Original Article

Does Proton Pump Inhibitor Use Lead to a Higher Risk of Coronavirus Disease 2019 Infection and Progression to Severe Disease? a Meta-analysis

Cunye Yan^{1†}, Yue Chen^{2†}, Chenyu Sun^{3*}, Mubashir Ayaz Ahmed³, Chandur Bhan³, Zhichun Guo⁴, Hongru Yang⁴, Yijing Zuo⁴, Yue Yan⁴, Lei Hu², Yiceng Sun¹, Yao Li¹, and Qin Zhou⁵

¹Department of Breast and Thyroid Surgery, Chongqing General Hospital, University of Chinese Academy of Sciences, Chongqing; ²Department of Clinical Medicine, School of the First Clinical Medicine, Anhui Medical University, Anhui, P.R. China; ³AMITA Health Saint Joseph Hospital Chicago, Chicago, IL; ⁴Massachusetts College of Pharmacy and Health Sciences, Boston, MA; and ⁵Radiation Oncology, Mayo Clinic, Rochester, MN, USA

ABSTRACT: The findings of previous research on the association between proton pump inhibitor (PPI) use and the treatment and prevention of coronavirus disease 2019 (COVID-19) are inconsistent. Therefore, this meta-analysis was conducted to clarify the outcomes of patients taking PPIs. This analysis included 14 articles with more than 268,683 subjects. PPI use was not associated with increased or decreased risk of COVID-19 infection (odds ratio [OR] 1.64, 95% confidence interval [CI] = 0.54–5.00, $P = 0.39$) or mortality (OR = 1.91, 95% CI = 0.86–4.24, $P = 0.11$). However, PPI use increased the risks of severe disease (OR 1.67, 95% CI = 1.37–2.02, $P < 0.00001$) and secondary infection (OR 4.62, 95% CI = 2.55–8.39, $P < 0.00001$). In summary, PPI use was not associated with an increased risk of infection and mortality in COVID-19 but appeared to be associated with an increased risk of progression to severe disease and secondary infection. However, more original studies are urgently needed to further clarify the relationship between PPI use and COVID-19.

INTRODUCTION

In March 2020, the World Health Organization (WHO) pronounced coronavirus disease 2019 (COVID-19) as a pandemic (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 due to the disease (2) and the pandemic is not yet under control. This global pandemic has seriously affected public health and socioeconomic development worldwide. Therefore, it is of great significance to identify the risk factors and proper treatment modalities for COVID-19.

Previous studies demonstrated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, enters the human body through the respiratory and gastrointestinal systems (3). The virus can rapidly invade and replicate intestinal cells using the angiotensin-converting enzyme-2 receptor,

which is widely expressed in the gastrointestinal tract (4). Nearly half of patients with COVID-19 have viral RNA in their feces (5). These results suggest 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 drugs for acid suppression, proton pump inhibitors (PPIs), and COVID-19 infection. While PPIs have been postulated to be beneficial in COVID-19 treatment and prevention (6), other studies have suggested that PPI could potentially aggravate the condition of patients with COVID-19, leading to increased mortality (7). Owing to these controversial conclusions, we conducted this meta-analysis to further explore the relationship between PPI use and COVID-19, with more detailed subgroup analyses of different outcome indexes.

METHODS

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

Literature search strategy: Articles were collected through November 2020 from the PubMed, Google Scholar, Embase, medRxiv, Web of Science, CNKI,

Received February 10, 2021. Accepted April 27, 2021.
J-STAGE Advance Publication May 31, 2021.
DOI: 10.7883/yoken.JJID.2021.074

*Corresponding author: Mailing address: AMITA Health Saint Joseph Hospital Chicago, 2900 N. Lake Shore Drive, Chicago, IL 60657, USA. Tel: +1-828-372-4658, Fax: +1-828-372-4658, E-mail: drsunchenyu@yeah.net

†These authors contributed equally to this work.

Wanfang, and VIP databases. 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"). The reference lists of the retrieved articles were also reviewed to identify additional eligible studies.

Identification of eligible studies: Two authors (C. Yan and C. Sun) independently performed the search and resolved disagreements by consensus. The abstracts of the retrieved studies were initially reviewed and excluded if deemed irrelevant. The full texts of the relevant studies were reviewed for eligibility. If there were duplicate publications from the same study, the one with the most detailed information and complete data was included.

The studies included in this meta-analysis met all of the following criteria: (i) Either randomized controlled trials or observational studies (including cohort and case-control studies). (ii) The research was conducted to investigate COVID-19 outcomes, including infection risk, progression to severe cases, death, and the risk of secondary infection. (iii) PPI use was the exposure for the experimental group, and any feasible intervention without PPI use could be implemented in the control group. (iv) Relative risk (RR), hazard ratio (HR), or odds ratio (OR) with corresponding 95% confidence intervals (CIs) were extracted or recalculated. (v) The studies were published in English or Chinese. The exclusion criteria were: (i) An article type that could not be accurately determined. (ii) No valid account of the ending data could be derived from this article. (iii) Duplicate articles. (iv) Reviews, case reports, animal studies, and in vitro studies

Data extraction and quality evaluation. Each of the 2 authors (C. Yan and C. Sun) independently extracted the data from the literature. If discrepancies arose, a consensus was reached by consulting a third person (Y. Chen), with comprehensive comparison of the data and through conferral. The following information was collected: first author, publication year, country, study design, research outcome, Newcastle-Ottawa Scale (NOS) scores, number of cases and controls, and ORs with corresponding 95% CIs.

The methodological quality of the observational studies was appraised using the validated NOS based on 3 broad subscales including study group selection (0–4 points), group comparability (0–2 points), and exposure and outcome elucidation (0–3 points). A total score of 4–6 points was considered moderate, while a score of 7 or more was defined as high quality. Two evaluators (C. Yan and Y. Chen) independently conducted the quality assessment. Divergences of opinion were resolved by mutual communication.

Statistical analysis and evaluation of publication bias: Review Manager (RevMa) software (version 5.3; Cochrane Library) and STATA statistical software (version 14.0; StataCorp, College Station, TX, USA) were used to perform the statistical analyses. The associations between PPI use and the risk of COVID-19

infection; progression to severe disease and death; and risk of secondary infection were analyzed by pooling the ORs and corresponding 95% CIs.

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

RESULTS

Study selection and characteristics: Figure 1 outlines the inclusion process. The electronic search finally identified 600 records. After eliminating duplicate literature and screening titles and abstracts, we selected 127 potentially relevant articles for further screening, among which 36 full-text articles were assessed for eligibility. Nineteen of these articles lacked sufficient data, one article had no target outcomes, and the exposure of 2 articles was not PPI use. Finally, we identified 14 articles published through November 2020, comprising more than 268,683 subjects, including 7 cohort studies and 7 case-control studies. The detailed characteristics of the included studies are presented in Table 1. All studies were of moderate or high quality.

Meta-analysis: Association between PPI use and the risk of COVID-19 infection: Analysis of 7 studies (9–15) on the risk of COVID-19 infection found that PPI use was not associated with increased or decreased risks of COVID-19 infection (OR 1.64, 95%CI = 0.54–5.00, $P = 0.390$; $I^2 = 100\%$; $P_{\text{heterogeneity}} < 0.00001$) (Fig. 2). The subgroup analysis by study design showed no statistically significant associations in the cohort (OR 1.19, 95%CI = 0.79–1.79, $P = 0.420$; $I^2 = 89\%$, $P_{\text{heterogeneity}} = 0.001$) and case-control studies (OR 2.08, 95%CI = 0.36–12.13, $P = 0.410$; $I^2 = 100\%$, $P_{\text{heterogeneity}} < 0.001$). Regarding different geographic location, no statistically significant associations were observed in Western (OR 1.70, 95%CI = 0.33–8.67, $P = 0.520$; $I^2 = 100\%$, $P_{\text{heterogeneity}} < 0.001$) and Asian (OR 1.30, 95%CI = 0.74–2.29, $P = 0.360$; $I^2 = 97\%$, $P_{\text{heterogeneity}} < 0.001$) countries. The sensitivity analysis, in which studies were omitted one by one, showed that the combined results did not change significantly when any of the articles were excluded. Additionally, no publication bias was detected by Begg's ($z = 0.600$, $P = 0.548$) and Egger's ($t = -0.440$, $P = 0.677$) tests.

Association between PPI use and the risk of severe disease in patients with COVID-19: The results of 9 studies from 8 original articles (7,9,16–21) showed that PPI use was associated with an increased risk of severe disease, including admission to the intensive care unit, intubation, and death, in patients with COVID-19 (OR 1.67, 95% CI = 1.37–2.02, $P < 0.00001$; $I^2 = 67\%$, $P_{\text{heterogeneity}} = 0.002$) (Fig. 3). In subgroup analysis by study design revealed a non-significant increased risk in cohort studies (OR 1.39, 95%CI = 0.96–2.01, $P =$

Fig. 1. (Color online) Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

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

First author	Year	Country	Study design	Outcome	PPI use <i>n</i>	Non-PPI use <i>n</i>	NOS score
Almario	2020	America	Case-control	Morbidity;	16,547	36,583	7
Argenziano	2020	America	Case-control	Severity;	163	837	8
Cheung	2020	China	Cohort	Severity;	4	47	9
Corcoles	2020	Spain	Cohort	Morbidity;	99	11,708	8
Freedberg	2020	America	Cohort	Severity;	N/A	N/A	8
Huh	2020	South Korea	Case-control	Morbidity;	660	14,167	8
Jimenez	2020	Brazil	Cohort	Severity;	N/A	N/A	6
Lee	2020	Korean	Cohort	Morbidity; Severity;	20,405	111,911	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;	2,378	34,013	8
Ramachandran	2020	America	Cohort	Severity; Mortality;	46	249	7
Tarlow	2020	America	Case-control	Morbidity;	355	2,535	6
Ullah	2020	Britain	Cohort	Morbidity; Mortality;	5,908	9,678	8

PPI, proton pump inhibitor; N/A, not applicable; NOS, Newcastle-Ottawa Scale.

0.080; $I^2 = 65\%$, $P_{\text{heterogeneity}} = 0.060$), and a significantly increased risk in case-control studies (OR 1.86, 95%CI = 1.46–2.37, $P = 0.410$; $I^2 = 56\%$, $P_{\text{heterogeneity}} = 0.040$). Regarding geographic locations, increased risks were observed in both Western (OR 1.67, 95%CI = 1.33–2.09, $P < 0.001$; $I^2 = 73\%$, $P_{\text{heterogeneity}} = 0.001$) and Asian (OR 1.75, 95%CI = 1.28–2.41, $P < 0.001$; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.420$) countries. The same method was used for the sensitivity analysis. The pooled OR fluctuated between 1.58 and 1.77, with a lower limit of 95% CI that remained above 1 and with P -values < 0.05 . In addition, neither Begg's ($z = 0.310$, $P = 0.754$) nor Egger's ($t =$

1.050, $P = 0.327$) tests showed evidence of publication bias.

Association between PPI use and mortality risk in patients with COVID-19: We observed no association between PPI use and increased or decreased mortality risk in patients with COVID-19 (OR 1.91, 95% CI = 0.86–4.24, $P = 0.11$; $I^2 = 73\%$, $P_{\text{heterogeneity}} = 0.030$) based on 3 included studies (7,11,17) (Fig. 4). A significant change in the pooled OR and heterogeneity was observed after excluding the article by Ullah et al. (11). Furthermore, no publication bias was shown for these 3 studies (Begg's test: $z = 1.040$, $P = 0.296$; Egger's test: $t =$

Fig. 2. (Color online) Forest plot: association between PPI use and risk of COVID-19 infection

Fig. 3. (Color online) Forest plot: association between PPI use and risk of severe disease for COVID-19 patients.

Fig. 4. (Color online) Forest plot: association between PPI use and mortality risk for COVID-19 patients

Fig. 5. (Color online) Forest plot: association between PPI use and risk of secondary infection for COVID-19 patients

= 1.78, $P = 0.325$).

Association between PPI use and the risk of secondary infection in patients with COVID-19. Analysis of 2 articles (12,17) investigating PPI use and the risk of secondary infection showed that PPI use was associated with an increased risk of secondary infection (OR 4.62, 95% CI = 2.55–8.39, $P < 0.00001$; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.69$) (Fig. 5). As there were only 2 publications in this group, a test for publication bias and

sensitivity analysis were not performed.

DISCUSSION

This meta-analysis included a total of 14 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 by Yan et al. (23), the exposure for patients was acid-suppression

drugs instead of PPI only, which may have resulted in bias and obscured the results since acid-suppression drugs include not only PPIs 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 a PPI; however, almitrine is not a PPI but rather a respiratory stimulant (25). We performed an analysis based on 4 different clinical outcomes. First, PPI use was not linked to an increased risk of COVID-19 infection, and subgroup analysis also showed no increased risks in cohort and case-control studies, or in Asian and Western countries. Thus, 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, similar to the conclusion of a previous meta-analysis (26). PPIs act by inhibiting the hydrogen/potassium pump (H⁺/K⁺-ATPase pump) in 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 to survive in the stomach and infiltrate epithelial cells of the gastrointestinal tract (4). Although the risk of transmission through the gastrointestinal tract could not be ruled out (28), the respiratory route for SARS-CoV-2 is the most significant transmission route, including droplet and aerosol transmission (29–30), which may affect the effects of PPI on the gastrointestinal tract in terms of COVID-19 infection. Therefore, we need to be prudent when interpreting the current results of infection risks for COVID-19 among PPI users.

Second, a 67% increased risk of serious illness in COVID-19 patients, including ICU admission, intubation, and death, was observed in PPI users. This is similar to the results of a previous meta-analysis in which PPI was associated with an increased risk of severe COVID-19 (31). Therefore, PPI use should be carefully considered in patients with COVID-19, especially when prophylaxis for stress ulcers and gastrointestinal bleeding is needed in hospitalized patients. Subgroup analyses showed increased risks in both Asian and Western countries and case-control studies; however, in cohort studies, the increased risk was not statistically significant. Heterogeneity was observed in the subgroup of PPI use and risk of severe disease, likely as 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, there was no connection between PPI use and higher or lower risks of death in patients with COVID-19. This implies that it may not be necessary to discontinue PPI use in patients simply due to an increased risk of mortality. This is contrary to the conclusion drawn by Hariyanto et al. (31); however, one of the studies in their meta-analysis was excluded as the eligible data should have been for the endpoint of death only, while Hariyanto et al. extracted data for a composite endpoint (admission to the intensive care unit, invasive ventilation, or death) (9). However, in sensitivity analysis, the results of mortality changed significantly after excluding the study by Ullah et al., suggesting that 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 did not adjust the ORs based on multivariate analyses (11); therefore, the findings regarding the risk of mortality due to COVID-19 in PPI users should be interpreted cautiously.

Lastly, the subsequent risk of secondary infections is increased with PPI use. As mentioned above, PPIs suppress acid secretion (27); thus, decreased gastric acid production may affect the gut microbial composition and increase the risk of intestinal infection (27,32), including by *Clostridium difficile*, *Salmonella*, and *Campylobacter* (33,34). Compared to histamine-2 receptor blockers, PPI use was also reportedly associated with an increased risk of nosocomial pneumonia, especially in patients in the ICU (35). Therefore, we need to be more cautious regarding the use of PPIs in patients with COVID-19 who are already at high risk for secondary infection or who are immunocompromised. Nevertheless, only 2 original articles were included in the assessment of the risk of secondary infection; thus, these results should 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 affect the course of COVID-19, more in-depth subgroup analyses could not be performed due to a lack of data. However, most of the studies included in the present analysis also adjusted for these variables, providing a relatively reliable result. Second, the secondary infection subgroup included only 2 studies. Despite these limitations, the strengths of this study are as follows: First, no obvious publication bias was detected. Second, compared to previous meta-analyses, we included more studies and had more comprehensive subgroup analyses on different outcomes (22,26,38).

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

Conflict of interest None to declare.

REFERENCES

1. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available at <<https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>>. Accessed at November 24, 2021.
2. WHO. WHO Coronavirus Disease (COVID-19) Dashboard. Available at <<https://covid19.who.int>>. Accessed at November 18, 2020.
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: 1831-1833.e3.
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? *Med 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. doi:https://doi.org/10.1101/2020.07.12.20151084. Preprint.
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;8:336-341.
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*. 2021;70:76-84.
10. Almario CV, Chey WD, Spiegel BMR. Increased risk of COVID-19 among users of proton pump inhibitors. *Am J Gastroenterol*. 2020;115:1707-1715.
11. Ullah AZMD, 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. doi: https://doi.org/10.1101/2020.09.07.20189621. Preprint.
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. *Research Square*. 2020. doi: https://doi.org/10.21203/rs.3.rs-55958/v1. Preprint.
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;22:1379-1388.
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. doi: https://doi.org/10.1101/2020.05.04.20089904. Preprint.
15. Tarlow B, Gubatan J, Khan MA, et al. Are proton pump inhibitors contributing to SARS-CoV-2 infection? *Am J Gastroenterol*. 2020;115:1920-1921.
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;289:121-124.
18. McKeigue PM, Kennedy S, Weir A, et al. Relation of severe COVID-19 to polypharmacy and prescribing of psychotropic drugs: the REACT-SCOT case-control study. *BMC Med*. 2021;19:51.
19. Jimenez L, Codo AC, Sampaio VS, et al. The influence of pH on SARS-CoV-2 infection and COVID-19 severity. *medRxiv*. 2020. doi: https://doi.org/10.1101/2020.09.10.20179135. Preprint.
20. Cheung KS, Hung IFN, Leung WK. Association between famotidine use and COVID-19 severity in Hong Kong: a territory-wide study. *Gastroenterology*. 2021;161:1898-1899.
21. Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: a propensity score matched retrospective cohort study. *Gastroenterology*. 2020;159:1129-1131.e3.
22. Li GF, An XX, Yu Y, et al. Do proton pump inhibitors influence SARS-CoV-2 related outcomes? a meta-analysis. *Gut*. 2020;70:1806-1808.
23. Yan S, Song X, Lin F, et al. Clinical characteristics of coronavirus disease 2019 in Hainan, China. *medRxiv*. 2020. doi: https://doi.org/10.1101/2020.03.19.20038539. Preprint.
24. Losser MR, 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;39:467-469.
25. Smith PD, Gotz VP, Ryerson GG. Almitrine bismesylate. *Drug Intell Clin Pharm*. 1987;21:417-421.
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;160:455-458.e5.
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;25:2706-2719.
28. Peng X, Xu X, Li Y, et al. Transmission routes of 2019-nCoV and controls in dental practice. *Int J Oral Sci*. 2020;3:9.
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;52:1410-1412.
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;8:504-508.
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;174:564-574.
34. Imhann F, Bonder MJ, Vila VA, et al. Proton pump inhibitors affect the gut microbiome. *Gut*. 2016;65:740-748.
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;323:616-626.
36. Zhang XY, Zhang L, Zhao Y, et al. Risk assessment and prediction of severe or critical COVID-19 illness in older adults. *Clin Interv Aging*. 2020;15:2145-2153.
37. Zhang XY, Li T, Wu H, et al. Analysis of the effect of proton-pump inhibitors on the course of COVID-19. *J Inflamm Res*. 2021;14:287-298.
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*. 2021;298:125-128.