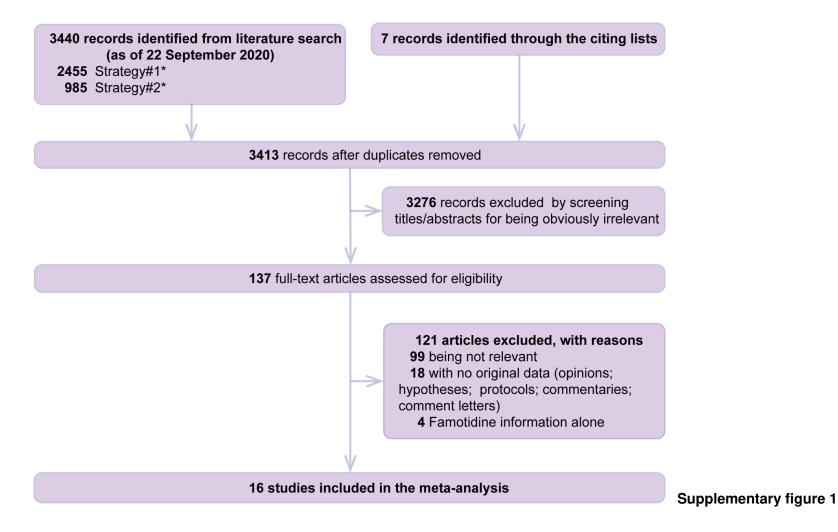
#### Supplementary figure 1: Flow chart for study selection

\*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] SI	<u>Weight</u>	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 Korean studies				
Huh K, et al. 2020	-0.478 0.047	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 <sup>2</sup> = 0.07	; Chi <sup>2</sup> = 24.46, df = 1 (P <	0.00001); 1	<sup>2</sup> = 96%	
Test for overall effect: Z =	1.57 (P = 0.12)	·		
1.2.2 non-Korean studies	i			
Almario CV, et al. 2020	1.026 0.266	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	7 20.0%	1.82 [1.36, 2.42]	
Subtotal (95% CI)		56.8%	1.94 [1.59, 2.36]	•
Heterogeneity: Tau <sup>2</sup> = 0.00	P; Chi <sup>2</sup> = 2.21, df = 2 (P = 0	.33); $I^2 = 9^{\circ}$	%	
Test for overall effect: Z = 6	6.56 (P < 0.00001)			
Total (95% CI)		100.0%	1.33 [0.86, 2.07]	-
Heterogeneity: Tau <sup>2</sup> = 0.23	; Chi <sup>2</sup> = 121.46, df = 4 (P ·	< 0.00001);	$I^2 = 97\%$	
Test for overall effect: Z =			0.2	
Test for subaroup difference	` '	< 0.00001	). I <sup>2</sup> = 95.1%	Favors with PPI Favors without PPI

# 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				Odds ratio (95% CI) with study 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	+	<b>-</b>		
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	-			
					0.1 Favo	0 1.0 ors with PPI	10.0 Favors without PPI		

## 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 (9 with study re	•		
	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		<del>_</del>
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		5.0
					Favo	ors with PPI Favo	ors without PPI

#### 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 <sup>1</sup>	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 <sup>2</sup>	Retrospective cohort	USA	May 3 to Jun 24, 2020	NR	48	53130	16547	SARS-CoV-2 infection	Yes
Ullah 2020 <sup>3</sup>	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 <sup>4</sup>	Retrospective cohort	Spain	May 1 to Apr 3, 2020	≥ 50	48.1	34936	11807	SARS-CoV-2 infection	No
Huh 2020 <sup>5</sup>	Case-control	Korea	Up to Apr 8, 2020	49	48.7	65149	14167	SARS-CoV-2 infection	Yes
Tarlow 2020 <sup>6</sup>	Retrospective cohort	USA	NR	NR	NR	84325	18240	SARS-CoV-2 infection	No
Ramachandran 2020 <sup>7</sup>	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 <sup>8</sup>	Retrospective cohort	Germany	NR	65	56.6	152	62	Severe outcomes of COVID-19*	No
McKeigue 2020 <sup>9</sup>	Case-control	Scotland	Up to Jun 6, 2020	NR	NR	41220	2715	Severe outcomes of COVID-19*	No
Argenziano 2020 <sup>10</sup>	Retrospective cohort	USA	Mar 1 to Apr 5, 2020	63	59.6	1000	163	Severe outcomes of COVID-19*	No
Cheung 2020 <sup>11</sup>	Retrospective cohort	Hongkong	Jan 1 to May 10, 2020	NR	NR	952	27	Severe outcomes of COVID-19*	Yes
Losser 2020 <sup>12</sup>	Case series (individual)	France	Mar16 to Apr 12, 2020	70	58.8	17	6	Severe outcomes of COVID-19*	No
Yan 2020 <sup>13</sup>	Retrospective cohort	China	Jan 22 to Mar 13, 2020	51	48.2	168	32	Severe outcomes of COVID-19*	No
Zhang 2020 <sup>14</sup>	Retrospective cohort	China	Jan 20 to Mar 16, 2020	50	55.2	58	29	Duration of hospital stay	Yes

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

<sup>\*</sup>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.