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 betweenstudy 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

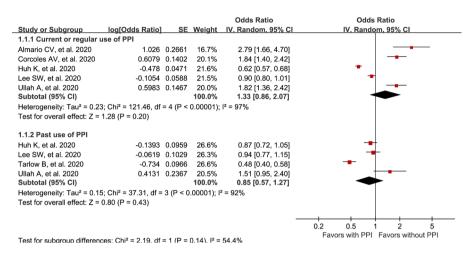
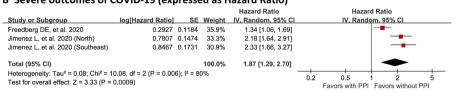


Figure 1 Forest plot showing the association between PPI use and SARS-CoV-2 infection. PPI, proton pump inhibitor.

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

	•	•		Odds Ratio		Odds Ratio	
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% C	IV	, Random, 95% Cl	
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]		+	
Cheung KS, et al. 2020	-0.2877	1.061	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]		-	
Losser MR, et al. 2020	0.9808	1.0607	2.3%	2.67 [0.33, 21.32]			
Luxenburger H, et al. 2020	0.9981	0.4297	9.4%	2.71 [1.17, 6.30]			
McKeigue PM, et al. 2020	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	12.3%	0.95 [0.50, 1.83]			
Yan S, et al. 2020	1.7579	0.4285	9.4%	5.80 [2.50, 13.43]			
Subtotal (95% CI)			100.0%	1.67 [1.19, 2.33]		•	
Heterogeneity: Tau ² = 0.12; Chi ²	² = 21.47, df = 8 (P =	= 0.006)	; I² = 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]		<u> </u>	
McKeigue PM, et al. 2020	0.0289	0.0968	95.5%	1.03 [0.85, 1.24]			
Ullah A, et al. 2020	-0.1889	0.5559	2.9%	0.83 [0.28, 2.46]			
Subtotal (95% CI)			100.0%	1.03 [0.85, 1.23]		•	
Heterogeneity: Tau ² = 0.00; Chi ²	² = 0.18, df = 2 (P =	0.91); l ²	= 0%				
Test for overall effect: Z = 0.26 (P = 0.79)						
					0.01 0.1	1 10	100
						vith PPI Favors without PP	
Test for subaroup differences: C	hi² = 6.25. df = 1 (P	9 = 0.01)	. I ² = 84.0	%			

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



C Duration of hospital stay

	PPI non-PPI						Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	ght IV. Random, 95% CI			andom, 9	5% 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%							-20	-10	0	10	20		
Test for overall effect: Z = 1.69 (P = 0.09)									F	avors with	PPI Favo	ors without	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.

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 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 to 2.70, p<0.001; n=2977 from two studies;^{15 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;^{7 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;¹³⁵⁶ 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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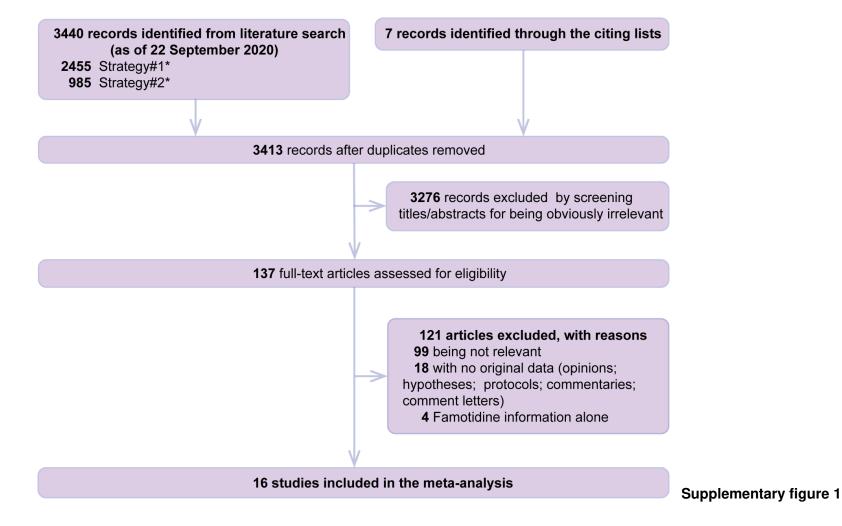
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Supplementary figure 1: Flow chart for study selection

Searches using strategy#1 ("proton pump inhibitor" or "PPI*" OR " H2-receptor antagonist*" OR hypochlorhydria OR "gastric acid" OR "gastric pH" OR omeprazole OR rabeprazole OR esomeprazole OR famotidine OR pantoprazole OR lansoprazole) or strategy#2 (gastrointestinal[title/abstract]) were performed in the COVID-19 Research Articles Downloadable Database by the US CDC (https://www.cdc.gov/library/researchguides/2019novelcoronavirus/researcharticles.html), which includes literature from 25 databases, such as Medline (Ovid and PubMed), Embase, Scopus, Cochrane Library, LitCovid, WHO COVID-19 website, medRxiv (preprints), bioRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).





Supplementary figure 2: Subgroup analysis of Korean versus non-Korean cohorts for the association between PPI use and risk of SARS-CoV-2 infection

			Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio] SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.2.1 Korean studies				
Huh K, et al. 2020	-0.478 0.0471	21.6%	0.62 [0.57, 0.68]	-
Lee SW, et al. 2020	-0.1054 0.0588	3 21.5%	0.90 [0.80, 1.01]	-
Subtotal (95% CI)		43.2%	0.75 [0.52, 1.07]	
Heterogeneity: Tau ² = 0.0	7; Chi² = 24.46, df = 1 (P <	0.00001); l ^a	² = 96%	
Test for overall effect: Z =	1.57 (P = 0.12)			
1.2.2 non-Korean studies	S			
Almario CV, et al. 2020	1.026 0.2662	16.7%	2.79 [1.66, 4.70]	
Corcoles AV, et al. 2020	0.6079 0.1402	20.1%	1.84 [1.40, 2.42]	
Ullah A, et al. 2020	0.5983 0.1467	20.0%	1.82 [1.36, 2.42]	
Subtotal (95% CI)		56.8%	1.94 [1.59, 2.36]	\bullet
Heterogeneity: Tau ² = 0.0	0; Chi² = 2.21, df = 2 (P = 0	.33); l² = 9%	6	
Test for overall effect: Z =	6.56 (P < 0.00001)			
Total (95% CI)		100.0%	1.33 [0.86, 2.07]	
Heterogeneity: Tau ² = 0.23	3; Chi² = 121.46, df = 4 (P <	< 0.00001);	l ² = 97%	
Test for overall effect: Z =	1.28 (P = 0.20)			Favors with PPI Favors without PPI
Test for subaroup differen	ces: Chi ² = 20.31. df = 1 (P	< 0.00001)	. I² = 95.1%	FAVOIS WILLEFT FAVOIS WILLOUL FFI

Supplementary figure 3: Forest plot showing leave-one-out sensitivity analysis for the association of PPI use with incidence of SARS-CoV-2 infection

Study name	Statistics with study removed						atio (95% Cl) udy removed	
	Point	Lower limit	Upper limit	z-Value	p-Value			
Almario CV, et al. 2020	1.150	0.730	1.790	0.600	0.550	-+=	_	
Corcoles AV, et al. 2020	1.220	0.780	1.910	0.860	0.390	-+=	_	
Huh K, et al. 2020	1.650	0.980	2.780	1.890	0.060	-	-	
Lee SW, et al. 2020	1.520	0.700	3.300	1.070	0.290			
Ullah A, et al. 2020	1.220	0.780	1.930	0.870	0.390	-+=	_	
	1.330	0.860	2.070	1.280	0.200	-	-	
					0.10 Favo) 1.0 prs with PPI	ا 10.0 Favors without PPI	I

Supplementary figure 4: Forest plot showing leave-one-out sensitivity analysis for the association of PPI use with severe outcomes of COVID-19

Study name		Statistics	with study	Odds ratio (95% CI) with study removed			
	Point	Lower limit	Upper limit	z-Value	p-Value		
Argenziano MG, et al. 2020	1.890	1.280	2.780	3.190	0.001		
Cheung KS, et al. 2020	1.710	1.210	2.410	3.050	0.002		
Lee SW, et al. 2020	1.670	1.140	2.460	2.610	0.009		
Losser MR, et al. 2020	1.650	1.170	2.330	2.870	0.004		
Luxenburger H, et al. 2020	1.580	1.120	2.240	2.590	0.009		
McKeigue PM, et al. 2020	1.830	1.130	2.950	2.470	0.010		
Ramachandran P, et al. 2020	1.590	1.120	2.270	2.590	0.010		
Ullah A, et al. 2020	1.820	1.260	2.630	3.180	0.001		
Yan S, et al. 2020	1.400	1.100	1.780	2.760	0.006		
	1.670	1.190	2.330	3.010	0.003	-	
					0.20		
					Favo	ors with PPI Favors without PI	P

Supplementary table: Summary characteristics of the included studies

Study	Study design	Country or region	Timing of data collection	Mean or median age (years)	Male subjects (%)	Number of subjects	Number of PPI users	Clinical outcome	Confounder adjustment
Lee 2020 ¹	Retrospective cohort	Korea	Jan 1 to May 15, 2020	48	51.0	132316	20405	SARS-CoV-2 infection; severe	Yes
Almario 2020 ²	Retrospective cohort	USA	May 3 to Jun 24, 2020	NR	48	53130	16547	outcomes of COVID-19* SARS-CoV-2 infection	Yes
Ullah 2020 ³	Retrospective cohort	UK	Feb 12 to Jun 12, 2020	57	43.9	15586	5908	SARS-CoV-2 infection; severe outcomes of COVID-19*	No
Corcoles 2020 ⁴	Retrospective cohort	Spain	May 1 to Apr 3, 2020	\geq 50	48.1	34936	11807	SARS-CoV-2 infection	No
Huh 2020 ⁵	Case-control	Korea	Up to Apr 8, 2020	49	48.7	65149	14167	SARS-CoV-2 infection	Yes
Tarlow 2020 ⁶	Retrospective cohort	USA	NR	NR	NR	84325	18240	SARS-CoV-2 infection	No
Ramachandran 2020 ⁷	Retrospective cohort	USA	Mar 1 to Apr 25, 2020	66	54.9	295	46	Severe outcomes of COVID-19*; duration of hospital stay	Yes
Luxenburger 2020 ⁸	Retrospective cohort	Germany	NR	65	56.6	152	62	Severe outcomes of COVID-19*	No
McKeigue 2020 ⁹	Case-control	Scotland	Up to Jun 6, 2020	NR	NR	41220	2715	Severe outcomes of COVID-19*	No
Argenziano 2020 ¹⁰	Retrospective cohort	USA	Mar 1 to Apr 5, 2020	63	59.6	1000	163	Severe outcomes of COVID-19*	No
Cheung 2020 ¹¹	Retrospective cohort	Hongkong	Jan 1 to May 10, 2020	NR	NR	952	27	Severe outcomes of COVID-19*	Yes
Losser 2020 ¹²	Case series (individual)	France	Mar16 to Apr 12, 2020	70	58.8	17	6	Severe outcomes of COVID-19*	No
Yan 2020 ¹³	Retrospective cohort	China	Jan 22 to Mar 13, 2020	51	48.2	168	32	Severe outcomes of COVID-19*	No
Zhang 2020 ¹⁴	Retrospective cohort	China	Jan 20 to Mar 16, 2020	50	55.2	58	29	Duration of hospital stay	Yes

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Jimenez 2020 ¹⁵	Retrospective cohort	Brazil	NR	NR	NR	1357	242	Severe outcomes of COVID-19*	Yes
Freedberg 2020 ¹⁶	Retrospective cohort	USA	Feb 25 to Apr 13, 2020	NR	NR	1620	NR	Severe outcomes of COVID-19*	Yes

*Severe outcomes of COVID-19 consisted of admission to the intensive care unit, mechanical ventilation, acute respiratory distress syndrome, or death.

COVID-19, Coronavirus Disease 2019; NR, not reported; PPI, proton pump inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.