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.

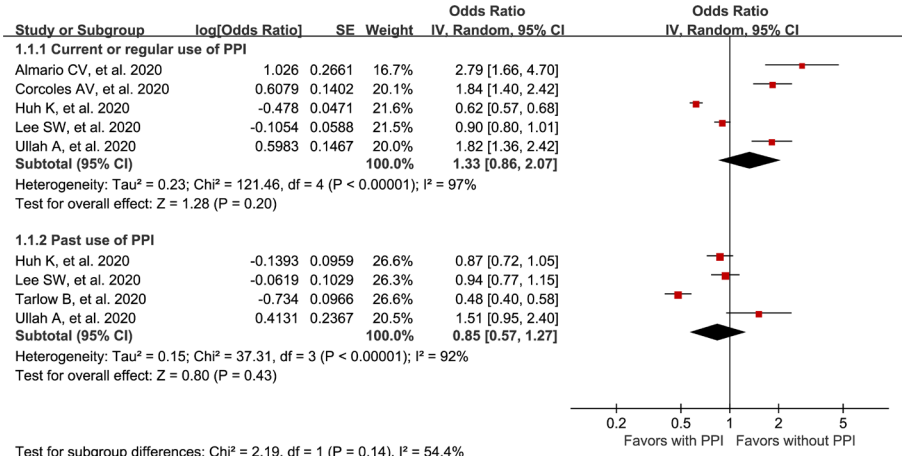

Figure 1 Forest plot showing the association between PPI use and SARS-CoV-2 infection. PPI, proton pump inhibitor.

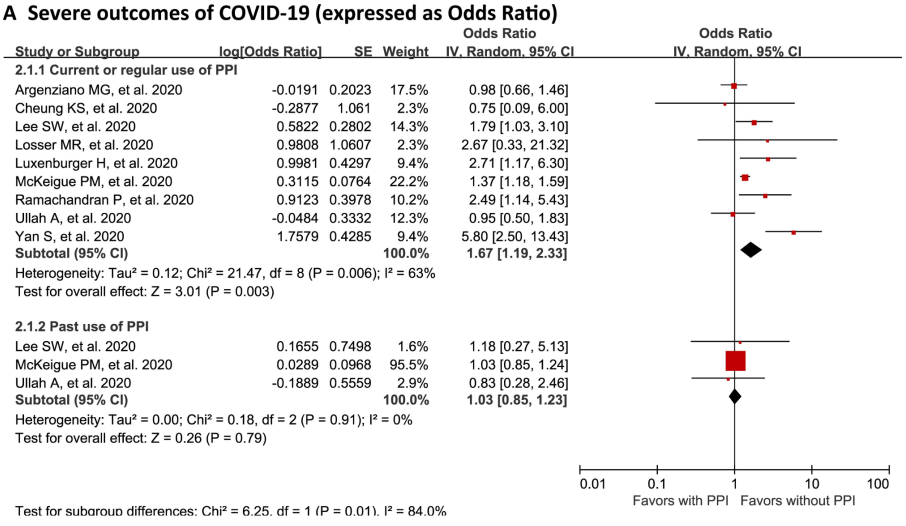

Figure 2 Forest plot showing the association of PPI use with severe outcomes of COVID-19 (A, OR; B, HR) or duration of hospital stay (C). PPI, proton pump inhibitor.

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 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[1–6] 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 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 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 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=172 833 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=40 097 from three studies;[1 3 9] 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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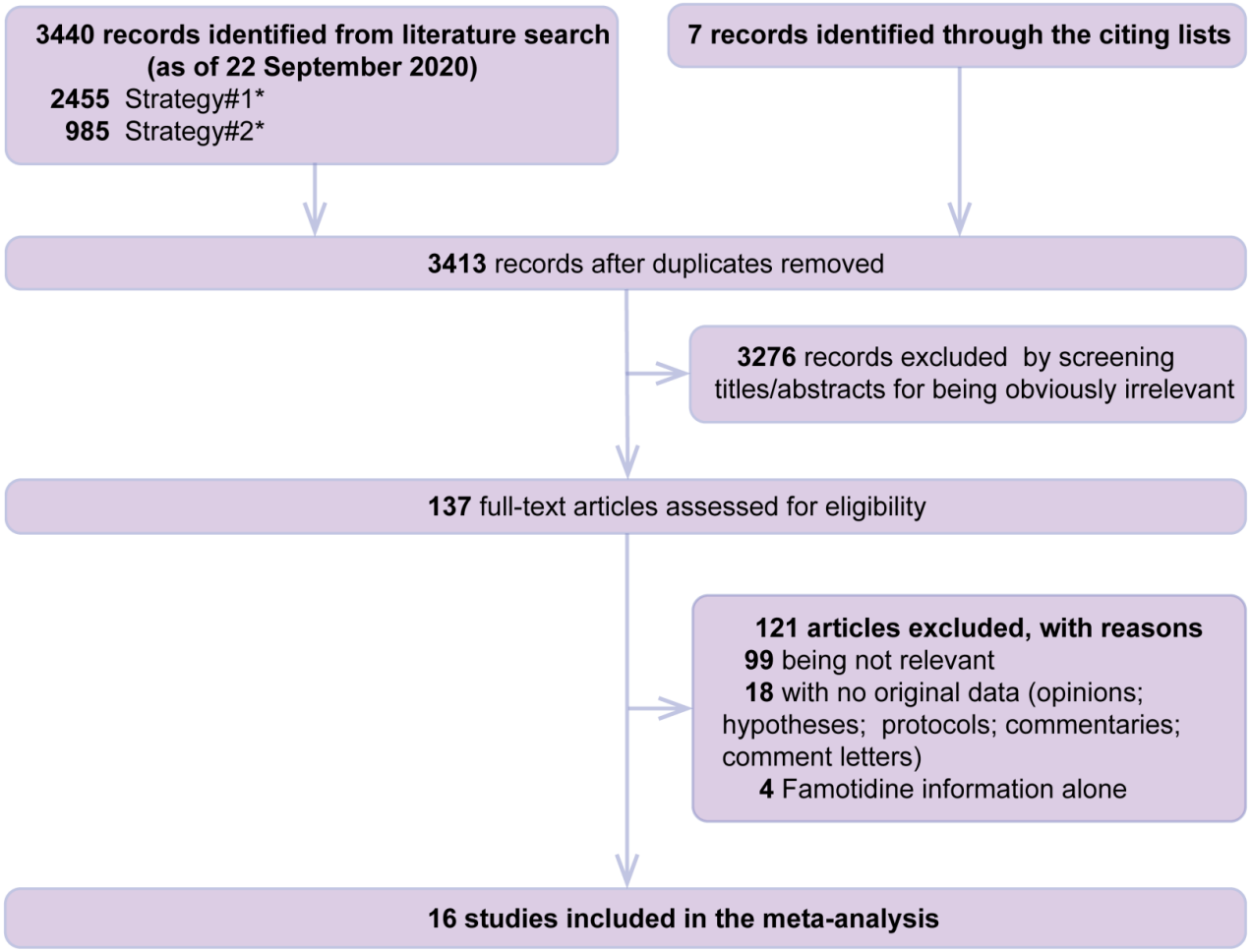
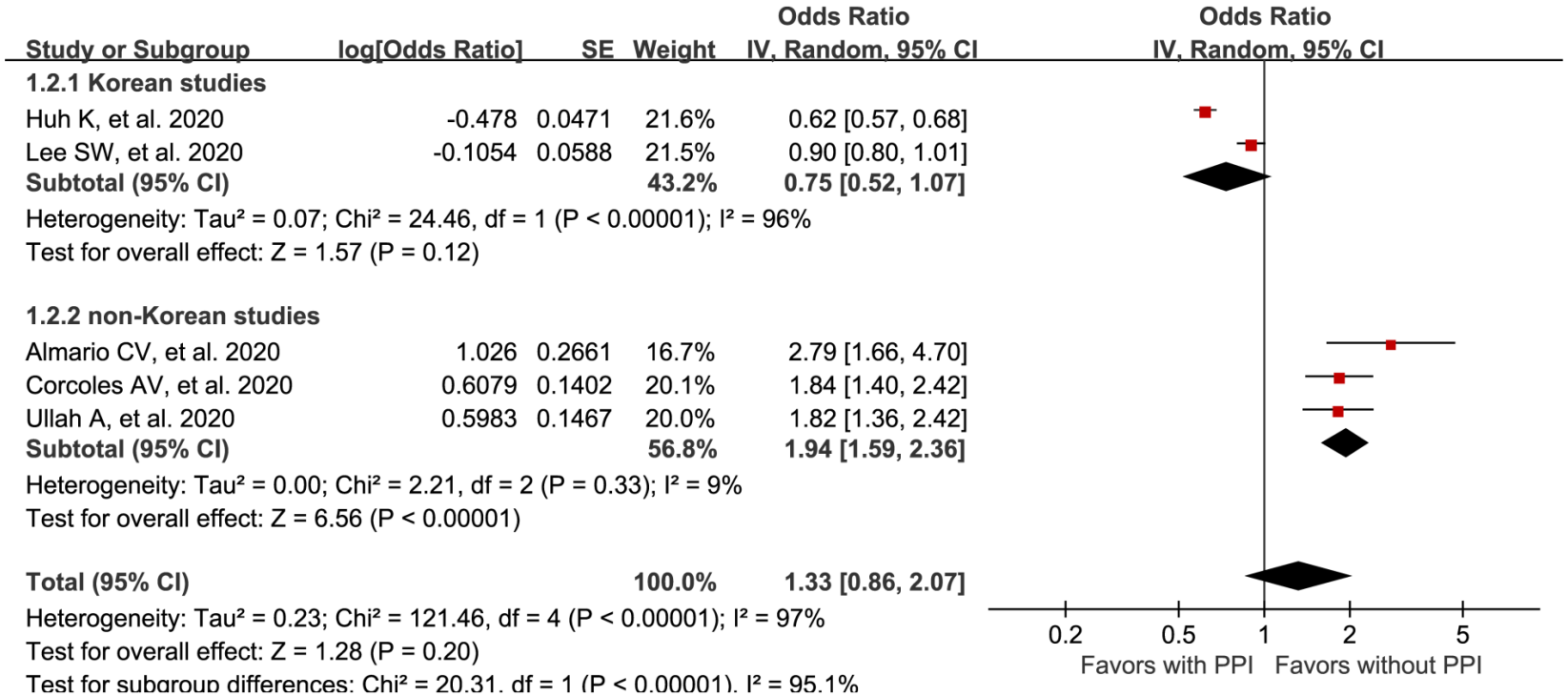
Supplementary figure 1: Flow chart for study selection

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).

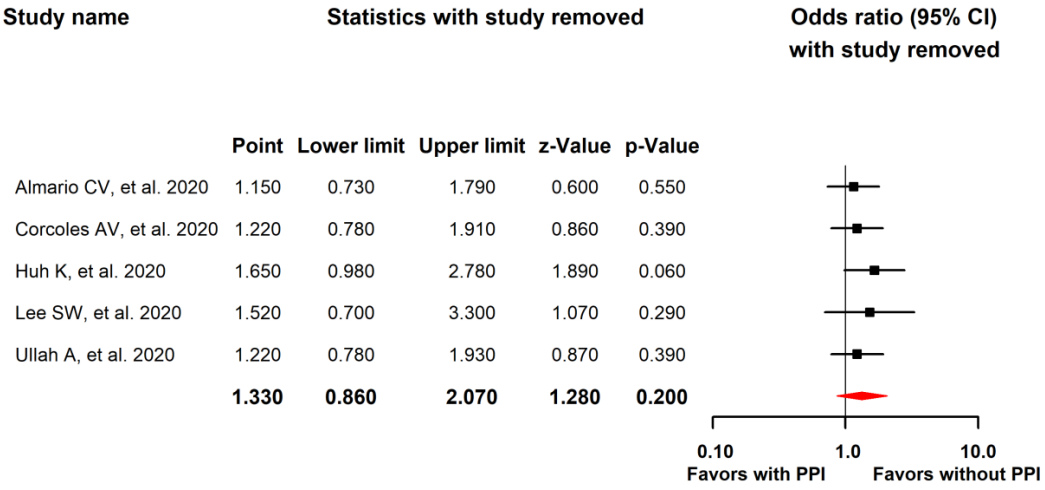


Supplementary figure 1

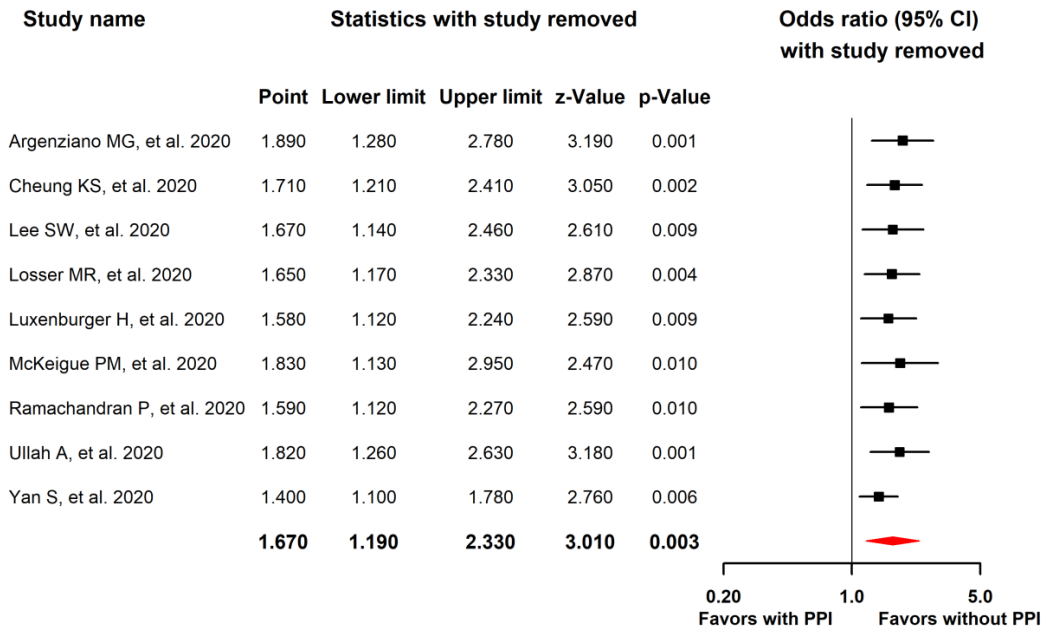
Supplementary figure 2: Subgroup analysis of Korean versus non-Korean cohorts for the association between PPI use and risk of SARS-CoV-2 infection



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



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



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 outcomes of COVID-19*	Yes
Almario 2020[2]	Retrospective cohort	USA	May 3 to Jun 24, 2020	NR	48	53130	16547	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	≥ 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

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.