

# **Will Proton Pump Inhibitors Lead to a Higher Risk of COVID-19 Infection**

## **and Progression to Severe Disease? A Meta-analysis**

**Cunye Yan<sup>1,a</sup>, Yue Chen<sup>2,a</sup>, Chenyu Sun<sup>3\*</sup>, Mubashir Ayaz Ahmed<sup>3</sup>, Chandur Bhan<sup>3</sup>, Zhichun Guo<sup>4</sup>, Hongru Yang<sup>4</sup>, Yijing Zuo<sup>4</sup>, Yue Yan<sup>4</sup>, Lei Hu<sup>2</sup>, Yiceng Sun<sup>1</sup>, Yao Li<sup>1</sup>, Qin Zhou<sup>5</sup>**

1. Department of Breast and Thyroid Surgery, Chongqing General Hospital, University of Chinese Academy of Sciences, Chongqing, P.R. China.
  2. Department of Clinical Medicine, School of the First Clinical Medicine, Anhui Medical University, No. 81 Meishan Road, Hefei 230032, Anhui, P.R. China.
  3. AMITA Health Saint Joseph Hospital Chicago, 2900 N. Lake Shore Drive, Chicago 60657, Illinois, USA
  4. Massachusetts college of Pharmacy and Health sciences, 179 Longwood Ave, Boston, MA 02115, USA
  5. Radiation Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905, USA
- a.** Cunye Yan and Yue Chen contributed equally to this work and should be considered as co-first authors.

**\*Corresponding author:**

Chenyu Sun, MD, MSc. AMITA Health Saint Joseph Hospital Chicago, 2900 N. Lake Shore Drive, Chicago 60657, Illinois, USA.

Tel: +1 (828)372-4658

Fax: +1 (828)372-4658

E-mail: drsunchenyu@yeah.net

**Running title:** COVID-19 and PPI

**Keywords:** proton pump inhibitor, COVID-19, meta-analysis; infection risk; mortality

## **Summary**

Previous researches on the association between proton pump inhibitors (PPIs) use and the treatment and prevention of COVID-19 has generated inconsistent findings. Therefore, this meta-analysis was conducted to clarify the outcome in patients who take PPIs.

Eight articles with more than 268,683 subjects were included. PPI use was not associated with increased or decreased risk of COVID-19 infection (OR=3.16, 95%CI = 0.74-13.43,  $P=0.12$ ) or mortality risk of COVID-19 patients (OR=1.91, 95%CI=0.86-4.24,  $P=0.11$ ). While it can add risk of severe disease (OR=1.54, 95%CI=1.20-1.99,  $P<0.001$ ;) and secondary infection (OR=4.33, 95% CI=2.57-7.29).

In summary, PPI use is not associated with an increased risk of infection and may not change the mortality risk of COVID-19, but appeared to be associated with an increased risk of progression to severe disease and secondary infection. However, more original studies to further clarify the relationship between PPI and COVID-19 are still urgently needed.

## **Introduction**

In March 2020, the World Health Organization (WHO) announced that Coronavirus Disease 2019 (COVID-19) would become a pandemic in 2020 (1). As of November 15, 2020, more than 53.5 million people have been diagnosed with COVID-19 and 1.3 million people have died of the virus (2), whereas the pandemic is not yet under control. This global pandemic has seriously affected public health and socio-economic development around the world. Therefore, it is of great significance to identify the risk factors of COVID-19 infection, as well as proper treatment modalities.

In previous studies, it was found that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, enters the human body not only through the respiratory system but also through the gastrointestinal system (3). The virus can rapidly invade and replicate intestinal cells using the angiotensin-converting enzyme-2 receptor, which is widely expressed in the GI tract (4). It has been reported that nearly half of COVID-19 patients have viral RNA in their feces (5). These results suggested a strong correlation between the gastrointestinal system and SARS-CoV-2 infection. Therefore, it is of great importance to study the relationship between the most commonly used acid suppressor, proton pump inhibitors (PPI), and COVID-19 infection. PPI was postulated to be beneficial in the treatment and prevention of COVID-19 (6), while other evidence suggested that PPI could potentially aggravate the condition of patients with COVID-19 and increase the mortality rate (7). As previous studies reached controversial conclusions, we conducted this meta-analysis to further explore the relationship between PPI use and COVID-19, with more

detailed subgroup analyses on different outcome indexes.

## **Methods**

This meta-analysis was reported in conformity to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (8). And it was registered on the International Prospective Register of Systematic Reviews (PROSPERO).

### **Literature search strategy**

The articles were collected until November 2020 from PubMed, Google Scholar, Embase, medRxiv, Web of Science, CNKI, Wanfang, and VIP database. The keywords were ("PPI" OR "PPIs" OR "proton pump inhibitors" OR "proton pump inhibitor" OR "omeprazole" OR "lansoprazole" OR "dexlansoprazole" OR "esomeprazole" OR "pantoprazole" OR "rabeprazole" OR "acid suppress" OR "acid suppression") AND ("COVID-19" OR "Novel coronavirus" OR "coronavirus disease" OR "SARS-CoV-2" OR "Severe acute respiratory syndrome coronavirus 2"). In addition, reference lists of the retrieved articles were reviewed to identify other eligible studies.

### **Identification of eligible studies**

Two authors (C. Yan and C. Sun) independently carried out the search and disagreements were solved by consensus. The abstract of the retrieved studies was reviewed initially and excluded if deemed irrelevant. The full text of the relevant studies was further reviewed for eligibility. If there were duplicate publications of the same study, the one with the most detailed information and complete data was included.

Studies included in this meta-analysis must meet all of the following criteria: 1. The type of study must be either a randomized controlled trial or an observational study (including cohort and case-control studies). 2. The research was conducted to investigate COVID-19 outcomes, including infection risk, progression to severe cases, death, and risk of secondary infection. 3. PPI use was the exposure for the experimental group and any feasible intervention without PPI use can be implemented on the control group. 4. Relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were able to be extracted or recalculated. 5. The studies were published in English or Chinese. The exclusion criteria were set for this study. 1. The type of articles cannot be accurately determined. 2. No valid account of ending data can be derived from the article. 3. Duplicate articles. 4. Reviews, case reports, animal studies, or in vitro studies.

### **Data extraction and quality evaluation**

Each of the two authors (C. Yan and C. Sun) independently disposed of the data from the literature, and if discrepancies arose, a consensus was reached by consulting a third person (Y. Chen), comprehensively comparing the data and through conferral. Information was collected as follows: first author, publication year, country, study design, the outcome of the research, NOS scores, the number of cases and controls, odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

The methodological quality of the observational researches was appraised using a validated Newcastle-Ottawa Scale. Three broad subscales including study group selection (0 to 4 points), the groups comparability (0 to 2 points), and the exposures

and outcomes elucidation (0 to 3 points). A score of 4-6 was considered moderate, and a score of 7 or more is defined as high quality. Two evaluators (C. Yan and Y. Chen) independently conducted the quality assessment and if there was a divergence of opinion, it would be resolved by mutual communication.

### **Statistical analysis and publication bias evaluation**

RevMan software (version 5.3; Cochrane Library) and STATA statistical software (version 14.0; StataCorp, College Station, TX) were utilized for statistical analysis.

The associations between PPI use and risk of COVID-19 infection, progression to severe disease, death, or risk of secondary infection were analyzed through pooling the ORs and corresponding 95% CIs.

Heterogeneity tests were performed based on the Q test and  $I^2$  statistics. For  $I^2 > 50\%$ , the random effects model was implemented to create forest plots. In contrast, the fixed-effects model was adopted if  $I^2$  was  $< 50\%$ . Sensitivity analysis was executed by sequentially excluding the incorporated studies and observing whether the combined results changed significantly. In addition, we conducted a series of subgroup analyses in accordance with the distinct characteristics of the different studies. Publication bias was assessable on a funnel plot qualitatively and Begg's test and Egger's test quantitatively. All p-values were two-tailed and  $P < 0.05$  was considered statistically significant.

## **Results**

### **Study selection and Study characteristics**

**Figure 1** gives the outline of the inclusion process, a final electronic search identified 600 records. After eliminating duplicate literature, screening titles and abstracts, we selected 127 potentially relevant articles for further screening, among which, 36 full-text were assessed for eligibility. Nineteen of these articles did not have sufficient data, 1 article had no target outcomes, and the exposure of 2 articles was not PPI use. Eventually, we identified 14 articles published by November 2020, comprising a total of more than 268,683 subjects, including 7 cohort studies and 7 case-control studies. Detailed characteristics of the included studies are shown in **Table 1**. All studies are of moderate or high quality.

## Meta-analysis

### Association between PPI use and risk of COVID-19 infection

Analysis of seven studies (9-15) on risk of COVID-19 infection found that the use of PPI was not associated with increased or decreased risk of COVID-19 infection (OR:1.64, 95%CI = 0.54-5.00,  $P=0.390$ ;  $I^2=100\%$ ,  $P_{heterogeneity} <0.001$ ). (**Figure 2**) In subgroup analysis by study designs, no statistically significant association was observed in cohort (OR:1.19, 95%CI = 0.79-1.79,  $P=0.420$ ;  $I^2=89\%$ ,  $P_{heterogeneity} =0.001$ ) and case-control studies (OR:2.08, 95%CI = 0.36-12.13,  $P=0.410$ ;  $I^2=100\%$ ,  $P_{heterogeneity} <0.001$ ). Regarding different geographic locations, no statistically significant association was observed in western countries (OR:1.70, 95%CI = 0.33-8.67,  $P=0.520$ ;  $I^2=100\%$ ,  $P_{heterogeneity} <0.001$ ) and Asian countries (OR:1.30, 95%CI = 0.74-2.29,  $P=0.360$ ;  $I^2=97\%$ ,  $P_{heterogeneity} <0.001$ ). When it comes to sensitive analysis, studies were omitted one by one. The combined result did not change significantly when any

of the articles was excluded. Additionally, no publication bias was detected by Begg's test ( $z=0.600$ ,  $P=0.548$ ) and Egger's test ( $t=-0.440$ ,  $P=0.677$ ).

### **Association between PPI use and risk of severe disease for COVID-19 patients.**

The result of nine studies from eight original articles (7,9, 16-21) showed that PPI use was associated with increased risk of severe disease, including admission to ICU, intubation, and death, for COVID-19 patients ( $OR=1.67$ , 95% CI=1.37-2.02,  $P<0.001$ ;  $I^2=67\%$ ,  $P_{heterogeneity}=0.002$ ) (**Figure 3**). In subgroup analysis by study designs, a non-significant increased risk was observed in cohort studies ( $OR:1.39$ , 95%CI = 0.96-2.01,  $P=0.080$ ;  $I^2=65\%$ ,  $P_{heterogeneity} =0.060$ ), and a statistically significant increased risk was found for case-control studies ( $OR:1.86$ , 95%CI = 1.46-2.37,  $P=0.410$ ;  $I^2=56\%$ ,  $P_{heterogeneity} =0.040$ ). Regarding different geographic locations, increased risks were found in both western countries ( $OR:1.67$ , 95%CI = 1.33-2.09,  $P<0.001$ ;  $I^2=73\%$ ,  $P_{heterogeneity}=0.001$ ) and Asian countries ( $OR:1.75$ , 95%CI = 1.28-2.41,  $P<0.001$ ;  $I^2=0\%$ ,  $P_{heterogeneity} =0.420$ ). The same method as above was used for sensitivity analysis. The pooled OR has been fluctuating between 1.58 and 1.77 with lower limit of 95% CI constantly remained more than 1 and the  $P$  value has always been less than 0.05. On top of that, neither Begg's test ( $z=0.310$ ,  $P=0.754$ ) nor Egger's test ( $t=1.050$ ,  $P=0.327$ ) exhibited evidential publication bias.

### **Association between PPI use and mortality risk for COVID-19 patients**

The results indicated no association between PPI use and increased or decreased mortality risk for COVID-19 patients ( $OR=1.91$ , 95% CI=0.86-4.24,  $P=0.11$ ;  $I^2=73\%$ ,  $P_{heterogeneity} =0.030$ ) based on three included studies (7,11,17) (**Figure 4**). Significant

change in pooled OR and heterogeneity was found after excluding the article by Ullah et al (11). Furthermore, no publication bias was suspected when three relative studies emerged. (Begg's test ( $z=1.040$ ,  $P=0.296$ ) and Egger's test ( $t=1.78$ ,  $P=0.325$ ).

### **Association between PPI use and risk of secondary infection for COVID-19 patients**

Two articles (12,17) investigating PPI use and risk of secondary infection were found in the database, we combined them and found that PPI use was associated with an increased risk of secondary infection. ( $OR=4.33$ , 95% CI=2.57-7.29,  $P<0.001$ ;  $I^2=0\%$ ,  $P_{heterogeneity}=0.570$ ) (**Figure 5**). Since there were only two publications in this group, a test for publication bias and sensitive analysis were not performed.

### **Discussion**

Overall, this meta-analysis included a total of fourteen original studies. Two original studies from a previous meta-analysis by Li et al (22) were excluded as they did not meet our inclusion criteria. In the study conducted by Yan et al (23), the exposure for patients is acid-suppression drugs instead of PPI only, which may result in bias and obscure the result since acid-suppression drugs include not only PPIs proton pump but also other classes of medications, such as histamine receptor blockers. Moreover, Li et al (22) categorized Almitrine from the study conducted by Losser et al (24) as PPI, however, Almitrine is not PPI but a respiratory stimulant (25). We performed an analysis based on four different clinical outcomes. Firstly, PPI use is not linked to increased risk of COVID-19 infection, and subgroup analysis also found no increased

risk in cohort studies and case-control studies, as well as Asian countries and western countries. This means patients in the general population who are taking PPIs may not need to stop taking them for fear of an increased risk of COVID-19 infection, same as the conclusion of a previous meta-analysis (26). PPIs act through the inhibition of the hydrogen/potassium pump ( $H^+/K^+$ -ATPase pump) in the gastric parietal cells (27). However, this strong inhibition of gastric acid secretion increases the alkalinity of gastric juice, thereby reducing the protective effect on the gastrointestinal tract, which might potentially help SARS-CoV-2 survive in the stomach and infiltrate GI epithelial cells (4). Although the risk of transmission through gastrointestinal tract could not be ruled out (28), the most significant transmission route for SARS-CoV-2 is the respiratory route, including droplet transmission and aerosol transmission (29-30), which may temper the effects of PPI on the gastrointestinal tract in terms of COVID-19 infection. Therefore, we need to be prudent when interpreting the current result of COVID-19 infection risk for PPI users.

Secondly, a 67% increased risk of serious illness in COVID-19 patients, including ICU admission, intubation, and death, was found for PPI users. This is similar to the result of a previous meta-analysis that PPI was found to be associated with an increased risk of severe COVID-19. (31) Hence, the use of PPI should be carefully considered in patients infected with COVID-19, especially when prophylaxis for stress ulcers and gastrointestinal bleeding is needed for hospitalized patients. In subgroup analysis, the increased risk was found in both Asian countries and western countries, and was also observed in case-control studies, but in cohort studies, the increased risk was not

statistically significant. Heterogeneity was found in the subgroup of PPI use and risk of severe disease, which is likely due to the criteria for defining severe illness varied among the included articles, such as admission to ICU, endotracheal intubation, and death. Despite the increased risk of severe illness, it is noteworthy that, there is no connection between PPI use and higher or lower risk of death in COVID-19 patients. This implies that it may not be necessary to discontinue PPI for patients simply for concern of increased mortality. This is contrary to the conclusion drawn by Hariyanto et al.,(31) however one of the studies in their meta-analysis was excluded by us, because the eligible data should be for the endpoint of death only, but Hariyanto et al. extracted the data for the composite endpoint (admission to the intensive care unit, invasive ventilation, or death) from that study (9). However, in sensitivity analysis, the results of mortality changed significantly after exclusion of the study conducted by Ullah et al., suggesting it could be the source of the heterogeneity in this meta-analysis, as this study was conducted on patients with hepatobiliary and pancreatic disease instead of the general population, and that the ORs were not adjusted based on multivariate analyses (11), therefore, the result of mortality risk of COVID-19 for PPI users should be interpreted cautiously.

Lastly, the subsequent risk of secondary infections is increased with the use of PPI. As mentioned above, PPI suppresses acid secretion (27), and it has been shown that a decrease in gastric acid production may affect the gut microbial composition and increase the risk of intestinal infection (27,32), including *Clostridioides difficile*, *Salmonella*, *Campylobacter* infection (33,34). As previously reported, PPI use was also

associated with a greater risk of nosocomial pneumonia, especially in ICU patients, compared with histamine-2 receptor blockers (35). Therefore, we need to be more cautious to use PPI for COVID-19 patients who already have a high risk of secondary infection or who are immunocompromised. Nevertheless, only two original articles were included for assessing the risk of secondary infection, so the result needs to be interpreted with caution.

The inherent limitations of this study are as follows. First, although previous studies raised concerns that age (36) and comorbidities (37) might be on the course of COVID-19, more in-depth subgroup analyses could not be performed due to the lack of data. However, most of the studies we included also adjusted for these variables, providing a relatively reliable result. Second, only two studies were included for the subgroup of secondary infection. Despite some of these limitations, the strengths of this study must be mentioned: First, no obvious publication bias in our study was detected. Second, compared with the previous meta-analysis, we included more literature and have more comprehensive subgroup analyses on different outcomes (22,26,38).

In summary, although PPI use is not associated with increased risk of infection and may not change the mortality risk of COVID-19, it appeared to be associated with increased risk of progression to severe disease, and increased risk of secondary infection. However, original studies included were limited, therefore more original studies to further clarify the relationship between PPI and COVID-19 are still urgently needed.

### **Supportive foundations**

No funding sources for this work.

### **Conflicts of interests**

The authors declare no conflicts of interest.

## References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available from:  
<https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>.
2. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. (Accessed by 18/11/2020). Available from: <https://covid19.who.int>
3. Trottein F, Sokol H. Potential causes and consequences of gastrointestinal disorders during a SARS-CoV-2 infection. *Cell Rep.* 2020;32:107915.
4. Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology.* 2020;158: 1831-33.
5. Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: Systematic review and meta-analysis. *Gastroenterology.* 2020;159:81–95.
6. Taştemur Ş, Ataseven H. Is it possible to use Proton Pump Inhibitors in COVID-19 treatment and prophylaxis? *Medical hypotheses.* 2020;143:110018.
7. Ramachandran P, Perisetti A, Gajendran M, et al. Prehospitalization proton pump inhibitor (PPI) use and clinical outcomes in COVID-19. *medRxiv.* 2020.
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8:336-41.
9. Lee SW, Ha EK, Yeniova AÖ, et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity

- score matching. *Gut*. 2020;30:gutjnl-2020-322248.
10. Almario CV, Chey WD, Spiegel BMR. Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors. *Am J Gastroenterol*. 2020;115:1707-15.
11. Ullah A Z M D, Sivapalan L, Chelala C, et al. COVID-19 in patients with hepatobiliary and pancreatic diseases in East London: A single-centre cohort study. *medRxiv*. 2020.
12. Li J, Cao J, Cai P, et al. Risk Factors of Secondary Infections in Severe and Critical Patients Hospitalized with COVID-19: A Case-Control Study. 2020. *Research Square*.
13. Vila-Corcoles A, Satue-Gracia E, Ochoa-Gondar O, 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. *J Clin Hypertens (Greenwich)*. 2020: 10.1111/jch.13948.
14. Huh K, Ji W, Kang M, et al. Association of previous medications with the risk of COVID-19: a nationwide claims-based study from South Korea. *medRxiv*. 2020.
15. Tarlow B, Gubatan J, Khan MA, et al. Are Proton Pump Inhibitors Contributing to SARS-CoV-2 Infection? *Am J Gastroenterol*. 2020 Sep 11:10.14309/ajg.0000000000000933.
16. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. *BMJ*. 2020;369:m1996.
17. Luxenburger H, Sturm L, Biever P, 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? *J Intern Med.* 2020;10.1111/joim.13121.
18. McKeigue P M, Kennedy S, Weir A, et al. Associations of severe COVID-19 with polypharmacy in the REACT-SCOT case-control study. *medRxiv.* 2020.
19. Jimenez L, Codo A C, Sampaio V S, et al. The influence of pH on SARS-CoV-2 infection and COVID-19 severity. *MedRxiv.* 2020.
20. Cheung K S, Hung I F, Leung W K. Association between famotidine use and COVID-19 severity in Hong Kong: a territory-wide study. *Gastroenterology.* 2020 Jul 16:S0016-5085(20)34940-4.
21. Freedberg D E, Conigliaro J, Wang T C, et al. Famotidine Use Is Associated With Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study. *Gastroenterology.* 2020 ;159(3):1129-31.
22. Li GF, An XX, Yu Y, et al. Do proton pump inhibitors influence SARS-CoV-2 related outcomes? A meta-analysis. *Gut.* 2020 Nov.
23. Yan S, Song X, Lin F, et al. Clinical characteristics of coronavirus disease 2019 in Hainan, China. *medRxiv.* 2020.
24. Losser M R, Lapoix C, Delannoy M, et al. Almitrine as a non-ventilatory strategy to improve intrapulmonary shunt in COVID-19 patients. *Anaesth Crit Care Pain Med.* 2020 Aug;39(4):467-9.
25. Smith PD, Gotz VP, Ryerson GG. Almitrine bismesylate. *Drug Intell Clin Pharm.*

- 1987;21:417-21.
26. Fan X, Liu Z, Miyata T, et al. Effect of Acid Suppressants on the Risk of COVID-19: A Propensity Score-Matched Study Using UK Biobank. *Gastroenterology*. 2020;S0016-5085(20)35209-4.
27. Bruno G, Zaccari P, Rocco G, et al. Proton pump inhibitors and dysbiosis: Current knowledge and aspects to be clarified. *World J Gastroenterol* 2019; 25: 2706-19.
28. Peng X, Xu X, Li Y, et al. Transmission routes of 2019-nCoV and controls in dental practice. *Int J Oral Sci*. 2020;12:9.
29. Nissen K, Krambrich J, Akaberi D, et al. Long-distance airborne dispersal of SARS-CoV-2 in COVID-19 wards. *Sci Rep*. 2020;10:19589.
30. Tang S, Mao Y, Jones RM, et al. Aerosol transmission of SARS-CoV-2? Evidence, prevention and control. *Environ Int*. 2020;144:106039.
31. Hariyanto TI, Prasetya IB, Kurniawan A. Proton pump inhibitor use is associated with increased risk of severity and mortality from coronavirus disease 2019 (COVID-19) infection. *Dig Liver Dis*. 2020;52:1410-2.
32. Lombardo L, Foti M, Ruggia O, et al. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. *Clin Gastroenterol Hepatol*. 2010;8:504-8.
33. MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. *JAMA Intern Med*. 2014;174:564-74.
34. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut

- microbiome. *Gut*. 2016;6:740-88.
35. PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group, et al. Effect of Stress Ulcer Prophylaxis With Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation: The PEPTIC Randomized Clinical Trial. *JAMA*. 2020;323:616-26.
36. Zhang XY, Zhang L, Zhao Y, Chen L. Risk Assessment and Prediction of Severe or Critical COVID-19 Illness in Older Adults. *Clin Interv Aging*. 2020;15:2145-53.
37. Zhang XY, Li T, Wu H, Ling Y, Qian ZP, Chen L. Analysis of the Effect of Proton-Pump Inhibitors on the Course of COVID-19. *J Inflamm Res*. 2021;14:287-98.
38. Kow CS, Hasan SS. Use of proton pump inhibitors and risk of adverse clinical outcomes from COVID-19: a meta-analysis. *J Intern Med*. 2020.

### Figure legends

Figure 1. PRISMA Flow Chart

Figure 2. Forest plot: Association between PPI use and risk of COVID-19 infection

Figure 3. Forest plot: Association between PPI use and risk of severe disease for COVID-19 patients.

Figure 4. Forest plot: Association between PPI use and mortality risk for COVID-19 patients

Figure 5. Forest plot: Association between PPI use and risk of secondary infection for COVID-19 patients

**Table 1. Main characteristics of studies included in this meta-analysis**

First Author	Year	Country	Study design	Outcomes	PPI use	Non-PPI use	NOS
					n (%)	n (%)	score
Almario	2020	America	Case-control	Morbidity;	16547	36583	7
Argenziano	2020	America	Case-control	Severity;	163	837	8
Cheung	2020	China	Cohort	Severity;	4	47	9
Corcoles	2020	Spain	Cohort	Morbidity;	99	11708	8
Freedberg	2020	America	Cohort	Severity;	N/A	N/A	8
Huh	2020	South Korea	Case-control	Morbidity;	660	14167	8
Jimenez	2020	Brazil	Cohort	Severity;	N/A	N/A	6
Lee	2020	Korean	Cohort	Morbidity; Severity;	20405	111911	8
Li	2020	China	Case-control	Morbidity; Infection;	95	143	8
Luxenburger	2020	Germany	Case-control	Severity; Mortality; Infection;	62	90	7
McKeigue	2020	Britain	Case-control	Severity;	2378	34013	8
Ramachandran	2020	America	Cohort	Severity; Mortality;	46	249	7
Tarlow	2020	America	Case-control	Morbidity;	355	2535	6
Ullah	2020	Britain	Cohort	Morbidity; Mortality;	5908	9678	8

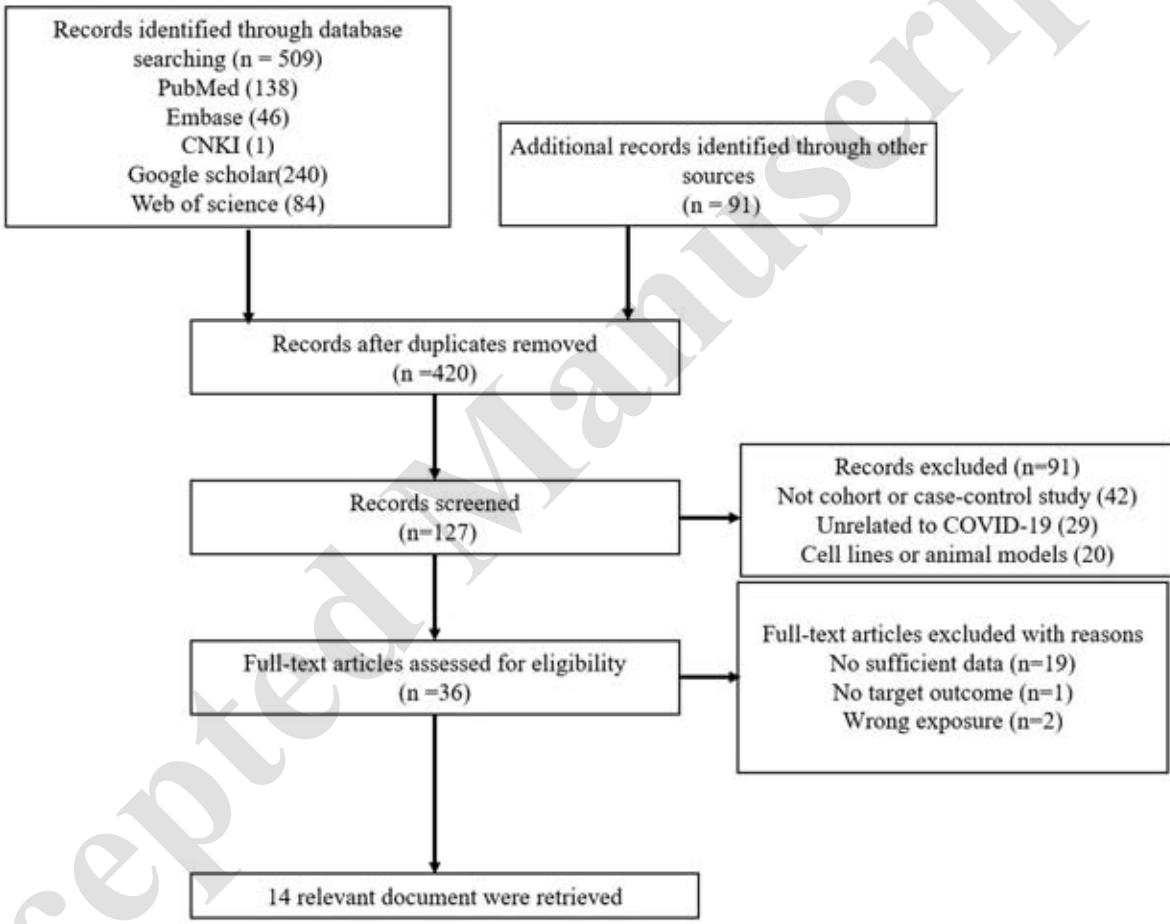
N/A: Not applicable

**Identification**

**Screening**

**Eligibility**

**Included**



Study or Subgroup	log(Odds Ratio)	SE	Weight	Odds Ratio	IV, Random, 95% CI
				IV, Random, 95% CI	
Almario et al.	2.1995	0.0425	14.4%	9.02 [8.30, 9.80]	
Corcoles et al.	0.0862	0.1578	14.3%	1.09 [0.80, 1.49]	
Huh et al.	-0.478	0.0429	14.4%	0.62 [0.57, 0.67]	
Lee et al.	-0.1054	0.073	14.4%	0.90 [0.78, 1.04]	
Li et al.	1.9881	0.3491	13.7%	7.30 [3.68, 14.47]	
Tarlow et al.	-0.734	0.1059	14.4%	0.48 [0.39, 0.59]	
Ullah et al.	0.5581	0.1384	14.3%	1.75 [1.33, 2.29]	
<b>Total (95% CI)</b>			<b>100.0%</b>	<b>1.64 [0.54, 5.00]</b>	

Heterogeneity:  $\tau^2 = 2.24$ ;  $\chi^2 = 2325.47$ ,  $df = 6$  ( $P < 0.00001$ );  $I^2 = 100\%$

Test for overall effect:  $Z = 0.87$  ( $P = 0.39$ )

