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Different Outcome in COVID-19 Patients with or without PPI Use: A Systematic Review and Meta-analysis

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Abstract

Background The coronavirus disease (COVID-19) pandemic still happening and when it's going to be resolved is not known. In this COVID-19 era, physicians need to better understand the risk and purpose of giving drugs that patients do not need. Proton pump inhibitors (PPI) are sometimes easily prescribed and misused by physicians. The study objective is to find out whether PPI use is associated with better or worse outcomes in patients with COVID-19.

Method We searched retrospective studies in various publication libraries like PubMed, Embase, and CENTRAL from 2020 to 2022. Inclusion criteria were studied which differentiated patients with COVID-19 who regularly used PPI and control which is COVID-19 patients who did not use PPI. That study also needs to report the outcomes. The outcome was then divided into two categories which are good outcomes and worse outcomes consisting of severe COVID-19 needing oxygen therapy, admission to intensive care unit (ICU), acute respiratory distress syndrome (ARDS), shock or mortality, to get each study and total odd ratio (OR), 95% confidence interval, and weight. Studies that did not report the outcomes were excluded. We also analyze the data using a fixed or random effect model accordingly and asses the possibility of publication bias using Egger's test.

Case Seven of 11 studies with more than 30.000 COVID-19 patients were analyzed in this study. These patients were divided into 2 groups: patients with COVID-19 who were using PPI up to 30 days before being infected and COVID-19 patients who didn't use PPI before. The total number of patients in the first group is 3531 patients and the second group is 38138 patients. After statistical analysis, we found that the data is heterogenous with p <0,05, I2 94,22% (95%CI 90,44-96,51%) suggesting the OR needs to be determined in the random effect model. We found that pooled OR is 1.99 (p 0.01, 95% CI, 1.18-3.38). Egger's test for the possibility of publication bias is 0,64 (95%CI -7,24-4,93).

Conclusion COVID-19 patients who use PPI are twice as likely to have a worse outcome than COVID-19 patients who don't use PPI. This study is statistically significant with a low possibility of publication bias.

Keywords: PPI; COVID-19; meta-analysis

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has destroyed healthcare systems where hospitals are overloaded with COVID-19 patients and mortality all over the world. COVID-19 is a highly contagious disease with symptoms varying from fever, nausea, and vomiting to abdominal pain.[1] Some cases of COVID-19 progress to severe conditions with poor prognosis, whereas other cases are mild and often asymptomatic.[2] Risk factors for COVID-19 progression to severe conditions are still poorly understood.

Proton pump inhibitors (PPI) are one of the most prescribed drugs in the world. PPI is commonly prescribed for patients with gastrointestinal symptoms like nausea, vomiting, epigastric pain, and other acid-related disease.[3] Research conducted on the population of Lebanon found that 71.4% of the population overused PPIs (59.2% overused the indication, 22.1% overused the duration, and 18.7% overused the dosage). Proton pump inhibitors (PPIs) attach permanently to the parietal cell's H+/K+ ATPase active site to prevent the generation of gastric acid. PPIs have been connected to several conditions, including gut dysbiosis, a higher risk of GI infections, community-acquired pneumonia, and a higher death rate from chronic renal disease or

cardiovascular disease. PPIs increase stomach pH, which may help spread SARS-CoV-2, but bacterial pneumonia or other GI-derived illnesses can make COVID-19 more difficult to treat clinically. Recently, a study reported that PPI use is associated with COVID-19 patients having more severe disease than those who never use PPI.[4] Similar studies also reported that PPI use is associated with poor outcomes in COVID-19 patients.[5]

This study aims to find out whether PPI users have worse outcomes than those who didn't. We hypothesized that PPI is associated with worse clinical outcomes in COVID-19 patients. To prove our hypothesis, we use systematic review and meta -analysis as tools for confirmation.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist were used as guidelines for conducting this systematic review and meta-analysis.[6,7]

Literature search strategy

An extensive search was conducted on publication libraries such as PubMed, Embase, and Cochrane library using keywords "proton pump inhibitor", "PPI', "omeprazole", "pantoprazole", "lansoprazole", "esomeprazole", "rabeprazole", "COVID-19", "coronavirus disease 2019", and "outcome" from earliest of 2020 to the latest 2021. Retrospective cohort and case-control study are sources of data in this meta-analysis because to this date there is no randomized clinical trial that assessed the risk of PPI use in COVID-19 patients. There are no language preferences in our search.

Study selection and eligibility criteria

Two authors (IMWW, and SLD) evaluated the search results to find out whether the articles were eligible to be included in the meta-analysis. Any disagreement about the articles is discussed between these two authors and resolved by either including or excluding the articles in the meta-analysis. Inclusion criteria that required to be fulfilled: (1) retrospective study either cohort, cross -sectional or case-control, (2) COVID-19 patients with current or history of PPI use, COVID-19 patients that did not use PPI is used as control group, (3) reported outcome of the COVID-19 patients which then group into 2 categories, worse or better clinical outcome. Studies that met these criteria are excluded: (1) case report, case series, or review article, (2) did not have information about the non-PPI user to be used as control group, or only have COVID-19 patients with current or history of PPI use, (3) did not report the outcome of the COVID-19 patients, and (4) did not have sufficient data to be analyzed in meta-analysis.

Data extraction and quality assessment

All studies that met the inclusion criteria were extracted to acquire needed data in meta-analysis. Data that were extracted were the last name of the first author, year of publication, location of the study, design of the study, period of the study, total participants for case and control, and clinical outcome of each group. Data was collected in an SPSS sheet to make analysis easier. Problems found in this process were assessed accordingly by both authors.

Newcastle-Ottawa Scale (NOS) which consists of selection, comparability, and outcome categories were used to evaluate the quality of each study.[8] NOS was a tool used to assess the quality of non-randomized studies like cohort or case-control in a systematic review and/or meta-analysis. NOS used stars as a scoring system where the total score of seven or more stars is considered a high-quality study.

Statistical analysis

Statistical analysis was evaluated after we concluded whether the study was heterogeneous or homogenous. The heterogeneity of the study was assessed according to the Cochrane review by I^2 and *p-value*. The study considered heterogenous if $I^2 > 50\%$ or *p-value* < 0.1 among studies. The heterogeneity test was calculated using Review Manager 5.3 software. The fixed effect model or random effect model was chosen according to the heterogeneity of this study, as it's going to impact the weight of each study. Statistical analysis was also done using the same software with a weighted odd ratio (OR) and 95% confidence interval (95% CI) as a result. In this meta-analysis, all *p* values were 2-tailed with a value < 0.05 considered as statistically significant.

The forest plot of each comparison will be reported which also includes pooled OR and its 95%CI. Publication bias was evaluated using MedCalc software. Egger's test was chosen as the tool to assess the risk of publication bias. In this study, a *p-value* of Egger's test < 0.05 is considered a high probability of publication bias.

Results and Discussion

Study characteristics

This meta-analysis includes 7 studies, which consist of 1 case-control, 1 cross-sectional and 5 cohort.[4,5,9,10,11,12,13] Initially, we tried to find a randomized clinical trial (RCT) to be included in this meta-analysis but we were unable to find any study. A flow diagram of the study selection process for meta-analysis is shown below (figure 1). We identified 97 potential studies from searching online publication libraries. Upon examination, we found 40 studies were duplicated and 36 studies were removed by the automation tool leaving only 21 studies. This study was then screened and sought for retrieval for eligibility. At the end of the selection, only 7 studies were included in the meta-analysis. Studies included in

the meta-analysis are summarized in Table 1.

PPI versus no PPI in COVID-19 patients

The total number of COVID-19 cases in this meta-analysis was 41,669 patients which were divided into two groups, COVID-19 cases that received PPI were 3,531 patients and COVID-19 cases that didn't receive PPI (no PPI) 38,138 patients. The definition of PPI used in this meta-analysis was different in each study. One study did not state the definition of PPI use. In contrast, other studies varied from active PPI use at home by the time of admission, PPI use at hospitalization, PPI prescribed up to 1 year before admission, and prescription of PPI up to 3 times in 2 years. As definition of no PPI also varied by each study, from never really using PPI to less than three prescriptions in 2 years.

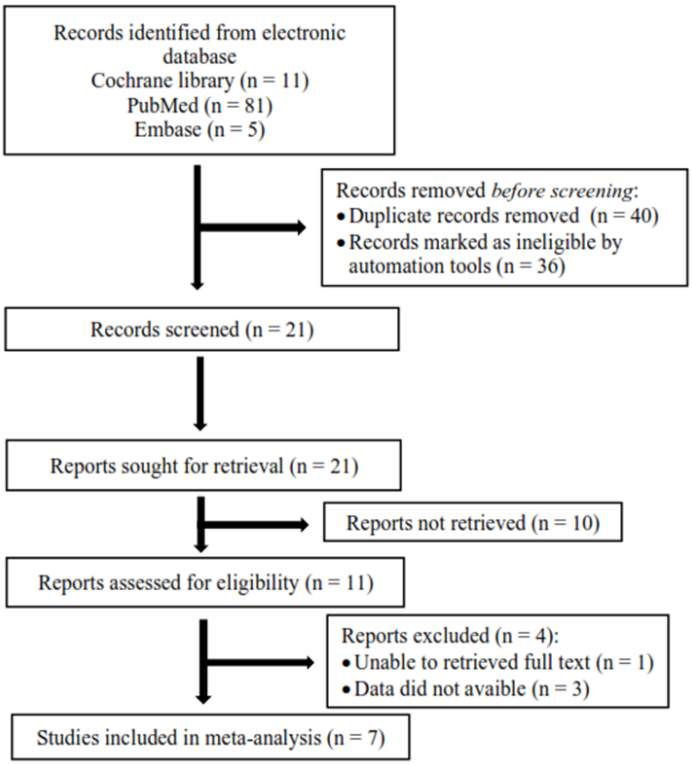

Figure 1. Flow diagram of study selection for the meta-analysis

In this meta-analysis, the clinical outcome that was reported by each study was grouped into worse and better outcomes. The worse outcome was admission to the intensive care unit (ICU), progression to acute respiratory distress syndrome (ARDS), and death. The better outcome was the opposite of the worse outcome. Worse outcomes and total events in each study group were inputted in review manager 5.3 to acquire the information of OR with 95%CI, to determine whether PPI would decrease or increase the odds of COVID-19 patients having worse outcomes.

Table 1. Included study general characteristic

References	Country	Period (2020)	Design	Participants
Luxenburger et al. (2021)	Germany	Not described	Cohort	62/90
Ullah et al. (2020)	UK	Feb 12 - Jun 12	Cross-sectional	91/62
Ramachandran et al. (2020)	USA	Mar 1 - Apr 15	Cohort	46/249
Lee et al. (2020)	South Korea	Jan 1 - May 15	Cohort	267/267
Argenziano et al. (2020)	USA	Mar 1 - Apr 5	Cohort	163/837
Zhou et al. (2020)	China	Jan 1 - Aug 22	Cohort	524/2620
McKeigue et al (2020)	UK	Jun 6 - 14	Case-control	2378/34013

A forest plot was generated after putting data into Review Manager 5.3. Test of heterogeneity results are $I^2 = 94\%$ and $p < 0.01$ which means this meta-analysis is heterogenous and a random effect model needs to be used to get the correct weighted OR for each study. Pooled OR also needs to be reported according to the random effect model. Two studies showed that there is no difference

between PPI and no PPI group in terms of worse outcomes. That was a study from Ullah et al. with OR 1.33 (95% CI, 0.66-2.66), and Argenziano et al. with OR 0.98 (95% CI, 0.66-1.46). Both studies' 95% CI crossed the line of no difference in the OR study according to the Mantel-Haenszel method. The rest of these studies consistently show that no PPI decrease the risk of having a worse outcome in COVID-19 patients. Pooled OR for risk of worse outcome result is 1.99 (*p* 0.01, 95% CI, 1.18-3.38), which means no PPI decrease the risk of worse outcome by 99% than COVID-19 patients that use PPI. This also means that COVID-19 patients who use PPI had an increased risk of worse outcomes twofold.

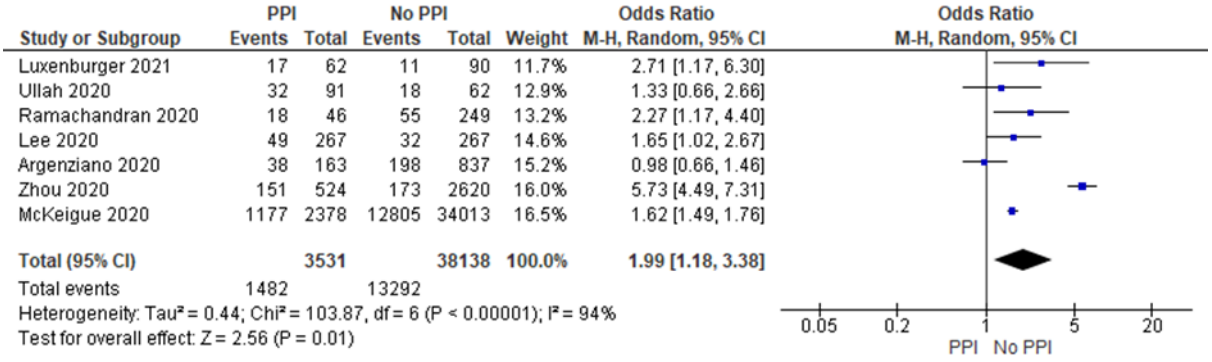

Figure 2. Forest plot of comparison between PPI vs no PPI in COVID-19 Patients

Publication bias

This meta-analysis produced an asymmetric funnel plot. These could be explained by the heterogeneous origin of this study, not because of publication bias. Egger's test confirmed that this meta-analysis did not have significant publication bias with *p* 0.64.

Discussion

PPI use has been known to be associated with an increased risk of getting pneumonia.[14] The pathophysiology, however, is still not well established yet.[15] Several mechanisms that were proposed included impaired immune system and increased alkalinity of the stomach. PPI impairs immune cells like natural killer cells, T cytotoxic, and neutrophils, that responsible for keeping bacterial activity under control in the respiratory tract.[16] PPI suppressed acid production in the stomach causing hypochlorhydria and diminishing the protective property of gastric acid.[17]

Israelson et al.'s 2020 meta-analysis revealed that PPI raised the chance of contracting COVID-19.[18] Pranta et al.'s 2021 update to this investigation showed no conclusive link between PPI use and COVID-19 vulnerability.[19] The assumption that using PPIs is linked to a marginally higher risk of contracting COVID-19 is supported by the current meta-analysis. In this meta-analysis, we found that PPI use is associated with an increase in the risk of worse outcomes in COVID-19 patients. Hariyanto et al. reported that the use of PPI in COVID-19 patients enhanced the risk of more severe illness and mortality, with a pooled risk ratio (RR) of 1.72 (p 0.04, 95% CI, 1.02-2.89) and 1.35 (p 0.003, 95% CI, 1.11-1.63) respectively.[20]

Regarding the relationship between PPIs and COVID-19 outcomes, recent research has shown contradictory findings. The Korean Nationwide Cohort Study, which Lee et al. performed with a sample size of 234,427 patients, was one of the earliest and largest studies investigating the connection. The use of PPIs raised the chance of severe COVID-19 infection but did not increase susceptibility to SARSCo-2 infection, according to the study's overall findings.[21] These results are not to be taken at face value. Several things need to be considered in this meta-analysis. First is the design of each study that was included, which was retrospective with each complexity level. COVID-19 patients in each study have different severity, comorbidity, polypharmacy, and background. This heterogenous nature needs to be interpreted cautiously. Adjustments are also being made in each study, which going to impact the result.

Limitations

There are several limitations in this meta-analysis. This meta-analysis needs to be interpreted cautiously because of the heterogeneity of the studies. The heterogeneity in the data can be attributed to a variety of methodological differences, including the degree of COVID-19 infection, the population's age and gender, the severity of the infection, and the wide range of comorbidities. The lack of RCT study also has to be taken into consideration.

Conclusion

PPI use is associated with an increased risk of worse outcomes in COVID-19 patients. However, to confirm our result several RCTs addressed specifically to these problems need to be done. For now, physicians need to prescribe PPI with clear indications to decrease the risk of worse outcomes

in COVID-19 patients.

Author contributions

IMWW write the full text, IMWW and SLD search the online publication library and review all related articles, IMWW and SLD make the meta-analysis. All authors review the full text.

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None

Conflict of interest

None to be disclosed

References

1. Johnson KD, Harris C, Cain JK, Hummer C, Goyal H, Perisetti A. pulmonary and extra-pulmonary clinical manifestations of COVID-19. Front Med (Lausanne) 2020; 7:526.
2. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
3. Xie Y, Bowe B, Yan Y, et al. Estimates of all-cause mortality and cause-specific mortality associated with proton pump inhibitors among US veterans: cohort study. BMJ 2019;365:l1580.
4. Lee SW, Ha EK, Yeniova AO, Moon SY, Kim SY, et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. Gut 2021;70:76–84. doi:10.1136/gutjnl-2020-322248.
5. Luxenburger H, Sturm L, Biever P, Rieg S, Duerschmied D, 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? JIM 2021; 289;121-124.
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W-65–94.
7. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283:2008–12.
8. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2000.
9. Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ 2020;369:m1996.
10. Zhou J, Wang X, Lee S, et al. Proton pump inhibitor or famotidine use and severe COVID-19 disease: a propensity score- matched territory-wide study. Gut Epub ahead of print: [12 March 2021]. doi:10.1136/gutjnl-2020-323668
11. McKeigue PM, Kennedy S, Weir A, Bishop J, McGurnaghan SJ, McAllister D, et al. Associations of severe COVID-19 with polypharmacy in the REACT-SCOT case-control study. medRxiv 2020.07.23.20160747. doi.org/10.1101/2020.07.23.20160747
12. Ullah AZMD, Sivapalan L, Kocher HM, Chelala C. COVID-19 in patients with hepatobiliary and pancreatic diseases: A single-centre cross-sectional study in East London. Pancreatology 2020;20;e15.
13. Ramachandran P, Perisetti A, Gajendran M, Jean-Loius F, Bansal P, et al. Pre-hospitalization proton pump inhibitor use and clinical outcomes in COVID-19. medRxiv. 2020. doi: 10.1101/2020.07.12.20151084.
14. Nguyen PA, Islam M, Galvin CJ, Chang CC, An SY, Yang HC, et al. Meta-analysis of proton pump inhibitors induced risk of community-acquired pneumonia. International Journal for Quality in Health Care, 2020, 32(5), 292–299. doi: 10.1093/intqhc/mzaa041
15. Dial MS. Proton pump inhibitor use and enteric infections. Am J Gastroenterol 2009;104:S10–S6.
16. Laheij RJF, Sturkenboom MCJM, Hassing R- J, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004;292:1955–60.
17. Buendgens L, Bruensing J, Matthes M, Dückers H, Luedde T, Trautwein C, et al. The administration of proton pump inhibitors in critically ill medical patients is associated with an increased risk of developing Clostridium difficile-associated diarrhoea. J Crit Care 2014; 29:696.e11–696.e15.
18. Israelsen S.B., Ernst M.T., Lundh A., Lundbo L.F., Sandholdt H., Hallas J., Benfield T. Proton Pump Inhibitor Use Is Not Strongly Associated With SARS -CoV-2 Related Outcomes: A Nationwide Study and Meta-analysis. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 2021;19:1845–1854.e6.
19. Pranata R., Huang I., Lawrensia S., Henrina J., Lim M.A., Lukito A.A., Kuswardhani R.A.T., Wibawa I.D.N. Proton pump inhibitor on susceptibility to COVID-19 and its severity: A systematic review and meta-analysis. Pharmacol. Rep. 2021;73:1642–1649. doi: 10.1007/s43440-021-00263-x.
20. 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. Digestive and liver disease 2020;52;1410-1412.
21. Lee, S. W., Ha, E.K., Yeniova, A. Ö., et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. GUT 0: 1–9 (2020).