Do proton pump inhibitors influence SARS-CoV-2 related outcomes? A meta-analysis

The article by Lee *et al*[1] showed that the current use of proton pump inhibitors

(PPIs) increased the risk of severe clinical outcomes of COVID-19 rather than the susceptibility to SARS-CoV-2 infection in a Korean nationwide cohort. Instead, a significant association between susceptibility to SARS-CoV-2 infection and current use of PPIs, either one time or two times a day, was found by another recent study[2] based on US nationwide data. The conflicting results of these two large-scale observational studies may be due to regional epidemiological differences or considerable between-study variance and might compromise clinical decision-making. As the impact of PPI use on SARS-CoV-2 infection has very relevant clinical implications, we performed a meta-analysis to address the aforementioned discrepancies, which could lead to better informed clinical decision-making on PPI use during the ongoing pandemic.

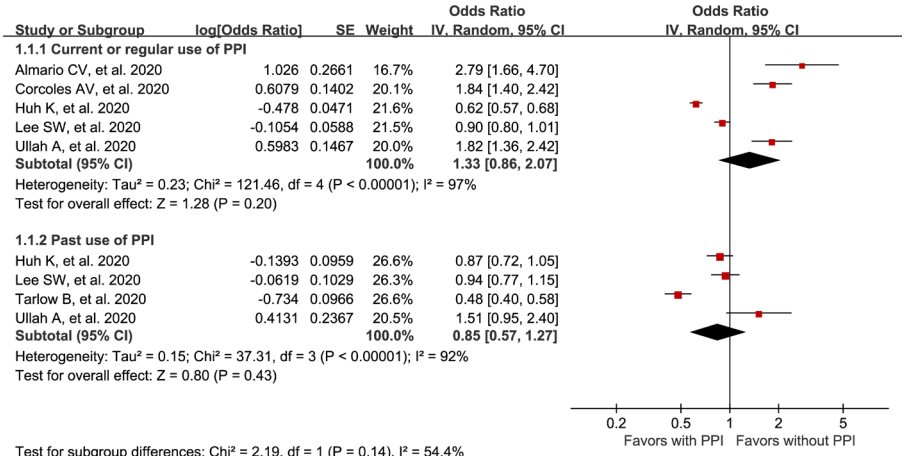

Figure 1 Forest plot showing the association between PPI use and SARS-CoV-2 infection. PPI, proton pump inhibitor.

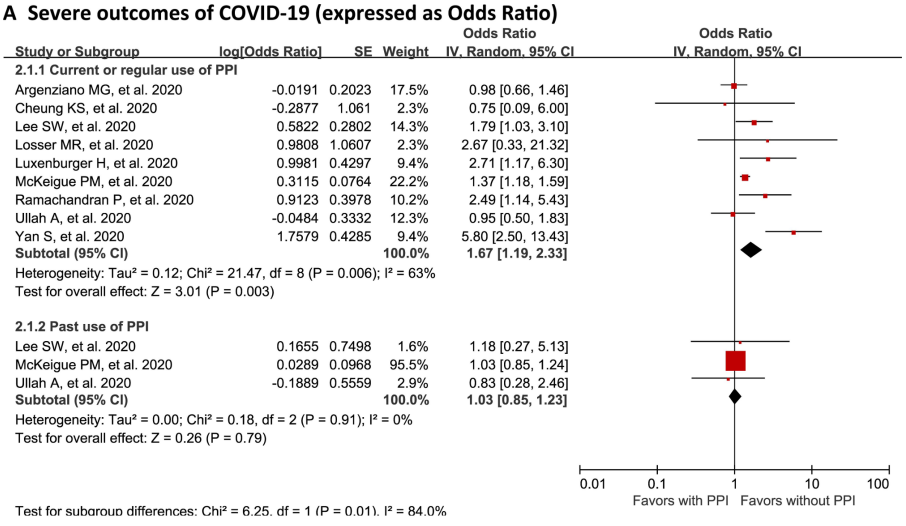

Figure 2 Forest plot showing the association of PPI use with severe outcomes of COVID-19 (A, OR; B, HR) or duration of hospital stay (C). PPI, proton pump inhibitor.

We scrutinised 3413 records retrieved from a comprehensive search using the COVID-19 Research Articles Downloadable Database maintained by the US CDC (https://www.cdc.gov/library/researchguides/2019novelcoronavirus/researcharticles.html) and ultimately included 16 studies[1–16] from 10 countries or regions reporting comparative data on PPI use and clinical outcomes of COVID-19 (online supplemental figure 1 and table). We pooled the data using an inverse variance-weighted random-effect model. Pooled estimates are presented as OR, HR or mean difference (MD), with associated 95% CIs. Intensive care unit admission, mechanical ventilation, acute respiratory distress syndrome or death were considered severe outcomes of COVID-19.

Six studies[1–6] including 318 261 participants reported data on PPI usage and the risk of SARS-CoV-2 infection. Among them, five studies had information of current PPI users compared with non-users and four on past PPI users versus non-users. Analysis of five studies[1–5] encompassing 145 428 patients who were tested for SARS-CoV-2 showed that the risk of SARS-CoV-2 infection was higher, although not significantly, among current PPI users (OR 1.33, 95% CI 0.86 to 2.07, p=0.20; figure 1) compared with PPI non-users, with evidence of substantial between-study heterogeneity (I^2=97%). Moreover, in a subgroup analysis of non-Korean cohorts,[2–4] we found a significant association between current use of PPIs and increased risk of SARS-CoV-2 infection (OR 1.94, 95% CI 1.59 to 2.36, p<0.0001; online supplemental figure 2). Furthermore, a leave-one-out sensitivity analysis revealed that the summary estimate of the association between current PPI usage and SARS-CoV-2 infection was overly influenced by a single Korean study[5] (online supplemental figure 3).

Instead, current or regular PPI users were more likely to have severe outcomes of COVID-19 than PPI non-users, with a pooled OR of 1.67 (95% CI 1.19 to 2.33, p=0.003; n=42 405 from nine studies;[1 3 7–13] I^2=63%; figure 2) and a pooled HR of 1.87 (95% CI 1.29 to 2.70, p<0.001; n=2977 from two studies;[15 16] I^2=80%; figure 2). These results were consistent with our leave-one-out sensitivity analysis (online supplemental figure 4), indicating that this association was strong. Furthermore,

current PPI users tended to hospitalised longer than PPI non-users, although not by a statistically significant margin (n=353 from two studies;[7 14] MD 1.13, 95% CI −0.18 to 2.43, p=0.09; figure 2). Finally, past use of PPIs was not associated with increased susceptibility to SARS-CoV-2 infection (n=172 833 from four studies;[1 3 5 6] OR 0.85, 95% CI 0.57 to 1.27, p=0.43; I^2=92%; figure 1) or with severe outcomes of COVID-19 (n=40 097 from three studies;[1 3 9] OR 1.03, 95% CI 0.85 to 1.23, p=0.79; I^2=0%; figure 2).

In summary, this meta-analysis shows that regional differences can explain the heterogeneous findings concerning the association between current PPI use and incidence of SARS-CoV-2 infection and further underscores the increased risk of severe COVID-19 outcomes associated with current PPI use, highlighting that caution should be exercised when treating patients receiving PPIs during the COVID-19 pandemic. Further studies investigating different dosing regimens and durations of PPI use on COVID-19 outcomes should be warranted.

Guo-Fu Li ,[1,2] **Xiao-Xiao An**,[2,3] **Yichao Yu**,[4] **Li-Rong Jiao**,[2,3] **Daniele Canarutto**,[5] **Guo Yu** ,[1,2] **Guangji Wang**,[6] **Dan-Na Wu**,[7] **Yin Xiao**[8]

[1]Clinical Medical College, Yangzhou University, Yangzhou, China
[2]Institution of Drug Clinical Trial, Subei People's Hospital, Yangzhou, China
[3]College of Pharmacy, Dalian Medical University, Dalian, Liaoning, China
[4]Department of Pharmaceutics, University of Florida, Gainesville, Florida, USA
[5]Faculty of Medicine and Surgery, Vita Salute San Raffaele University, Milan, Italy
[6]Key Laboratory of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing, China
[7]Department of Pharmacy, Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University), Haikou, China
[8]Department of Pharmacy, Haikou Affiliated Hospital of Central South University Xiangya School of Medicine, Haikou, China

Correspondence to Dr Guo Yu, Clinical Medical College, Yangzhou University, Yangzhou 225009, China; guoyu@yzu.edu.cn

Contributors Concept and design: G-FL and GY. Acquisition, analysis and interpretation of data: G-FL, X-XA, GY, YY, L-RJ, D-NW, YX. Drafting of the manuscript: GFL. Supervision: GY. Critical revision of the manuscript: DC, G-FL, GW and YY. Final approval: all authors.

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ORCID iDs
Guo-Fu Li http://orcid.org/0000-0002-4628-9941
Guo Yu http://orcid.org/0000-0001-6685-2167

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