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 study² 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/researchguides/2019novelcoronavirus/researcharticles.html) and ultimately included 16 studies¹⁻¹⁶ 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 studies¹⁻⁶ 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 nonusers and four on past PPI users versus non-users. Analysis of five studies¹⁻⁵ 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

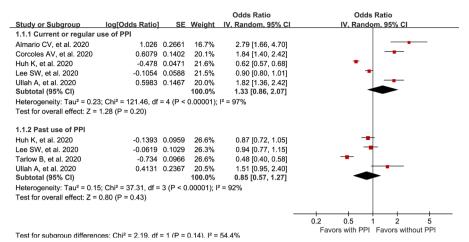


Figure 1 Forest plot showing the association between PPI use and SARS-CoV-2 infection. PPI, proton pump inhibitor.

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 study⁵ (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;^{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)

Odds Ratio Odds Ratio Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI IV, Random, 95% C 2.1.1 Current or regular use of PPI Argenziano MG, et al. 2020 -0.0191 0.2023 17.5% 0.98 [0.66, 1.46] 1,061 Cheung KS, et al. 2020 -0 2877 2.3% 0.75 [0.09, 6.00] Lee SW. et al. 2020 0.5822 0.2802 14.3% 1.79 [1.03, 3.10] 2.67 [0.33, 21.32] Losser MR, et al. 2020 0.9808 1.0607 2.3% Luxenburger H, et al. 2020 McKeigue PM, et al. 2020 0.9981 0.4297 9.4% 2.71 [1.17, 6.30] 0.3115 0.0764 22.2% 1.37 [1.18, 1.59] Ramachandran P, et al. 2020 0.9123 0.3978 10.2% 2.49 [1.14, 5.43] Ullah A. et al. 2020 -0.0484 0.3332 0.95 [0.50, 1.83] 12.3% Yan S, et al. 2020 Subtotal (95% CI) 1.7579 0.4285 9.4% 5.80 [2.50, 13.43] 100.0% 1.67 [1.19, 2.33] Heterogeneity: Tau² = 0.12; Chi² = 21.47, df = 8 (P = 0.006); l² = 63% Test for overall effect: Z = 3.01 (P = 0.003) 2.1.2 Past use of PPI Lee SW. et al. 2020 0.1655 0.7498 1.6% 1.18 [0.27, 5.13] McKeigue PM, et al. 2020 0.0289 0.0968 95.5% 1.03 [0.85, 1.24] Illah A et al 2020 -0.1889 0.5559 2 9% 0 83 10 28 2 461 Subtotal (95% CI) 100.0% 1.03 [0.85, 1.23] Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0% Test for overall effect: Z = 0.26 (P = 0.79) 0.01 0.1 10 100 Favors with PPI Favors without PPI

Test for subaroup differences: $Chi^2 = 6.25$. df = 1 (P = 0.01). $I^2 = 84.0\%$

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

$\begin{array}{c} \text{Jinterize L, et al. 2020 (Volinit)} & 0.7607 0.1474 & 53.5\% & 2.16 [1.59, 2.91] \\ \text{Jinterize L, et al. 2020 (Southeast)} & 0.8467 & 0.1731 & 30.9\% & 2.33 [1.66, 3.27] \\ \text{Total (95% CI)} & 100.0\% & 1.87 [1.29, 2.70] \\ \text{Heterogeneity: Tau2 = 0.08; Chi2 = 10.08, df = 2 (P = 0.006); I2 = 80\% \\ \text{Totat for correct of force: T = 3 33 (P = 0.0009)} \\ \hline \end{array}$				•					
Freedberg DE, et al. 2020 0.2927 0.1184 35.9% 1.34 [1.06, 1.69] Jimenez L, et al. 2020 (North) 0.7807 0.1474 33.3% 2.18 [1.64, 2.91] Jimenez L, et al. 2020 (Southeast) 0.8467 0.1731 30.9% 2.33 [1.66, 3.27] Total (95% Cl) 100.0% 1.87 [1.29, 2.70]				Hazard Ratio	Hazard Ratio				
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Study or Subgroup	log[Hazard Ratio]	SE Weight	IV, Random, 95% CI	IV, Random, 95% Cl				
Jinteriez L, et al. 2020 (Notifit) 0.7607 0.1474 35.3% 2.16 [1.54, 2.91] Jimenez L, et al. 2020 (Southeast) 0.8467 0.1731 30.9% 2.33 [1.66, 3.27] Total (95% CI) 100.0% 1.87 [1.29, 2.70]	Freedberg DE, et al. 2020	0.2927 0.11	84 35.9%	1.34 [1.06, 1.69]					
Total (95% Cl) 100.0% 1.87 [1.29, 2.70] Heterogeneity: Tau ² = 0.08; Chi ² = 10.08, df = 2 (P = 0.006); l ² = 80% 0.2 0.5 1 2	Jimenez L, et al. 2020 (North)	0.7807 0.14	74 33.3%	2.18 [1.64, 2.91]	_ _ _				
Heterogeneity: Tau ² = 0.08; Chi ² = 10.08, df = 2 (P = 0.006); l ² = 80% Test for overall effect: Z = 3.33 (P = 0.0000) 0.2 0.5 1 2	Jimenez L, et al. 2020 (Southeast)	0.8467 0.17	31 30.9%	2.33 [1.66, 3.27]					
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	Heterogeneity: Tau ² = 0.08; Chi ² = 10								
	Test for overall effect: Z = 3.33 (P = 0	Favors with PPI Favors without PPI							

C Duration of hospital stay

e burution of hosp	itui J	u y												
	PPI			non-PPI				Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Ran	dom, 95	% CI		
Ramachandran P, et al. 2020	7	4.44	46	6	4.44	249	87.3%	1.00 [-0.40, 2.40]						
Zhang XY, et al. 2020	21	8.15	29	19	5.93	29	12.7%	2.00 [-1.67, 5.67]			+			
Total (95% CI)			75			278	100.0%	1.13 [-0.18, 2.43]			•			
Heterogeneity: Tau ² = 0.00; Chi ² = 0.25, df = 1 (P = 0.62); l ² = 0% Test for overall effect: Z = 1.69 (P = 0.09)								-20	-10 Favors with Pl	0 PI Favo	10 rs withou	20 ut PPI)	

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.

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to 2.70, p<0.001; n=2977 from two studies; 15 16 $I^2 = 80\%$; figure 2). These results were consistent with our leaveone-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 $(n=353 \text{ from two studies};^{7 14} \text{ MD } 1.13,$ 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;^{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=40097 from three studies;¹³⁹ 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.

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