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 infection 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 (online supplemental figure 3).

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

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>IV, Random, 95% CI</th>
<th>Odds Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almarco CV, et al. 2020</td>
<td>1.026</td>
<td>0.2661</td>
<td>16.7%</td>
<td>2.79 [1.56, 4.70]</td>
<td>1.151</td>
<td>0.960 to 1.384</td>
</tr>
<tr>
<td>Concolles AV, et al. 2020</td>
<td>0.6079</td>
<td>0.1402</td>
<td>20.1%</td>
<td>1.84 [1.40, 2.42]</td>
<td>1.089</td>
<td>0.877 to 1.353</td>
</tr>
<tr>
<td>Huh K, et al. 2020</td>
<td>-0.478</td>
<td>0.3471</td>
<td>21.6%</td>
<td>0.62 [0.57, 0.68]</td>
<td>1.000</td>
<td>0.946 to 1.060</td>
</tr>
<tr>
<td>Lee SW, et al. 2020</td>
<td>-0.1054</td>
<td>0.0988</td>
<td>21.3%</td>
<td>0.90 [0.85, 0.96]</td>
<td>1.000</td>
<td>0.946 to 1.060</td>
</tr>
<tr>
<td>Ullah A, et al. 2020</td>
<td>0.5983</td>
<td>0.1467</td>
<td>20.0%</td>
<td>1.82 [1.36, 2.42]</td>
<td>1.000</td>
<td>0.946 to 1.060</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.23; Chi² = 121.46, df = 4 (p < 0.0001); I² = 97%

Test for overall effect: Z = 1.28 (p = 0.20)

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>IV, Random, 95% CI</th>
<th>Hazard Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedberg DE, et al. 2020</td>
<td>-0.927</td>
<td>0.1194</td>
<td>35.9%</td>
<td>1.34 [1.06, 1.69]</td>
<td>1.091</td>
<td>0.883 to 1.360</td>
</tr>
<tr>
<td>Jimenez L, et al. 2020 (North)</td>
<td>0.7807</td>
<td>0.1474</td>
<td>33.3%</td>
<td>2.18 [1.64, 2.91]</td>
<td>1.000</td>
<td>0.946 to 1.060</td>
</tr>
<tr>
<td>Jimenez L, et al. 2020 (Southwest)</td>
<td>0.8467</td>
<td>0.1731</td>
<td>30.9%</td>
<td>2.33 [1.66, 3.27]</td>
<td>1.000</td>
<td>0.946 to 1.060</td>
</tr>
</tbody>
</table>

Total (95% CI): 100.0% | 1.87 [1.28, 2.70]

Heterogeneity: Tau² = 0.08; Chi² = 10.08, df = 2 (p = 0.005); I² = 80%

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 SD</th>
<th>Total Mean SD</th>
<th>Total Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramachandran P, et al. 2020</td>
<td>74.44</td>
<td>46</td>
<td>4.44</td>
<td>249</td>
<td>87.3%</td>
</tr>
<tr>
<td>Zheng XY, et al. 2020</td>
<td>21.81</td>
<td>16.5</td>
<td>19</td>
<td>5.93</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

Total (95% CI): 75 | 278 100.0% | 1.13 [0.18, 2.43]

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (p = 0.62); I² = 0%

Test for overall effect: Z = 1.68 (p = 0.09)
to 2.70, p<0.001; n=2977 from two studies\cite{13,16} \( I^2 = 80\% \); \textit{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\cite{14} MD 1.13, 95% CI -0.18 to 2.43, p=0.09; \textit{figure 2}). Finally, past use of PPIs was not associated with increased susceptibility to SARS-CoV-2 infection (n=172833 from four studies\cite{13,14,15} OR 0.85, 95% CI 0.57 to 1.27, p=0.43; \( I^2 = 92\% \); \textit{figure 1}) or with severe outcomes of COVID-19 (n=40097 from three studies\cite{3,3,9} OR 1.03, 95% CI 0.85 to 1.23, p=0.79; \( I^2 = 0\% \); \textit{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.

**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.

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**REFERENCES**


