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.

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\(^1\)–\(^{16}\) 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\(^1\)–\(^4\),\(^6\) 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 (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

### A Severe outcomes of COVID-19 (expressed as Odds Ratio)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(IV, Random, 95% CI)</td>
<td>(IV, Random, 95% CI)</td>
</tr>
<tr>
<td>1.1.1 Current or regular use of PPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almarino CV, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
</tr>
<tr>
<td>Corcoles AV, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
</tr>
<tr>
<td>Huh K, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
</tr>
<tr>
<td>Lee SW, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
</tr>
<tr>
<td>Ullah A, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau\(^2\)= 0.02; Chi\(^2\)= 31.63, df = 2 (p<0.0001); I\(^2\)= 92%

Test for overall effect: Z = 9.28 (p = 0.047; n = 16,600)

### B Severe outcomes of COVID-19 (expressed as Hazard Ratio)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(IV, Random, 95% CI)</td>
<td>(IV, Random, 95% CI)</td>
</tr>
<tr>
<td>Freedberg DE, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
</tr>
<tr>
<td>Jimenez L, et al. 2020 (North)</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
</tr>
<tr>
<td>Jimenez L, et al. 2020 (Southwest)</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 1.87 [1.29, 2.76]

Heterogeneity: Tau\(^2\)= 0.00; Chi\(^2\)= 10.88, df = 2 (p = 0.005); I\(^2\)= 90%

Test for overall effect: Z = 3.33 (p = 0.0009)

### C Duration of hospital stay

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Diff. (SD)</th>
<th>SE</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Diff. (SD)</th>
<th>SE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almarino et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corcoles AV, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huh K, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee SW, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ullah A, et al. 2020</td>
<td>(-0.267)</td>
<td>0.030</td>
<td>7.44</td>
<td>0.77</td>
<td>0.60 (0.40, 1.02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau\(^2\)= 0.00; Chi\(^2\)= 0.00, df = 1 (p = 0.000); I\(^2\)= 0%

Test for overall effect: Z = 1.89 (p = 0.059)

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.\textsuperscript{11, 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;\textsuperscript{13, 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;\textsuperscript{13, 16} 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=40097 from three studies;\textsuperscript{13, 19} 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,\textsuperscript{1, 2} Xiao-Xiao An,\textsuperscript{3, 4} Yichao Yu,\textsuperscript{4} Li-Rong Jiao,\textsuperscript{2, 5} Daniele Caranuutto,\textsuperscript{2} Guo Yu,\textsuperscript{1, 2} Guangji Wang,\textsuperscript{6} Dan-Na Wu,\textsuperscript{7} Yin Xiao\textsuperscript{8}

\textsuperscript{1}Clinical Medical College, Yangzhou University, Yangzhou, China
\textsuperscript{2}Institution of Drug Clinical Trial, Subei People’s Hospital, Yangzhou, China
\textsuperscript{3}College of Pharmacy, Dalian Medical University, Dalian, Liaoning, China
\textsuperscript{4}Department of Pharmaceutics, University of Florida, Gainesville, Florida, USA
\textsuperscript{5}Faculty of Medicine and Surgery, Vita Salute San Raffaele University, Milan, Italy
\textsuperscript{6}Key Laboratory of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing, China
\textsuperscript{7}Department of Pharmacy, Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University), Haikou, China
\textsuperscript{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-XX, 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.

Funding This work was supported by Jiangsu Provincial Medical Talent Programme (QNR2016323), 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.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

OPEN ACCESS

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made are indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

© Author(s) (or their employer(s)) 2020. Reuse permitted under CC BY, non-commercial licence. BMJ may not have commissioned and/or peer reviewed this work. BMJ Publishing Group Limited (BMJ) and its subsidiaries are not responsible for any errors or omissions in editorial content. A copyright form for this journal is available from http://creativecommons.org/licenses/by-nc/4.0/


Gut 2020;69:323366

Corrigendum

Gut 2020;69:323366


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

Gut 2020;69:323366

Guo Yu http://orcid.org/0000-0002-4628-9941

REFERENCES


Copyright © 2022 BMJ Publishing Group Ltd. All rights reserved. For permission to reuse any element of this article, please go to: http://creativecommons.org/licenses/by-nc/4.0/