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 318261 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 145428 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=42405 from nine studies; F²=63%; figure 2) and a pooled HR of 1.87 (95% CI 1.29 to 2.78; figure 2).

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>Almario CV, et al. 2020</td>
<td>1.026</td>
<td>0.2961</td>
<td>16.7%</td>
<td>2.79 [1.56, 4.70]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concoles 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></td>
<td></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></td>
<td></td>
</tr>
<tr>
<td>Lee SW, et al. 2020</td>
<td>-0.1054</td>
<td>0.0568</td>
<td>21.5%</td>
<td>0.90 [0.86, 1.01]</td>
<td></td>
<td></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></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1.33 [0.86, 2.07]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²= 0.23; Chi²= 121.46, df = 4 (p < 0.00001); 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>0.2927</td>
<td>0.1194</td>
<td>35.9%</td>
<td>1.34 [1.06, 1.69]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jimenez L, et al. 2020 (North)</td>
<td>0.7807</td>
<td>0.1474</td>
<td>33.3%</td>
<td>2.16 [1.64, 2.91]</td>
<td></td>
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</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></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>1.87 [1.28, 2.70]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²= 0.06; Chi²= 10.08, df = 2 (p = 0.006); I²= 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</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
<th>Total Mean</th>
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<th>Total Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramachandran P, et al. 2020</td>
<td>7.44</td>
<td>6.44</td>
<td>28.87</td>
<td>3.01</td>
<td>8.00</td>
<td>4.07</td>
<td>8.00</td>
<td>4.07</td>
<td>8.00</td>
<td>4.07</td>
<td>8.00</td>
<td>4.07</td>
<td>8.00</td>
<td>4.07</td>
</tr>
<tr>
<td>Zheng XY, et al. 2020</td>
<td>8.15</td>
<td>5.93</td>
<td>29.12</td>
<td>2.27</td>
<td>8.00</td>
<td>4.04</td>
<td>8.00</td>
<td>4.04</td>
<td>8.00</td>
<td>4.04</td>
<td>8.00</td>
<td>4.04</td>
<td>8.00</td>
<td>4.04</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>75</td>
<td>278</td>
<td>100.0%</td>
<td>1.13</td>
<td>8 [18, 24.3]</td>
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</tbody>
</table>

Heterogeneity: Tau²= 0.00; Chi²= 0.25, df = 1 (p = 0.62); I²= 0% Test for overall effect: Z = 1.69 (p = 0.09)
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;15 16 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 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 14 19 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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