958 US veterans who tested positive for SARS-CoV-2, showing no significant difference in severe COVID-19 outcomes (mechanical ventilation, death, ICU admission, or hospitalization) with proton pump inhibitor (PPI) use compared to non-use in a propensity score weighted analysis.

Shokri



Shokri: Retrospective 670 COVID-19 patients in Iran showing significantly higher COVID-19 severity scores and more symptomatic presentation in patients with a history of proton pump inhibitor (PPI) use. Adjusted results are only provided for severity. Several values in Table 4 are likely misreported raising concern for the reliability of the main result.

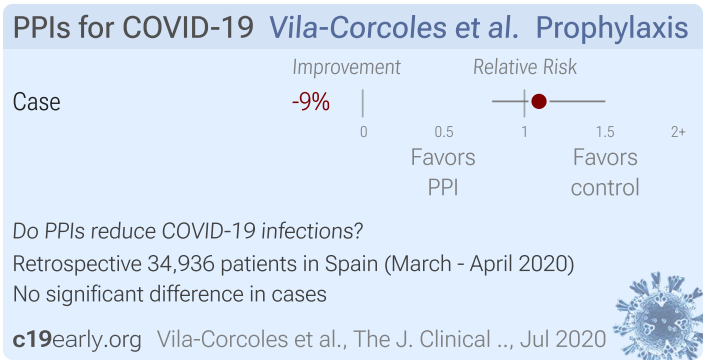
Shupp



Shupp: Retrospective 2,594 COVID-19 patients in the United States showing no significant association between proton pump inhibitor (PPI) use and COVID-19 severity, including need for hospitalization or 30-day mortality.

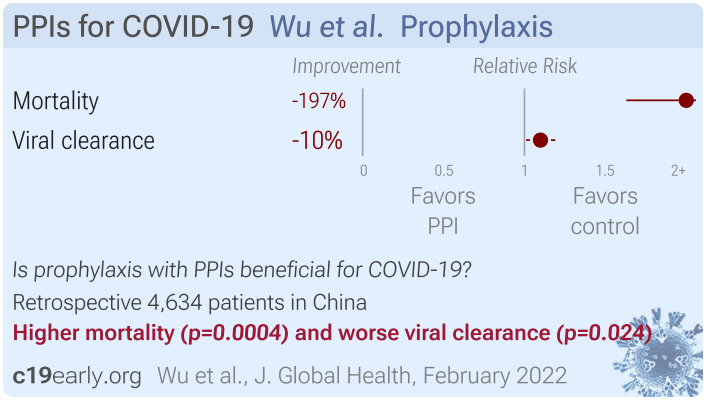
There was increasing mortality with increasing PPI use with 14%, 20%, and 27% mortality for low, standard, and high use, without statistical significance.

Vila-Corcoles



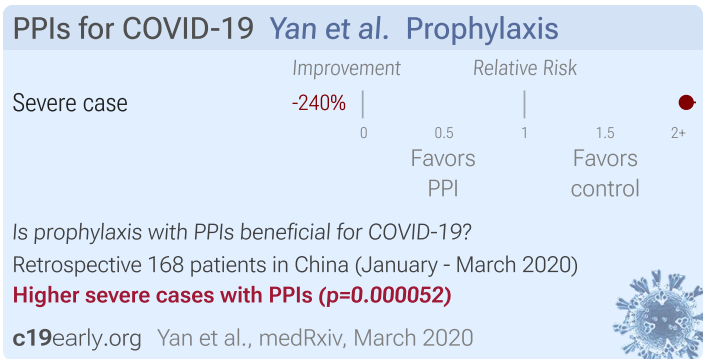
Vila-Corcoles: Retrospective 34,936 hypertensive outpatients in Spain showing no significant difference in COVID-19 cases with PPIs and antihistamine H1RAs.

Wu



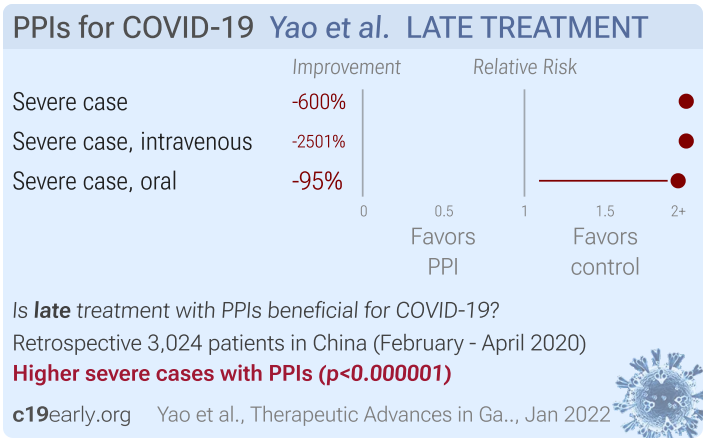
Wu: Retrospective 4,634 hospitalized COVID-19 patients in China, showing higher mortality and slower viral clearance with proton pump inhibitor (PPI) use. Authors hypothesize that PPIs may increase susceptibility to COVID-19 by increasing ACE2 expression.

Yan



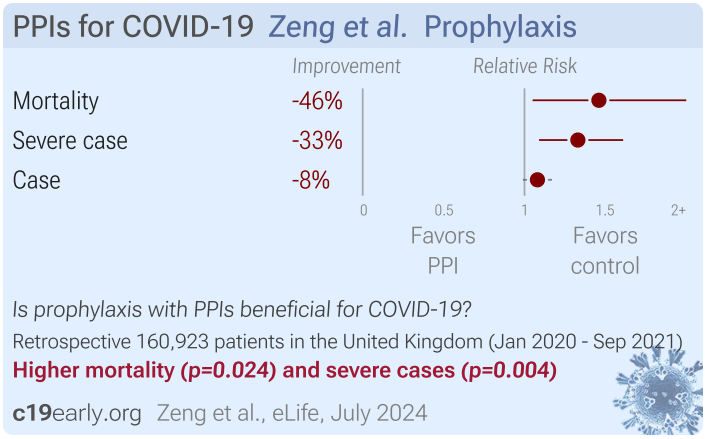
Yan (B): Retrospective 168 hospitalized COVID-19 patients in China showing higher risk of severe cases with acid suppression drugs.

Yao



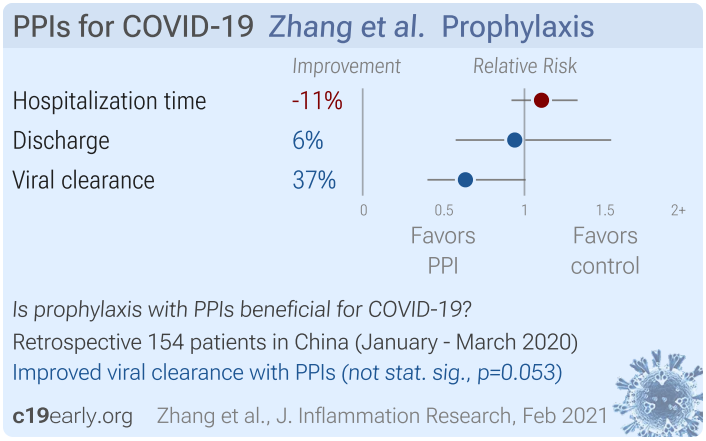
Yao: Retrospective 3,024 hospitalized COVID-19 patients in China showing increased risk of the composite outcome of ICU admission, mechanical ventilation, or death with proton pump inhibitor (PPI) use. Intravenous administration was significantly worse than oral. Authors hypothesize that PPIs may lead to worse COVID-19 outcomes by increasing the risk of secondary infections, cardiac damage, renal damage, and liver complications.

Zeng



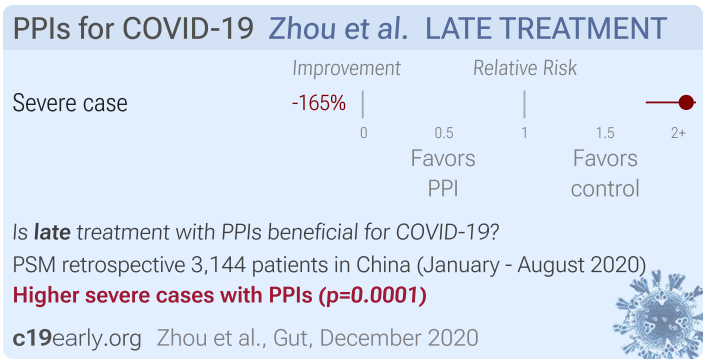
Zeng: UK Biobank retrospective with 160,923 patients showing increased risks of influenza, pneumonia, COVID-19 severity, and COVID-19 mortality with proton pump inhibitor (PPI) use.

Zhang



Zhang: Retrospective 154 hospitalized moderate COVID-19 patients in China showing no significant difference in viral clearance time or hospital stay duration with proton pump inhibitor (PPI) use. There was no association between PPI use and viral clearance or hospital stay duration in univariate or multivariate analysis. The same results were obtained after propensity score matching.

Zhou



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

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 PPI 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 PPI 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[94]. 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[97]. 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 (3.12.5) with scipy (1.14.1), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.2), and plotly (5.23.0).

Forest plots are computed using PythonMeta[98] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective[13,14].

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/ppimeta.html.

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.

Liwang, 8/3/2022, retrospective, Indonesia, peer-reviewed, median age 55.0, 4 authors, study period June 2021 - September 2021.	risk of death, 204.0% higher, OR 3.04, $p = 0.02$, treatment 216, control 149, adjusted per study, multivariable, RR approximated with OR.
Yao, 1/31/2022, retrospective, China, peer-reviewed, median age 60.0, 17 authors, study period February 2020 - April 2020.	risk of severe case, 600.0% higher, OR 7.00, $p < 0.001$, treatment 694, control 2,330, adjusted per study, multivariable, RR approximated with OR.
	risk of severe case, 2501.0% higher, OR 26.01, $p < 0.001$, treatment 82, control 2,330, adjusted per study, intravenous, multivariable, RR approximated with OR.
	risk of severe case, 95.0% higher, OR 1.95, $p = 0.02$, treatment 537, control 2,330, oral, RR approximated with OR.
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, 165.0% higher, HR 2.65, $p < 0.001$, treatment 151 of 524 (28.8%), control 173 of 2,620 (6.6%), adjusted per study, death/intubation/ICU, propensity score matching, multivariable, Cox proportional hazards.

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.

Al-Momani, 6/30/2024, retrospective, Jordan, peer-reviewed, mean age 59.7, 2 authors, study period 6 May, 2022 - 6 August, 2022.	**risk of death, 100% higher, RR 2.00, $p = 0.39$**, treatment 3 of 69 (4.3%), control 4 of 184 (2.2%).
	risk of mechanical ventilation, 48.1% higher, RR 1.48, $p = 0.54$, treatment 5 of 69 (7.2%), control 9 of 184 (4.9%).
	risk of ICU admission, 25.5% higher, RR 1.25, $p = 0.64$, treatment 8 of 69 (11.6%), control 17 of 184 (9.2%).
Almario, 8/25/2020, retrospective, USA, peer-reviewed, 3 authors, study period 3 May, 2020 - 24 June, 2020.	**risk of case, 178.5% higher, RR 2.79, $p < 0.001$**, treatment 7,387, control 44,586, adjusted per study, combined.
	risk of case, 267.0% higher, OR 3.67, $p < 0.001$, treatment 1,157, control 44,586, adjusted per study, twice daily or less, multivariable, RR approximated with OR.
	risk of case, 115.0% higher, OR 2.15, $p < 0.001$, treatment 7,387, control 44,586, adjusted per study, once daily, multivariable, RR approximated with OR.
Argenziano, 5/29/2020, retrospective, USA, peer-reviewed, median age 63.0, 48 authors, study period 1 March, 2020 - 5 April, 2020.	**risk of ICU admission, 1.5% lower, RR 0.99, $p = 1.00$**, treatment 38 of 163 (23.3%), control 198 of 837 (23.7%), NNT 292.
	risk of hospitalization, 9.1% higher, RR 1.09, $p = 0.01$, treatment 149 of 163 (91.4%), control 701 of 837 (83.8%).
Blanc, 5/2/2020, retrospective, France, preprint, mean age 84.1, 22 authors, study period 2 March, 2020 - 8 April, 2020.	**risk of case, 56.2% lower, OR 0.44, $p = 0.005$**, treatment 63, control 116, RR approximated with OR.
Cheung, 5/5/2024, retrospective, China, peer-reviewed, mean age 65.6, 6 authors, study period 23 February, 2021 - 31 March, 2022.	**risk of death, 49.5% higher, RR 1.49, $p = 0.005$**, adjusted per study, all patients.
	risk of death, 54.5% higher, RR 1.54, $p < 0.001$, adjusted per study, 2 dose.
	risk of death, 20.6% lower, RR 0.79, $p = 0.73$, treatment 6 of 94,180 (0.0%), control 7 of 95,180 (0.0%), NNT 101656, adjusted per study, 3 dose.
	risk of severe case, 36.3% higher, RR 1.36, $p = 0.27$, adjusted per study, all patients.
	risk of severe case, 56.9% higher, RR 1.57, $p < 0.001$, adjusted per study, 2 dose.
	risk of severe case, 21.1% lower, RR 0.79, $p = 0.67$, treatment 7 of 94,180 (0.0%), control 11 of 95,180 (0.0%), adjusted per study, 3 dose.
	risk of hospitalization, 19.7% higher, RR 1.20, $p < 0.001$, adjusted per study, all patients.
	risk of hospitalization, 19.5% higher, RR 1.20, $p < 0.001$, adjusted per study, 2 dose.

	risk of hospitalization, 21.3% higher, RR 1.21, $p = 0.17$, treatment 132 of 94,180 (0.1%), control 107 of 95,180 (0.1%), adjusted per study, 3 dose.
	risk of case, 9.1% higher, RR 1.09, $p < 0.001$, adjusted per study, all patients.
	risk of case, 7.5% higher, RR 1.07, $p < 0.001$, adjusted per study, 2 dose.
	risk of case, 11.4% higher, RR 1.11, $p < 0.001$, treatment 6,625 of 94,180 (7.0%), control 6,082 of 95,180 (6.4%), adjusted per study, 3 dose.
Cheung (B), 4/30/2021, retrospective, China, peer-reviewed, 3 authors.	**risk of severe case, 25.0% lower, OR 0.75, $p = 0.80$**, treatment 4, control 948, adjusted per study, multivariable, RR approximated with OR.
Elkanzi, 11/17/2023, retrospective, United Kingdom, peer-reviewed, 8 authors.	**risk of death, 17.1% higher, RR 1.17, $p = 0.49$**, treatment 36 of 159 (22.6%), control 29 of 150 (19.3%).
	risk of ICU admission, 24.9% higher, RR 1.25, $p = 0.05$, treatment 90 of 159 (56.6%), control 68 of 150 (45.3%).
	ASA 4, 126.4% higher, RR 2.26, $p = 0.14$, treatment 12 of 159 (7.5%), control 5 of 150 (3.3%).
	ASA ≥3, 32.6% higher, RR 1.33, $p = 0.006$, treatment 104 of 159 (65.4%), control 74 of 150 (49.3%).
	hospitalization time, 19.0% lower, relative time 0.81, $p = 0.18$, treatment mean 9.8 (±13.1) n=159, control mean 12.1 (±16.6) n=150.
Elmunzer, 3/31/2021, retrospective, multiple countries, peer-reviewed, 124 authors, study period 15 April, 2020 - 5 June, 2020.	**risk of death, 13.0% lower, OR 0.87, $p = 0.31$**, treatment 417, control 1,429, adjusted per study, multivariable, RR approximated with OR.
	risk of mechanical ventilation, 2.0% higher, OR 1.02, $p = 0.89$, treatment 417, control 1,429, adjusted per study, multivariable, RR approximated with OR.
Fan, 1/31/2021, retrospective, United Kingdom, peer-reviewed, 8 authors, study period 16 March, 2020 - 29 June, 2020.	**risk of death, 17.1% higher, RR 1.17, $p = 0.69$**, all upper gastrointestinal disease patients, propensity score matching.
	risk of death, 4.0% lower, HR 0.96, $p = 0.88$, positive upper gastrointestinal disease patients only, propensity score matching.
	risk of death, 13.6% lower, HR 0.86, $p = 0.59$, all patients, propensity score matching.
	risk of death, 20.0% lower, HR 0.80, $p = 0.18$, all positive patients, propensity score matching.

	risk of case, 22.0% higher, OR 1.22, *p* = 0.15, upper gastrointestinal disease patients, propensity score matching, RR approximated with OR.
	risk of case, 8.0% higher, OR 1.08, *p* = 0.44, all patients, propensity score matching, RR approximated with OR.
Freedberg, 5/21/2020, retrospective, propensity score matching, USA, peer-reviewed, 15 authors.	risk of death/intubation, 34.0% higher, HR 1.34, *p* = 0.01, 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.
García-Menaya, 9/16/2020, retrospective, Spain, peer-reviewed, mean age 67.6, 5 authors, study period 16 March, 2020 - 24 April, 2020.	risk of death, 228.0% higher, RR 3.28, *p* = 0.008, treatment 15 of 54 (27.8%), control 5 of 59 (8.5%), adjusted per study, multivariable.
	risk of ICU admission, 392.0% higher, RR 4.92, *p* = 0.02, treatment 9 of 54 (16.7%), control 2 of 59 (3.4%), adjusted per study, multivariable.
Gramont, 4/15/2024, retrospective, France, peer-reviewed, 13 authors, study period March 2020 - February 2021.	risk of severe case, 59.0% higher, OR 1.59, *p* = 0.002, treatment 424, control 410, propensity score weighting, RR approximated with OR.
Hirsch, 6/27/2024, retrospective, USA, peer-reviewed, 3 authors.	risk of hospitalization, 15.0% lower, RR 0.85, *p* = 0.27, adjusted per study, multivariable.
	risk of case, 15.0% lower, RR 0.85, *p* = 0.002.
Israelsen, 9/30/2021, retrospective, Denmark, peer-reviewed, 7 authors, study period 27 February, 2020 - 1 December, 2020, trial EUPAS35835.	risk of death, 5.0% lower, RR 0.95, *p* = 0.70, treatment 166 of 3,955 (4.2%), control 189 of 3,955 (4.8%), NNT 172, adjusted per study, all patients, propensity score matching, multivariable.
	risk of death, 12.0% lower, RR 0.88, *p* = 0.22, treatment 166 of 3,955 (4.2%), control 189 of 3,955 (4.8%), NNT 172, adjusted per study, within cases, propensity score matching, multivariable.
	risk of mechanical ventilation, 8.0% higher, RR 1.08, *p* = 0.73, treatment 55 of 3,955 (1.4%), control 55 of 3,955 (1.4%), adjusted per study, all patients, propensity score matching, multivariable.
	risk of mechanical ventilation, no change, RR 1.00, *p* = 1.00, treatment 55 of 3,955 (1.4%), control 55 of 3,955 (1.4%), adjusted per study, within cases, propensity score matching, multivariable.
	risk of ICU admission, 4.8% higher, RR 1.05, *p* = 0.80, treatment 92 of 3,955 (2.3%), control 95 of 3,955 (2.4%), NNT 1318, adjusted per study, all patients, propensity score matching, multivariable.

	risk of ICU admission, 3.0% lower, RR 0.97, p = 0.84, treatment 92 of 3,955 (2.3%), control 95 of 3,955 (2.4%), NNT 1318, adjusted per study, within cases, propensity score matching, multivariable.
	risk of hospitalization, 22.0% higher, RR 1.22, p = 0.005, treatment 734 of 3,955 (18.6%), control 650 of 3,955 (16.4%), adjusted per study, all patients, propensity score matching, multivariable.
	risk of hospitalization, 13.0% higher, RR 1.13, p = 0.010, treatment 734 of 3,955 (18.6%), control 650 of 3,955 (16.4%), adjusted per study, within cases, propensity score matching, multivariable.
	risk of case, 8.0% higher, OR 1.08, p = 0.001, treatment 4,473 of 63,886 (7.0%) cases, 17,553 of 259,089 (6.8%) controls, adjusted per study, case control OR, current vs. non-use, multivariable.
Jimenez, 8/20/2021, retrospective, Brazil, peer-reviewed, 21 authors, southeast region.	risk of death, 124.4% higher, HR 2.24, p < 0.001, adjusted per study, both regions combined.
	risk of death, 118.3% higher, HR 2.18, p < 0.001, adjusted per study, multivariable, Cox proportional hazards.
	risk of death, 133.2% higher, HR 2.33, p < 0.001, adjusted per study, multivariable, Cox proportional hazards.
Kim, 3/21/2023, retrospective, South Korea, peer-reviewed, 8 authors, study period 1 January, 2020 - 4 June, 2020.	risk of death, 28.4% higher, RR 1.28, p = 0.63, treatment 9 of 437 (2.1%), control 7 of 437 (1.6%), odds ratio converted to relative risk, propensity score matching, model 3.
	risk of mechanical ventilation, 74.8% higher, RR 1.75, p = 0.37, treatment 7 of 437 (1.6%), control 4 of 437 (0.9%), odds ratio converted to relative risk, propensity score matching, model 3.
	risk of ICU admission, 150.5% higher, RR 2.50, p = 0.11, treatment 10 of 437 (2.3%), control 4 of 437 (0.9%), odds ratio converted to relative risk, propensity score matching, model 3.
	risk of progression, 21.1% higher, RR 1.21, p = 0.60, treatment 17 of 437 (3.9%), control 14 of 437 (3.2%), odds ratio converted to relative risk, propensity score matching, model 3.
	risk of case, 37.2% lower, RR 0.63, p < 0.001, treatment 226 of 9,913 (2.3%), control 341 of 9,913 (3.4%), NNT 86, adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable, model 3.
Kodvanj, 10/5/2022, retrospective, Croatia, peer-reviewed, 3 authors, study period 25 February, 2020 - 15 August, 2021.	risk of death, 7.0% lower, RR 0.93, p = 0.12, treatment 41,195, control 17,334.
	risk of hospitalization, 4.0% higher, OR 1.04, p = 0.32, treatment 41,195, control 17,334, RR approximated with OR.

Lee, 7/30/2020, retrospective, South Korea, peer-reviewed, 12 authors, study period 1 January, 2020 - 15 May, 2020.	**risk of severe case, 79.0% higher, OR 1.79, $p = 0.009$**, treatment 267, control 267, adjusted per study, ICU, mechanical ventilation, death, propensity score matching, multivariable, RR approximated with OR.
	risk of severe case, 63.0% higher, OR 1.63, $p = 0.03$, treatment 267, control 267, adjusted per study, oxygen, ICU, mechanical ventilation, death, propensity score matching, multivariable, RR approximated with OR.
	risk of case, 10.0% lower, OR 0.90, $p = 0.11$, treatment 13,873, control 13,873, adjusted per study, propensity score matching, multivariable, RR approximated with OR.
Liu, 5/27/2021, retrospective, USA, peer-reviewed, 20 authors, study period 15 March, 2020 - 15 August, 2020.	**risk of death, 126.9% higher, RR 2.27, $p < 0.001$**, treatment 68 of 227 (30.0%), control 53 of 459 (11.5%), adjusted per study, odds ratio converted to relative risk, multivariable.
Luxenburger, 7/31/2020, retrospective, Germany, peer-reviewed, 9 authors.	**risk of death, 248.4% higher, RR 3.48, $p = 0.02$**, treatment 12 of 62 (19.4%), control 5 of 90 (5.6%), adjusted per study, multivariable, excluded in exclusion analyses: unadjusted differences between groups.
	risk of ARDS, 124.3% higher, RR 2.24, $p = 0.02$, treatment 17 of 62 (27.4%), control 11 of 90 (12.2%), adjusted per study, multivariable, excluded in exclusion analyses: unadjusted differences between groups.
	secondary infection, 86.0% higher, RR 1.86, $p = 0.03$, treatment 30 of 62 (48.4%), control 18 of 90 (20.0%), adjusted per study, odds ratio converted to relative risk, multivariable.
Mas Romero, 10/27/2020, retrospective, Spain, peer-reviewed, 26 authors, study period 6 March, 2020 - 5 June, 2020.	**risk of death, 25.9% lower, RR 0.74, $p = 0.44$**, treatment 11 of 82 (13.4%), control 21 of 116 (18.1%), NNT 21.
	risk of symptomatic case, 8.0% higher, RR 1.08, $p = 0.54$, treatment 58 of 82 (70.7%), control 76 of 116 (65.5%).
McKeigue, 2/22/2021, retrospective, Scotland, peer-reviewed, 18 authors, trial EUPAS35558.	**risk of severe case, 44.0% higher, OR 1.44, $p < 0.001$**, treatment 1,168 of 2,357 (49.6%) cases, 12,745 of 33,803 (37.7%) controls, adjusted per study, case control OR.
Morán Blanco, 4/30/2021, retrospective, Spain, peer-reviewed, mean age 85.0, 6 authors, study period March 2020 - April 2020.	**risk of symptomatic case, 30.8% lower, RR 0.69, $p = 0.34$**, treatment 12 of 48 (25.0%), control 13 of 36 (36.1%), NNT 9.0.
Patil, 12/31/2023, retrospective, USA, peer-reviewed, mean age 52.0, 7 authors.	**risk of death, 48.0% higher, OR 1.48, $p < 0.001$**, treatment 4,566, control 15,349, adjusted per study, multivariable, RR approximated with OR.
	risk of ARDS, 119.0% higher, OR 2.19, $p < 0.001$, treatment 4,566, control 15,349, adjusted per study, multivariable, RR approximated with OR.

	sepsis, 88.0% higher, OR 1.88, $p < 0.001$, treatment 4,566, control 15,349, adjusted per study, multivariable, RR approximated with OR.
	risk of oxygen therapy, 73.0% higher, OR 1.73, $p < 0.001$, treatment 4,566, control 15,349, adjusted per study, multivariable, RR approximated with OR.
Ramachandran, 11/30/2021, retrospective, USA, peer-reviewed, 7 authors, study period 1 March, 2020 - 25 April, 2020.	**risk of death, 92.0% higher, RR 1.92, $p = 0.02$**, treatment 16 of 46 (34.8%), control 40 of 249 (16.1%), adjusted per study, odds ratio converted to relative risk, multivariable.
	ARDS, 80.1% higher, RR 1.80, $p = 0.01$, treatment 18 of 46 (39.1%), control 55 of 249 (22.1%), adjusted per study, odds ratio converted to relative risk, multivariable.
Shafrir, 2/4/2022, retrospective, Israel, peer-reviewed, 9 authors, study period March 2020 - November 2020.	**risk of severe case, 46.7% higher, RR 1.47, $p = 0.32$**, treatment 22 of 655 (3.4%), control 15 of 655 (2.3%), propensity score matching.
	risk of severe case, 15.7% higher, RR 1.16, $p = 0.28$, treatment 113 of 1,608 (7.0%), control 797 of 42,789 (1.9%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of case, 7.9% lower, RR 0.92, $p = 0.06$, treatment 880 of 6,835 (12.9%), control 956 of 6,835 (14.0%), NNT 90, propensity score matching.
	risk of case, 4.8% lower, RR 0.95, $p = 0.10$, adjusted per study, odds ratio converted to relative risk, multivariable.
Shah, 10/18/2021, retrospective, USA, peer-reviewed, 16 authors, study period January 2020 - May 2020.	**risk of death, 3.0% lower, OR 0.97, $p = 0.66$**, treatment 6,262, control 8,696, propensity score weighting, RR approximated with OR.
	risk of mechanical ventilation, 21.0% higher, OR 1.21, $p = 0.06$, treatment 6,262, control 8,696, propensity score weighting, RR approximated with OR.
	risk of ICU admission, 13.0% higher, OR 1.13, $p = 0.06$, treatment 6,262, control 8,696, propensity score weighting, RR approximated with OR.
	risk of hospitalization, 5.0% higher, OR 1.05, $p = 0.26$, treatment 6,262, control 8,696, propensity score weighting, RR approximated with OR.
Shokri, 3/31/2023, retrospective, Iran, peer-reviewed, mean age 44.2, 6 authors, study period 10 September, 2021 - 18 January, 2022, excluded in exclusion analyses: potential data issue.	**risk of severe case, 81.0% higher, RR 1.81, $p = 0.046$**, treatment 121, control 549, all patients.
	risk of severe case, 137.6% higher, OR 2.38, $p < 0.001$, treatment 40, control 549, short-term, RR approximated with OR.
	risk of severe case, 30.5% higher, OR 1.30, $p = 0.36$, treatment 81, control 549, long-term, RR approximated with OR.

Shupp, 5/9/2022, retrospective, USA, peer-reviewed, mean age 52.6, 8 authors, study period March 2020 - August 2020.	**risk of death, 19.0% lower, OR 0.81, $p = 0.32$**, treatment 448, control 2,048, adjusted per study, multivariable, RR approximated with OR.
	risk of hospitalization, 10.0% higher, OR 1.10, $p = 0.51$, treatment 448, control 2,048, adjusted per study, multivariable, RR approximated with OR.
Vila-Corcoles, 7/25/2020, retrospective, Spain, peer-reviewed, mean age 70.9, 11 authors, study period 1 March, 2020 - 30 April, 2020.	**risk of case, 9.0% higher, HR 1.09, $p = 0.58$**, treatment 11,807, control 23,129, adjusted per study, multivariable, Cox proportional hazards.
Wu, 2/19/2022, retrospective, China, peer-reviewed, 8 authors.	**risk of death, 197.0% higher, OR 2.97, $p < 0.001$**, treatment 1,046, control 3,588, propensity score weighting, model 4, RR approximated with OR.
	risk of no viral clearance, 9.9% higher, HR 1.10, $p = 0.02$, treatment 1,046, control 3,588, inverted to make HR<1 favor treatment, propensity score matching, Cox proportional hazards.
Yan (B), 3/23/2020, retrospective, China, preprint, median age 51.0, 17 authors, study period 22 January, 2020 - 13 March, 2020.	**risk of severe case, 240.0% higher, RR 3.40, $p < 0.001$**, treatment 16 of 32 (50.0%), control 20 of 136 (14.7%).
Zeng, 7/16/2024, retrospective, United Kingdom, peer-reviewed, mean age 56.5, 13 authors, study period January 2020 - September 2021.	**risk of death, 46.0% higher, HR 1.46, $p = 0.02$**, treatment 9,997, control 150,926, adjusted per study, multivariable, Cox proportional hazards.
	risk of severe case, 33.0% higher, HR 1.33, $p = 0.004$, treatment 9,997, control 150,926, adjusted per study, multivariable, Cox proportional hazards.
	risk of case, 8.0% higher, HR 1.08, $p = 0.10$, treatment 9,997, control 150,926, adjusted per study, multivariable, Cox proportional hazards.
Zhang, 2/28/2021, retrospective, China, peer-reviewed, median age 52.0, 6 authors, study period 20 January, 2020 - 16 March, 2020.	**hospitalization time, 10.5% higher, relative time 1.11, $p = 0.29$**, treatment median 21.0 IQR 11.0 n=29, control median 19.0 IQR 8.0 n=29, propensity score matching.
	risk of no hospital discharge, 6.0% lower, HR 0.94, $p = 0.82$, treatment 35, control 119, adjusted per study, inverted to make HR<1 favor treatment, multivariable.
	risk of no viral clearance, 36.5% lower, HR 0.63, $p = 0.05$, treatment 35, control 119, adjusted per study, inverted to make HR<1 favor treatment, multivariable.

Supplementary Data

Supplementary Data

References

1. ***Hariyanto*** et al., *Proton pump inhibitor use is associated with increased risk of severity and mortality from coronavirus disease 2019 (COVID-19) infection*, Digestive and Liver Disease, doi:10.1016/j.dld.2020.10.001.

2. ***Fatima*** et al., *The Use of Proton Pump Inhibitors and COVID-19: A Systematic Review and Meta-Analysis*, Tropical Medicine and Infectious Disease, doi:10.3390/tropicalmed7030037.

3. ***Toubasi*** et al., *Proton Pump Inhibitors: Current Use and the Risk of Coronavirus Infectious Disease 2019 Development and its Related Mortality. Meta-analysis*, Archives of Medical Research, doi:10.1016/j.arcmed.2021.03.004.

4. ***Wardhana*** et al., *Different Outcome in COVID-19 Patients with or without PPI Use: A Systematic Review and Meta-analysis*, International Journal of Biomedical Science and Travel Medicine, doi:10.22225/ijbstm.1.1.2024.19-23.

5. ***Yan*** et al., *Does Proton Pump Inhibitor Use Lead to a Higher Risk of Coronavirus Disease 2019 Infection and Progression to Severe Disease? a Meta-analysis*, Japanese Journal of Infectious Diseases, doi:10.7883/yoken.JJID.2021.074.

6. ***Li*** et al., *Do proton pump inhibitors influence SARS-CoV-2 related outcomes? A meta-analysis*, Gut, doi:10.1136/gutjnl-2020-323366.

7. ***Pranata*** et al., *Proton pump inhibitor on susceptibility to COVID-19 and its severity: a systematic review and meta-analysis*, Pharmacological Reports, doi:10.1007/s43440-021-00263-x.

8. ***Kow*** et al., *Use of proton pump inhibitors and risk of adverse clinical outcomes from COVID-19: a meta-analysis*, Journal of Internal Medicine, doi:10.1111/joim.13183.

9. ***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.

10. ***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.

11. ***Luxenburger*** et al., *Treatment with proton pump inhibitors increases the risk of secondary infections and ARDS in hospitalized patients with COVID-19: coincidence or underestimated risk factor?*, Journal of Internal Medicine, doi:10.1111/joim.13121.

12. ***Shokri*** et al., *What is the role of proton pump inhibitors consumption on the clinical presentation and severity of COVID-19 infection?*, Annales Pharmaceutiques Françaises, doi:10.1016/j.pharma.2022.08.013.

13. ***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.

14. ***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.

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

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

17. ***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.

18. **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.

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

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

21. **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.

22. **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.

23. **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.

24. **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.

25. **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.

26. **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.

27. **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.

28. **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.

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

30. **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.

31. **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.

32. **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.

33. **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.

34. **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.

35. **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.

36. **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.

37. **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.

38. **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.

39. **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.

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

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

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

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

44. **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.

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

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

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

48. **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.

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

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

51. **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.

52. **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.

53. **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.

54. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.

55. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.

56. **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.

57. **c19early.org**, c19early.org/treatments.html.

58. **c19early.org (B)**, c19early.org/timeline.html.

59. **Al-Momani** et al., *Proton pump inhibitors and gastrointestinal symptoms among patients with COVID-19 infection*, Annals of Medicine, doi:10.1080/07853890.2024.2355581.

60. **Almario** et al., *Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors*, American Journal of Gastroenterology, doi:10.14309/ajg.0000000000000798.

61. **Argenziano** et al., *Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series*, BMJ, doi:10.1136/bmj.m1996.

62. **Blanc** et al., *Interest of Proton Pump Inhibitors in Reducing the Occurrence of COVID-19: A Case-Control Study*, Preprints, doi:10.20944/preprints202005.0016.v1.

63. **Cheung** et al., *Proton pump inhibitors associated with severe COVID-19 among two-dose but not three-dose vaccine recipients*, Journal of Gastroenterology and Hepatology, doi:10.1111/jgh.16601.

64. **Cheung (B)** 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.

65. **Elkanzi** et al., *Effect of Preadmission Proton Pump Inhibitor (PPI) on the clinical outcome of Covid-19 Hospitalised Patients during the Pandemic*, Academic Journal of Gastroenterology & Hepatology, doi:10.33552/AJGH.2023.03.000568.

66. **Elmunzer** et al., *Association Between Preadmission Acid Suppressive Medication Exposure and Severity of Illness in Patients Hospitalized With COVID-19*, Gastroenterology, doi:10.1053/j.gastro.2020.11.007.

67. **Fan** et al., *Effect of Acid Suppressants on the Risk of COVID-19: A Propensity Score-Matched Study Using UK Biobank*, Gastroenterology, doi:10.1053/j.gastro.2020.09.028.

68. **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.

69. **García-Menaya** et al., *Outcomes and Laboratory and Clinical Findings of Asthma and Allergic Patients Admitted With Covid-19 in a Spanish University Hospital*, Frontiers in Pharmacology, doi:10.3389/fphar.2020.570721.

70. **Gramont** et al., *Proton pump inhibitors and risk of severe COVID-19 in older people*, Age and Ageing, doi:10.1093/ageing/afae082.

71. **Hirsch** et al., *Proton Pump Inhibitors and Risk of COVID-19 Infection in Children*, The Journal of Pediatrics, doi:10.1016/j.jpeds.2024.114179.

72. **Israelsen** et al., *Proton Pump Inhibitor Use Is Not Strongly Associated With SARS-CoV-2 Related Outcomes: A Nationwide Study and Meta-analysis*, Clinical Gastroenterology and Hepatology, doi:10.1016/j.cgh.2021.05.011.

73. **Jimenez** et al., *Acid pH Increases SARS-CoV-2 Infection and the Risk of Death by COVID-19*, Frontiers in Medicine, doi:10.3389/fmed.2021.637885.

74. **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.

75. **Kodvanj** et al., *People exposed to proton-pump inhibitors shortly preceding COVID-19 diagnosis are not at an increased risk of subsequent hospitalizations and mortality: A nationwide matched cohort study*, British Journal of Clinical Pharmacology, doi:10.1111/bcp.15525.

76. **Lee** et al., *Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching*, Gut, doi:10.1136/gutjnl-2020-322248.

77. **Liu** et al., *Increased ACE2 Levels and Mortality Risk of Patients With COVID-19 on Proton Pump Inhibitor Therapy*, American Journal of Gastroenterology, doi:10.14309/ajg.0000000000001311.

78. **Liwang** et al., *High vs Low Dose Proton Pump Inhibitor (PPI) related Mortality in Hospitalized Coronavirus Disease-19 (COVID-19): A Retrospective Cohort Study*, Journal Of The Indonesian Medical Association, doi:10.47830/jinma-vol.72.2-2022-802.

79. **Mas Romero** et al., *COVID-19 outbreak in long-term care facilities from Spain. Many lessons to learn*, PLOS ONE, doi:10.1371/journal.pone.0241030.

80. **McKeigue** et al., *Relation of severe COVID-19 to polypharmacy and prescribing of psychotropic drugs: the REACT-SCOT case-control study*, BMC Medicine, doi:10.1186/s12916-021-01907-8.

81. **Morán Blanco** et al., *Antihistamines and azithromycin as a treatment for COVID-19 on primary health care – A retrospective observational study in elderly patients*, Pulmonary Pharmacology & Therapeutics, doi:10.1016/j.pupt.2021.101989.

82. **Patil** et al., *Factors Associated With Poor Outcomes Among Patients With SARS-CoV-2 Coronavirus Infection and Gastrointestinal Symptoms*, Gastro Hep Advances, doi:10.1016/j.gastha.2022.08.004.

83. **Ramachandran** et al., *Pre-hospitalization proton pump inhibitor use and clinical outcomes in COVID-19*, European Journal of Gastroenterology & Hepatology, doi:10.1097/MEG.0000000000002013.

84. **Shafrir** et al., *The Association Between Proton Pump Inhibitors and COVID-19 is Confounded by Hyperglycemia in a Population-Based Study*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.791074.

85. **Shah** et al., *Proton-pump inhibitor use is not associated with severe COVID-19-related outcomes: a propensity score-weighted analysis of a national veteran cohort*, Gut, doi:10.1136/gutjnl-2021-325701.

86. **Shupp** et al., *Proton pump inhibitor therapy usage and associated hospitalization rates and critical care outcomes of COVID-19 patients*, Scientific Reports, doi:10.1038/s41598-022-11680-0.

87. **Vila-Corcoles** et al., *Use of distinct anti-hypertensive drugs and risk for COVID-19 among hypertensive people: A population-based cohort study in Southern Catalonia, Spain*, The Journal of Clinical Hypertension, doi:10.1111/jch.13948.

88. **Wu** et al., *Use of proton pump inhibitors are associated with higher mortality in hospitalized patients with COVID-19*, Journal of Global Health, doi:10.7189/jogh.12.05005.

89. **Yan (B)** et al., *Clinical Characteristics of Coronavirus Disease 2019 in Hainan, China*, medRxiv, doi:10.1101/2020.03.19.20038539.

90. **Yao** et al., *Impact of proton pump inhibitors on the in-hospital outcome of COVID-19 patients: a retrospective study*, Therapeutic Advances in Gastroenterology, doi:10.1177/17562848221104365.

91. **Zeng** et al., *Associations of proton pump inhibitors with susceptibility to influenza, pneumonia, and COVID-19: Evidence from a large population-based cohort study*, eLife, doi:10.7554/elife.94973.

92. **Zhang** et al., *Analysis of the Effect of Proton-Pump Inhibitors on the Course of COVID-19*, Journal of Inflammation Research, doi:10.2147/JIR.S292303.

93. **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.

94. **Zhang (B)** 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.

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

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

97. **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.

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