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

The article by Lee et al 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 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.

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/research-guides/2019novelcoronavirus-researcharticles.html) and ultimately included 16 studies 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 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 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 1.94, 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 (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; I²=63%; figure 2) and a pooled HR of 1.87 (95% CI 1.29 to 2.73; figure 2).

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.
to 2.70, p<0.001; n=2977 from two studies.15 16 I²=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;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=172833 from four studies;13 15 16 OR 0.85, 95% CI 0.57 to 1.27, p=0.43; I²=92%; figure 1) or with severe outcomes of COVID-19 (n=40097 from three studies;13 15 16 OR 1.03, 95% CI 0.85 to 1.23, p=0.79; I²=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.

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Funding This work was supported by Jiangsu Provincial Medical Youth Talent programme (QNRC2016323), Jiangsu Province 333 Project (to GY) and Jiangsu Provincial Science Fund for Distinguished Young Scholars (to GY).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-323366).


Received 13 October 2020
Revised 28 October 2020
Accepted 30 October 2020

Gut 2020:0–1. doi:10.1136/gutjnl-2020-323366

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We aim to improve the reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and are not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

This content has been externally peer reviewed.

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Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-323366).


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Gut first published as 10.1136/gutjnl-2020-323366 on 10 November 2020. Downloaded from http://gut.bmj.com/ on July 28, 2021 by guest. Protected by copyright.