ORIGINAL RESEARCH

Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching

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ABSTRACT

Objective The adverse effects of proton pump inhibitors (PPIs) have been documented for pneumonia; however, there is no consensus regarding whether the use of PPIs might be harmful regarding the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In this regard, we aimed to measure the potential associations of the current use of PPIs with the infection rates of COVID-19 among patients who underwent SARS-CoV-2 testing.

Design Data were derived from a Korean nationwide cohort study with propensity score matching. We included 132 316 patients older than 18 years who tested for SARS-CoV-2 between 1 January and 15 May 2020. Endpoints were SARS-CoV-2 positivity (primary) and severe clinical outcomes of COVID-19 (secondary: admission to intensive care unit, administration of invasive ventilation or death).

Results In the entire cohort, there were 111 911 non-users, 14 163 current PPI users and 6242 past PPI users. After propensity score matching, the SARS-CoV-2 test positivity rate was not associated with the current or past use of PPIs. Among patients with confirmed COVID-19, the current use of PPIs conferred a 79% greater risk of severe clinical outcomes of COVID-19, while the relationship with the past use of PPIs remained insignificant. Current PPI use starting within the previous 30 days was associated with a 90% increased risk of severe clinical outcomes of COVID-19.

Conclusion Patients taking PPIs are at increased risk for severe clinical outcomes of COVID-19 but not susceptible to SARS-CoV-2 infection. This suggests that physicians need to assess benefit–risk assessments in the management of acid-related diseases amid the COVID-19 pandemic.

Significance of this study

What is already known on this subject?

- A novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a global respiratory disease outbreak called COVID-19 that was first reported in December 2019.
- The adverse effects of proton pump inhibitor (PPI) have been documented several times over the past decade in patients with pneumonia, in association with ventilator-associated adverse events, and even mortality.

What are the new findings?

- We found that PPI usage, including current and past use, did not increase susceptibility to SARS-CoV-2 infection in a Korean nationwide cohort.
- Current PPI usage was associated with worse outcomes of COVID-19.
- The short-term current use of PPIs (<1 month) conferred a significantly increased risk of worse clinical outcomes of COVID-19.

How might it impact on clinical practice in the foreseeable future?

- Our findings provide an improved understanding of the relationship of COVID-19 and PPIs and suggest that clinicians should be aware of the increased risks of these agents in patients with COVID-19.
- This suggests that physicians need to assess benefit–risk assessments in the management of acid-related diseases amid the COVID-19 pandemic.

INTRODUCTION

A novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a global respiratory disease outbreak called COVID-19 that was first reported in December 2019.[1 2] Mortality rates have varied widely among nations and patient cohorts, and COVID-19-related risks are still being identified.[3 4] There are several confirmed risk factors of COVID-19, including old age,[1] chronic pulmonary disease and smoking,[3] cardiovascular disease,[3] chronic kidney disease,[3] diabetes mellitus and obesity,[5] malignancy[6] and chronic HIV infection.[7] Concerns have been raised regarding the use of various medications with respect to the risk of COVID-19; nevertheless, these issues have not been completely confirmed. Recently, it was found that ACE inhibitors possess possible modulating effects on disease severity; nevertheless, there is no evidence of the association of the

use of renin–angiotensin–aldosterone system inhibitors in the context of COVID-19 infection.[8]

Proton pump inhibitors (PPIs) have been commonly prescribed for the management of gastrointestinal acid-related disorders (GERD and peptic ulcer disease).[9] The adverse effects of PPI have been documented several times over the past decade in patients with pneumonia,[10] in association with ventilator-associated adverse events,[11] and even mortality.[9] Nevertheless, with respect to the risk and severity of SARS-CoV-2 infection, there is no consensus regarding whether the use of PPIs might be beneficial or harmful.

Given these reports and observations, we developed the hypothesis that the current use of PPIs might influence the susceptibility to SARS-CoV-2 infection and would increase the likelihood of worse clinical outcomes of COVID-19. Using a large-scale, population-based, nationwide cohort in Korea, we measured the potential associations of the current use of PPIs with the infection rates of COVID-19 among patients who underwent SARS-CoV-2 testing; we also assessed the influence of current PPI administrations to the disease severity of COVID-19 in patients with laboratory-confirmed COVID-19.

METHODS

Data source

Data were obtained from the Korean national health insurance claims-based database. This large-scale cohort provided data of all individuals who underwent SARS-CoV-2 testing in South Korea through services facilitated by the Health Insurance Review & Assessment Service of Korea, Korea Centers for Disease Control and Prevention and Ministry of Health and Welfare between 1 January 2020 and 15 May 2020 by medical or Korea Centers for Disease Control referral (excluding self-referral) (n=234 427). The Korean Government provided mandatory and complementary health insurance for all patients with COVID-19 during the pandemic. Therefore, access to information consisting of personal data, healthcare records of inpatients and outpatients within 3 years (including healthcare visits, prescriptions, diagnoses and procedures), pharmaceutical visits, COVID-19-related outcomes and death records were available in this cohort database. All patient-related records used in our study were anonymised to ensure confidentiality.

Study population

The date of the first SARS-CoV-2 test for each patient was defined as the entry date (individual index date) of the cohort. Among the total of 234 427 patients who underwent SARS-CoV-2 tests, patients were excluded if they were younger than 18 years (n=14 467); if they had a record of an H2-blocker prescription within 1 year of the index date (n=87 784) or if they had a record of a non-steroidal anti-inflammatory drug (NSAID) new prescription within 1 month of the index date (n=2347). The final sample who underwent SARS-CoV-2 tests comprised 132 316 individuals, of whom 4785 showed positive results for SARS-CoV-2.

The laboratory confirmation of SARS-CoV-2 infection was defined as a positive result of real-time reverse transcriptase PCR assay of nasal and pharyngeal swabs, in accordance with World Health Organization guidelines.[8] We combined the claims-based data from the national health insurance service between 1 January 2017 and 15 May 2020 and extracted information on the age, sex and region of residence from the insurance eligibility data. The history of underlying diseases (diabetes mellitus, hypertension, cardiovascular disease,

Table 1 Baseline characteristics of all patients who underwent SARS-CoV-2 testing in Korean nationwide cohort (N=132 316)

		Entire cohort		
Characteristic	Entire cohort	None	Current use of PPI	Past use of PPI
Total, N (%)	132 316	111 911	14 163	6242
Age, years, mean (SD)	48.0 (19.7)	46.7 (19.6)	56.3 (18.9)	52.2 (18.7)
Sex, n (%)				
Male	67 480 (51.0)	57 408 (51.3)	7070 (49.9)	3002 (48.1)
Female	64 836 (49.0)	54 503 (48.7)	7093 (50.1)	3240 (51.9)
Region of residence, n (%)				
Rural	59 364 (44.1)	49 760 (44.5)	5927 (41.9)	2677 (42.9)
Urban	73 952 (55.9)	62 151 (55.5)	8236 (58.2)	3565 (57.1)
History of diabetes mellitus, n (%)	20 419 (15.4)	15 235 (13.6)	3840 (27.1)	1344 (21.5)
History of cardiovascular disease, n (%)	17 392 (13.1)	12 667 (11.3)	3621 (25.6)	1104 (17.7)
History of cerebrovascular disease, n (%)	11 986 (9.1)	9183 (8.2)	2145 (15.2)	658 (10.5)
History of COPD, n (%)	8745 (6.6)	6293 (5.6)	1806 (12.8)	646 (10.4)
History of asthma, n (%)	14 531 (11.0)	10 648 (9.5)	2828 (20.0)	1055 (16.9)
History of hypertension, n (%)	36 134 (27.3)	27 699 (24.8)	6288 (44.4)	2147 (34.4)
History of chronic kidney disease, n (%)	9046 (6.8)	6947 (6.2)	1570 (11.1)	529 (8.5)
Charlson Comorbidity Index, n (%)				
0	78 981 (59.7)	70 954 (63.4)	5150 (36.4)	2877 (46.1)
1	13 828 (10.5)	11 042 (9.9)	1890 (13.3)	896 (14.4)
≥2	39 507 (29.9)	29 945 (26.7)	7123 (50.3)	2469 (39.6)
Current use of medication, n (%)				
Systemic steroid	38 237 (28.9)	30 270 (27.1)	5762 (40.7)	2205 (35.3)
Metformin	10 158 (7.7)	7672 (6.9)	1879 (13.3)	607 (9.7)
Aspirin	8049 (6.1)	5769 (5.2)	1787 (12.6)	493 (7.9)

COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

cerebrovascular disease, chronic obstructive pulmonary diseases (COPD), asthma and chronic kidney disease) were confirmed by the assignment of at least two claims within 1 year using the appropriate International Classification of Diseases, 10th revision (ICD-10) code.[12] The Charlson Comorbidity Index score was calculated from the ICD-10 codes by previously reported methods.[12] The region of residence was classified as rural (ie, Gyeonggi, Gangwon, Gyeongsangbuk, Gyeongsangnam, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam and Jeju) or urban (eg, Seoul, Sejong, Busan, Incheon, Daegu, Gwangju, Daejeon and Ulsan).[13–15] The current use of selected drugs taken within 30 days before the index date included systemic steroids, metformin and aspirin.[16]

Exposure

We identified all PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, dexlansoprazole, ilaprazole and rabeprazole) prescribed within 1 year before the index date. Current PPI users were defined as patients who took PPIs 1–30 days before the index date. Past PPI users were defined as patients who took PPIs 31–365 days before the index date.[16 17] Non-users were defined as patients who had never received PPIs within 1 year before the index date.[16 17]

Outcomes

The primary outcome was defined as a positive laboratory test result for SARS-CoV-2.[18] The secondary outcomes were a composite endpoint 1 (requirement of oxygen therapy, intensive care unit admission, administration of invasive ventilation or death) and a composite endpoint 2 (severe clinical outcomes of COVID-19, intensive care unit admission, administration of invasive ventilation or death).[3]

Statistical analysis

We performed four rounds of propensity score matching to balance the baseline characteristics of the two groups and to reduce potential confounders using a logistic regression model with adjustment for the following: age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension or chronic kidney disease; Charlson Comorbidity Index (0, 1 or ≥2); and current use of systemic steroid, metformin or aspirin. We assessed each propensity score matching of the two groups in a 1:1 ratio using a 'greedy nearest-neighbour' algorithm and calculated the predicted probability of (1) current PPI users versus non-users among all patients who underwent SARS-CoV-2 testing (n=132 316), (2) past PPI users versus non-users among all patients who underwent SARS-CoV-2 testing, (3) current PPI users versus non-users among patients with confirmed COVID-19 (n=4785) and (4) past PPI users versus non-users among patients with confirmed COVID-19. Adequacy matching for no major imbalance of each baseline covariate was assessed by comparing distributions of propensity score (online supplementary figures S1–S4) and

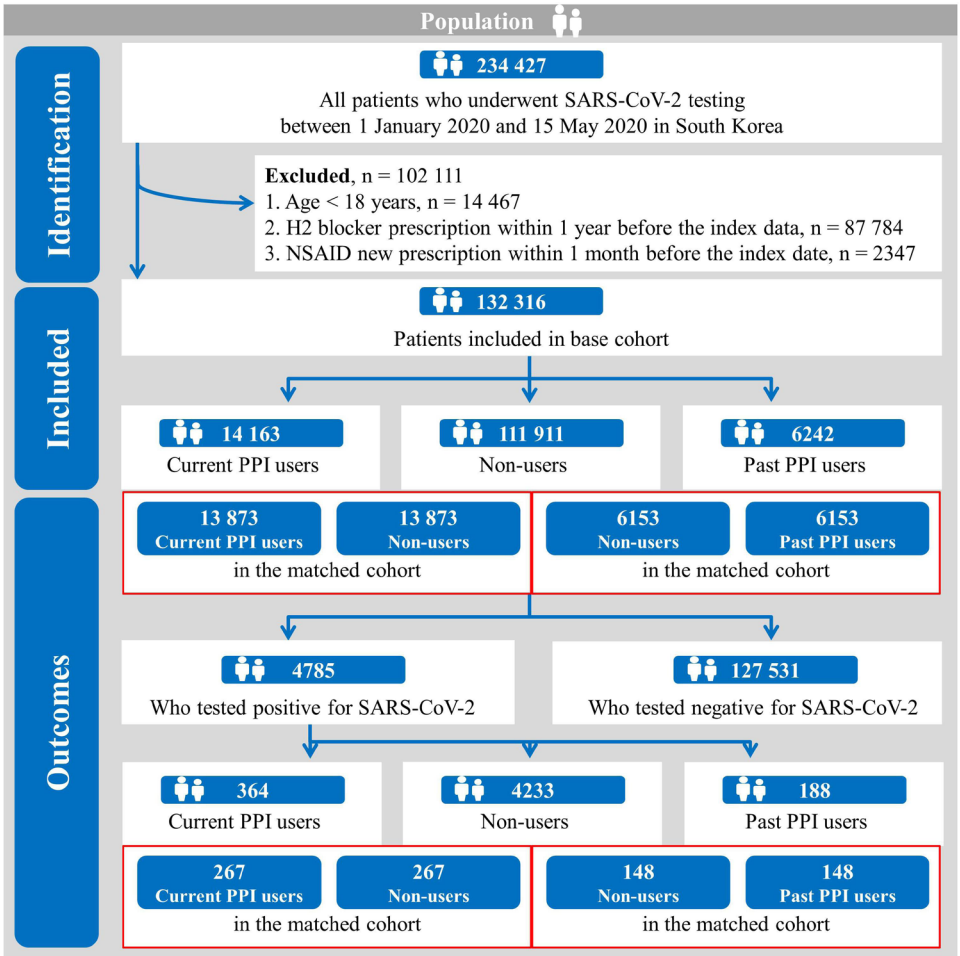


Figure 1 Disposition of patients in the Korean nationwide cohort. NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

standardised mean differences (SMDs), which is more meaningful than calculating the p-values of t-tests.[12]

The exposure was the current or past use of PPIs. The primary endpoint was SARS-CoV-2 test result positivity. The secondary endpoints were the composite endpoint and severe clinical outcomes of COVID-19 among patients with confirmed COVID-19. Data were analysed using logistic regression models and were expressed as adjusted ORs (aORs) with 95% CIs for the two groups after adjustment for potential confounders as follows: age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension and chronic kidney disease; Charlson Comorbidity Index; and current use of systemic steroid, metformin and aspirin. Additional analyses were performed to establish the robustness of our results; current PPI users were stratified by duration of use (<30 vs ≥30 days).

Patient and public involvement

No patients were directly involved in designing the research question or in conducting the research. No patients were asked for advice on interpretation or writing up of the results. There are no plans to involve patients or the relevant patient community in dissemination of study findings at this time.

RESULTS

Descriptive overview

Among the total of 132 316 patients who underwent SARS-CoV-2 testing, we identified 14 163 patients with current use of PPIs, 6242 with past use of PPIs and 111 911 without any history of PPI administration in the full unmatched cohort. The baseline characteristics of the entire cohort are displayed in table 1. The mean age at entry to the study was 48.0 years (SD 19.7 years) in the entire cohort, and 67 480 (51%) were males. Individuals with no history of PPI usage were likely to be younger, with lower rates of comorbidities and other concurrent medications (table 1 and figure 1).

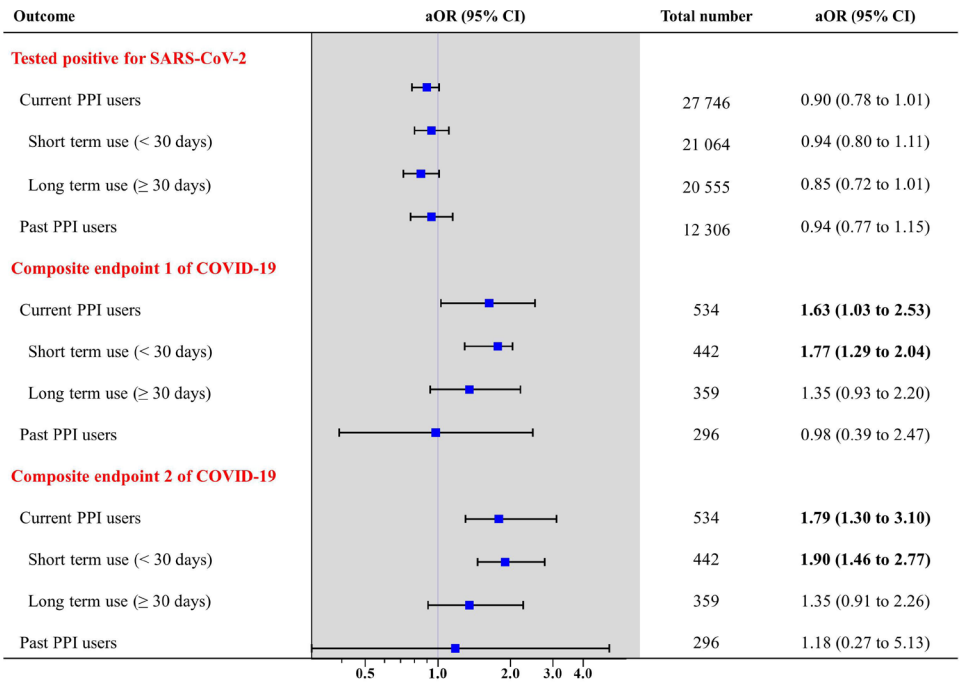
SARS-CoV-2 test result positivity risks for current and past PPI administration

In the two cohorts, individuals with current use of PPIs (n=13 873) and those with history of past use of PPIs (n=6153) were matched individually to an equal number of non-PPI exposed patients in our two propensity score-matched cohorts (table 2). No major imbalances in the demographics and clinical characteristics were observed when evaluated using SMD within groups in the propensity-matched cohorts (table 2 and figure 2; SMD all <0.05). The SARS-CoV-2 test positivity rate in patients without history of PPI use was 3.1% (434/13 874)

Table 2 Propensity score-matched baseline characteristics and SARS-CoV-2 infection test positivity among none versus current use of PPI groups or none versus past use of PPI usage groups in all patients tested for SARS-CoV2

	None versus current use of PPI			None versus past use of PPI		
Characteristic	None	Current use of PPI	SMD	None	Past use of PPI	SMD
Total, N (%)	13 873	13 873		6153	6153	
Age, years (SD)	56.9 (19.7)	55.9 (18.8)	0.048	52.3 (19.3)	51.9 (18.6)	0.020
Sex, n (%)			0.023			0.008
Male	6754 (48.7)	6915 (49.9)		2979 (48.4)	2953 (48.0)	
Female	7119 (51.3)	6958 (50.2)		3174 (51.6)	3200 (52.0)	
Region of residence, n (%)			0.009			0.003
Rural	5762 (41.5)	5825 (42.0)		2629 (42.7)	2639 (42.9)	
Urban	8111 (58.5)	8048 (58.0)		3524 (57.3)	3514 (57.1)	
History of diabetes mellitus, n (%)	3536 (25.5)	3631 (26.2)	0.017	1262 (20.5)	1282 (20.8)	0.009
History of cardiovascular disease, n (%)	3201 (23.1)	3367 (24.3)	0.031	957 (15.6)	1041 (16.9)	0.039
History of cerebrovascular disease, n (%)	1998 (14.4)	2040 (14.7)	0.009	589 (9.6)	649 (10.6)	0.033
History of COPD, n (%)	1525 (11.0)	1646 (11.9)	0.030	525 (8.5)	592 (9.6)	0.040
History of asthma, n (%)	2544 (18.3)	2612 (18.8)	0.014	972 (15.8)	986 16.0)	0.007
History of hypertension, n (%)	6116 (44.1)	6018 (43.4)	0.015	2065 (33.6)	2080 (33.8)	0.005
History of chronic kidney disease, n (%)	1423 (10.3)	1503 (10.8)	0.021	470 (7.6)	515 (8.4)	0.028
Charlson Comorbidity Index, n (%)			0.010			0.002
0	5406 (39.0)	5150 (37.1)		2954 (48.0)	2876 (46.7)	
1	1845 (13.3)	1889 (13.6)		860 (14.0)	893 (14.5)	
≥2	6622 (47.7)	6834 (49.6)		2339 (38.0)	2384 (38.8)	
Current use of medication, n (%)						
Systemic steroid	5351 (38.6)	5503 (39.7)	0.023	2073 (33.7)	2132 (34.7)	0.021
Metformin	1733 (12.5)	1768 (12.7)	0.008	584 (9.5)	595 (9.7)	0.006
Aspirin	1540 (11.1)	1635 (11.8)	0.024	441 (7.2)	471 (7.7)	0.020
COVID-19, n (%)	434 (3.1)	362 (2.6)		201 (3.3)	188 (3.1)	
Minimally adjusted OR*	1.00 (reference)	0.88 (0.77 to 1.01)		1.00 (reference)	0.93 (0.76 to 1.14)	
Fully adjusted OR†	1.00 (reference)	0.90 (0.78 to 1.01)		1.00 (reference)	0.94 (0.77 to 1.15)	

An SMD <0.1 indicates no major imbalance. All SMD values were <0.05 in the each propensity score-matched cohort.
*Minimally adjusted: adjustment for age and sex.
†Fully adjusted: adjustment for age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension and chronic kidney disease; Charlson Comorbidity Index (0, 1 or ≥2); and current use of systemic steroid, metformin and aspirin.
COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, standardised mean difference.



Number in bold indicate significant differences (P < 0.05).

Figure 2 Propensity score-matched association of proton pump inhibitor (PPI) (1) tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among all patients who underwent SARS-CoV-2 testing, (2) composite endpoint of COVID-19 among patients who tested positive for SARS-CoV-2 and (3) severe outcomes of COVID-19 among patients who tested positive for SARS-CoV-2. Composite endpoint 1 consisted of requiring oxygen therapy, admission to the intensive care unit, invasive ventilation or death. Composite endpoint 2 consisted of admission to the intensive care unit, invasive ventilation or death. Risk factors were adjusted for age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension and chronic kidney disease; Charlson Comorbidity Index (0, 1 or ≥2); and current use of systemic steroid, metformin and aspirin. aOR, adjusted OR.

compared with 2.6% (362/13 874) in those with current use of PPI (no use of PPI versus current use of PPI (aOR, 0.90; 95% CI, 0.78 to 1.01). The SARS-CoV-2 test positivity rate in patients without history of PPI use was 3.3% (201/6153) compared with 3.1% (188/6153) with past use of PPI (aOR, 0.94; 95% CI, 0.77 to 1.15).

Characteristic features in patients who were diagnosed with COVID-19

The overall positivity rate of SARS-CoV-2 in our entire cohort was 3.61% (4785/132 316). Among these patients, 364 had a history of current use of PPIs, 188 used PPIs in the past and the remaining 4233 had no history of PPI usage. The baseline characteristics of patients with confirmed laboratory COVID-19 are displayed in table 3.

Baseline characteristics and clinical outcomes in patients with confirmed laboratory SARS-CoV-2 infection

We conducted a propensity score-matched analysis among patients with positive SARS-CoV-2 test results. Those diagnosed with COVID-19 plus history of current use of PPIs (n=267) and history of past use of PPIs (n=148) were matched to equal numbers of non-PPI-using patients. The baseline characteristics of patients with confirmed laboratory diagnosis of COVID-19 with or without current/past PPI administrations are displayed in table 3. No major imbalances in the demographics and clinical characteristics were observed when evaluated using SMD within groups in the propensity-matched cohorts (table 4; SMD all <0.1), except for the Charlson Comorbidity Index among none versus past use of PPI groups (SMD=0.134). Of note, the current use of PPIs was related to the increased risk of the composite endpoint 1 of COVID-19 (table 4 and figure 2; aOR 1.63; 95% CI, 1.03 to 2.53) while the relationship with past PPI use was insignificant (aOR 0.98; 95% CI, 0.39 to 2.47). The current use of PPIs was also related to increased risk for severe outcomes of COVID-19 (composite endpoint 2; aOR 1.79; 95% CI, 1.30 to 3.10), while the relationship with past PPI was insignificant (aOR 1.18; 95% CI, 0.27 to 5.13).

Association of the SARS-CoV-2 test result positivity with the duration of PPI usage

Regarding the duration of PPI usage, we performed a subgroup analysis comparing patients with no history of PPI usage to patients with current use of PPIs. The positivity of SARS-CoV-2 tests between these two groups were not significantly different when for those taking PPIs for less than 30 days (aOR 0.94; 95% CI, 0.80 to 1.11), 30 days or longer (aOR 0.85; 95% CI, 0.72 to 1.01). However, the risks of the composite endpoint 1 of COVID-19 (aOR 1.77; 95% CI, 1.29 to 2.04) and severe clinical outcomes (composite endpoint 2; aOR 1.90; 95% CI, 1.46 to 2.77) were significantly higher in patients who took PPIs for less than 30 days than in patients who have never taken PPIs (table 5 and figure 2).

DISCUSSION

In this Korean nationwide cohort, we investigated whether PPI usage increased susceptibility to SARS-CoV-2 infection among 132 316 patients who underwent SARS-CoV-2 testing, as well as whether there were worse outcomes of COVID-19 among 4785 patients. We found that PPI usage, including current and past

Table 3 Baseline characteristics of patients with confirmed laboratory COVID-19 in a Korean nationwide cohort (N=4785)

		Patients with confirmed laboratory COVID-19		
Characteristic	Entire cohort	None	Current use of PPI	Past use of PPI
Total, N (%)	4785	4233	364	188
Age, years, mean (SD)	45.4 (18.8)	44.4 (18.8)	53.8 (16.9)	52.4 (17.6)
Sex, n (%)				
Male	2103 (44.0)	1893 (44.7)	135 (37.1)	75 (39.9)
Female	2682 (56.1)	2340 (55.3)	229 (62.9)	113 (60.1)
Region of residence, n (%)				
Rural	2367 (49.5)	2096 (49.5)	184 (50.6)	87 (46.3)
Urban	2418 (50.5)	2137 (50.5)	180 (49.5)	101 (53.7)
History of diabetes mellitus, n (%)	524 (11.0)	435 (10.3)	57 (15.7)	32 (17.0)
History of cardiovascular disease, n (%)	263 (5.5)	209 (4.9)	35 (9.6)	19 (10.1)
History of cerebrovascular disease, n (%)	272 (5.7)	203 (4.8)	47 (12.9)	22 (11.7)
History of COPD, n (%)	185 (3.9)	142 (3.4)	31 (8.5)	12 (6.4)
History of asthma, n (%)	338 (7.1)	269 (6.4)	44 (12.1)	25 (13.3)
History of hypertension, n (%)	945 (19.8)	771 (18.2)	118 (32.4)	56 (29.8)
History of chronic kidney disease, n (%)	150 (3.1)	113 (2.7)	25 (6.9)	12 (6.4)
Charlson Comorbidity Index, n (%)				
0	3431 (71.7)	3148 (74.4)	180 (49.5)	103 (54.8)
1	439 (9.2)	356 (8.41)	61 (16.8)	22 (11.7)
≥2	915 (19.1)	729 (17.2)	123 (33.8)	63 (33.5)
Current use of medication, n (%)				
Systemic steroid	1030 (21.5)	848 (20.0)	131 (36.0)	51 (27.1)
Metformin	315 (6.6)	252 (6.0)	48 (13.2)	15 (8.0)
Aspirin	166 (3.5)	122 (2.9)	29 (8.0)	15 (8.0)

COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor.

use, did not increase susceptibility to SARS-CoV-2 infection; however, current PPI usage was associated with worse outcomes of COVID-19. Notably, patients with COVID-19 with short-term current use of PPI for less than 1 month had a significantly increased likelihood of worse clinical outcomes of COVID-19.

Possible explanations of our results (SARS-CoV-2 susceptibility and PPI)

In our study, PPI usage did not increase susceptibility to COVID-19. There is concern that PPI usage may increase the risk of pneumonia from a pharmacodynamic perspective. Previous studies suggested that PPI usage possibly impairs the immune system and influences susceptibility to infections, resulting in increased risks of pneumonia through effects on polymorphonuclear neutrophils, cytotoxic T lymphocytes and natural killer cell activities.[19] Furthermore, the excessive suppression of gastric acid likely caused by PPIs increases the alkalinity of the stomach, possibly resulting in insufficient eradication of ingested pathogens, with alteration of various immune-modulatory and anti-inflammatory effects.[20] However, a recent meta-analysis has reported that the association between PPIs and pneumonia may be overestimated due to heterogeneity and bias and failure to account for protopathic bias or reverse causality.[21] Short-term NSAID users for early pneumonia symptoms may initiated for PPIs, so we excluded short-term new NSAID users and then similar results described from previous study.[21]

Possible explanations of our results (severe clinical outcomes of COVID-19 and PPI)

SARS-CoV-2 most likely infects respiratory epithelial cells and spreads among humans via contact or inhalation of droplets.[22] It has been highlighted that ACE 2 of type 2 alveolar epithelial cells, which are also expressed in the testis, brain and intestinal cells, serve as receptors for severe acute respiratory syndrome coronavirus 1.[22 23] This suggests that not only the respiratory tract but also the GI tract may serve as points of entry.[24 25] The higher expression of ACE-2 allows higher viral entry to cells,[26] resulting in higher viral loads, possibly causing more severe disease due to cytokine storm. Because the GI tract expresses higher levels of ACE-2, individuals who use PPIs may be more vulnerable to the effect of high viral loads. Even in respiratory tract diseases, individuals with more virus colonisation in the stomach due to increased gastric alkalinity caused by PPI administration may be more susceptible to severe courses of COVID-19. Interestingly, patients with immune-mediated disorders (ie, rheumatoid arthritis, psoriasis, ankylosing spondylitis and IBDs) who are treated with anticytokine therapy are not vulnerable to severe clinical outcomes of COVID-19.[27] Anticytokine therapy may have a protective effect against the cytokine storm. In this respect, PPI usage may lead to worse outcomes of COVID-19, resulting from a more intense cytokine storm. In a study of Middle East respiratory syndrome coronavirus (MERS-CoV), lethal outcomes were observed in mice treated with PPIs after enteric infection for MERS-CoV by intragastric inoculation[28] ; this supports our finding of an association between severe coronaviral infection and PPI usage.

Previous studies reported that the short-term (usually less than 30–90 days) use of PPIs was more likely to be associated with the increased risk of pneumonia, while no increased risk was observed with the long term (>180 days) use of PPIs.[29–31] Moreover, patients with COVID-19 with other viral or bacterial coinfection are likely to experience a severe form of COVID-19,[32] and the short-term use of PPI may raise the risk of coinfection with SARS-CoV-2 infection. This might be explained by decreased immune regulation due to long-term PPI use and decreased compliance during long-term PPI administration, resulting in decreased gastric acid suppression compared with short-term usage.[29 30] In this respect, our study also showed similar results, in that the short-term current use of PPI was associated with worse outcomes in patients with COVID-19.

Strengths and limitations

The present study has several limitations. First, the majority of patients were included based on medication prescriptions. The ascertainment of medication use from the electronic health record may not reflect actual drug exposure; however, patients cannot receive PPIs without a prescription in Korea. PPI prescription from a physician can be thought as an absolute surrogate for PPI use in Korea.[33]

Table 4 Propensity score-matched baseline characteristics and clinical outcomes of COVID-19 among none versus current use of PPI groups or none versus past use of PPI usage groups in patients with confirmed laboratory SARS-CoV-2 infection

	None versus current use of PPI			None versus past use of PPI		
Characteristic	**None**	**Current use of PPI**	**SMD**	**None**	**Past use of PPI**	**SMD**
Total, N (%)	267	267		148	148	
Age, years (SD)	50.3 (17.9)	50.1 (16.6)	0.009	48.55 (17.1)	49.0 (16.9)	0.025
Sex, n (%)			0.007			0.069
Male	100 (37.5)	101 (37.8)		58 (39.2)	63 (42.6)	
Female	167 (62.6)	166 (62.2)		90 (60.8)	85 (57.4)	
Region of residence, n (%)			0.037			0.027
Rural	150 (56.2)	145 (54.3)		71 (48.0)	73 (49.3)	
Urban	117 (43.8)	122 (45.7)		77 (52.0)	75 (50.7)	
History of diabetes mellitus, n (%)	31 (11.6)	24 (9.0)	0.078	16 (10.8)	20 (13.5)	0.079
History of cardiovascular disease, n (%)	18 (6.7)	18 (6.7)	<0.001	6 (4.1)	8 (5.4)	0.051
History of cerebrovascular disease, n (%)	14 (5.2)	15 (5.6)	0.013	4 (2.7)	6 (4.1)	0.050
History of COPD, n (%)	4 (1.5)	6 (2.2)	0.052	7 (4.7)	5 (3.4)	0.063
History of asthma, n (%)	17 (6.4)	23 (8.6)	0.078	12 (8.1)	13 (8.8)	0.023
History of hypertension, n (%)	62 (23.2)	61 (22.9)	0.009	32 (21.6)	33 (22.3)	0.016
History of chronic kidney disease, n (%)	10 (3.7)	8 (3.0)	0.039	3 (2.0)	2 (1.4)	0.033
Charlson comorbidity index, n (%)			0.016			0.134
0	186 (69.7)	166 (62.2)		101 (68.2)	97 (65.5)	
1	29 (10.9)	43 (16.1)		21 (14.2)	16 (10.8)	
≥2	52 (19.5)	58 (21.7)		26 (17.6)	35 (23.7)	
Current use of medication, n (%)						
Systemic steroid	79 (29.6)	79 (29.6)	<0.001	36 (24.3)	30 (20.3)	0.096
Metformin	22 (8.2)	15 (5.6)	0.090	9 (6.1)	12 (8.1)	0.080
Aspirin	10 (3.8)	14 (5.2)	0.067	4 (2.7)	6 (4.1)	0.060
Composite endpoint 1*, n (%)	32 (12.0)	49 (18.4)		13 (8.8)	15 (10.1)	
Minimally adjusted OR†	1.00 (reference)	**1.69 (1.18 to 2.56)**		1.00 (reference)	1.11 (0.46 to 2.64)	
Fully adjusted OR‡	1.00 (reference)	**1.63 (1.03 to 2.53)**		1.00 (reference)	0.98 (0.39 to 2.47)	
Composite endpoint 2§, n (%)	14 (5.2)	24 (9.0)		5 (3.4)	7 (4.7)	
Minimally adjusted OR†	1.00 (reference)	**1.82 (1.34 to 2.98)**		1.00 (reference)	1.02 (0.29 to 3.65)	
Fully adjusted OR‡	1.00 (reference)	**1.79 (1.30 to 3.10)**		1.00 (reference)	1.18 (0.27 to 5.13)	

An SMD <0.1 indicates no major imbalance. All SMD values were <0.1 in the each propensity score-matched cohort, except Charlson Comorbidity Index among none versus past use of PPI groups. Numbers in bold indicate significant differences (p<0.05).
*Composite endpoint 1 consisted of requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation or death.
†Minimally adjusted: adjustment for age and sex.
‡Fully adjusted: adjustment for age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension and chronic kidney disease; Charlson Comorbidity Index (0, 1 or ≥2); and current use of systemic steroid, metformin and aspirin.
§Composite endpoint 2 consisted of admission to the intensive care unit, invasive ventilation or death.
COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, standardised mean difference.

Second, sensitivity for the laboratory SARS-CoV-2 test used in our cohort may be subject to false negatives and false positives. Although real-time reverse transcription PCR is currently the most reliable diagnostic method for COVID-19, it nevertheless suffers from limitations.[8 34] Inadequate specimen collection, date of collection and antiviral administration prior to testing generate false-negative results. However, in our study, every specimen was collected according to the guidelines of the Korea Centers for Disease Control and Prevention, suggesting that the accuracy was high because the specimens were collected by skilled medical personnel at designated hospitals.[34]

Third, there may be additional unmeasured confounders influencing our results, including genetic polymorphisms, smoking and body mass index. The pharmacodynamics and pharmacokinetics of PPIs are affected by each patient's Cytochrome P450 2C19 and gastric H^+ K^+-ATPase genotype.[35] The link between adverse drug reactions and genetic variability is complex; to date, no causal relationships (Mendelian randomisation studies) between CYP-enzyme polymorphisms and frequencies of adverse drug reactions have been directly documented.[35] Regarding missing covariates, including smoking status and body mass index, we adjusted the data for history of hypertension, diabetes and COPD, a well-known smoking-associated disorder.

Fourth, according to the period of PPI use, we did not consider over 3 years of PPI use. Because of the urgent global situation, the COVID-19-related data provided by Korea Government involved short-term data (maximum 3 years) for rapid processing. Furthermore, cumulative exposure, intermittent use and dose were not available. Long-term and short-term usage could be distinguished based on the interval of 30 days in our cohort. More longitudinal clinical studies are warranted to provide more information and to validate the association between PPIs and COVID-19.

Finally, our findings of SARS-CoV-2 susceptibility and PPI usage are based on a large sample data (n=234 427); however, we could not guarantee that most of the population had been exposed to SARS-CoV-2. Although we used a nationwide cohort sample, our result may have a selection bias. Nevertheless, our findings of clinical outcomes of COVID-19 and PPI usage accounted for protopathic bias since new NSAID users

Table 5 Propensity score-matched subgroup analyses for the potential association of the likelihood on SARS-CoV-2 test positivity with duration of PPI usage among all patients tested for SARS-CoV-2 and the likelihood on clinical outcomes with duration of PPI usage among patients with laboratory-confirmed SARS-CoV-2 infection

			Duration of PPI usage (days)	
Event	**Variable**	**None**	**<30**	**≥30**
None versus current use of PPI among all patients tested for SARS-CoV-2 (N=27 746)				
COVID-19	Event number/total number (%)	434/13873 (3.1)	212/7191 (2.9)	150/6682 (2.2)
	Minimally adjusted OR* (95% CI)	1 (reference)	0.92 (0.79 to 1.08)	0.86 (0.71 to 1.04)
	Fully adjusted OR† (95% CI)	1 (reference)	0.94 (0.80 to 1.11)	0.85 (0.72 to 1.01)
None versus current use of PPI among patients with laboratory-confirmed SARS-CoV-2 infection (N=534)				
Composite endpoint 1‡	Event number/total number (%)	32/267 (12.0)	34/175 (19.4)	15/92 (16.3)
	Minimally adjusted OR* (95% CI)	1 (reference)	**1.79 (1.37 to 2.34)**	1.40 (0.94 to 2.32)
	Fully adjusted OR† (95% CI)	1 (reference)	**1.77 (1.29 to 2.04)**	1.35 (0.93 to 2.20)
Composite endpoint 2§	Event number/total number (%)	14/267 (5.2)	18/175 (10.3	6/92 (6.5)
	Minimally adjusted OR* (95% CI)	1 (reference)	**1.92 (1.46 to 2.84)**	1.29 (0.90 to 2.05)
	Fully adjusted OR† (95% CI)	1 (reference)	**1.90 (1.46 to 2.77)**	1.35 (0.91 to 2.26)

Numbers in bold indicate significant differences (p<0.05).
*Minimally adjusted: adjustment for age and sex.
†Fully adjusted: adjustment for age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension and chronic kidney disease; Charlson Comorbidity Index (0, 1 or ≥2); and current use of systemic steroid, metformin and aspirin.
‡Composite endpoint 1 consisted of requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation or death.
§Composite endpoint 2 consisted of admission to the intensive care unit, invasive ventilation or death.
COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

were excluded from the study and propensity score matching was sufficiently designed. Furthermore, while we used the propensity score matching technique to reduce confounding, our statistical models might not completely eliminate channelling bias.[36] Since physicians are likely to prescript PPI to patients with more severe disease courses expected, the possibility of the channelling bias to occur cannot be excluded. Our study is preliminary but necessary for an ongoing global COVID-19 pandemic; however, a more precise research is needed later.

Despite the limitations, to the best of our knowledge, this is the first large-scale study to investigate the association between the risk of COVID-19 and PPI use. Our study provided potential evidence using a large sample size of patients (n=234 427), strict exclusion criteria (excluding H2-blocker users and NSAID new users) and a well-designed statistical technique using strict propensity score matching.

CONCLUSIONS

PPI usage including current and past did not increase susceptibility to SARS-CoV-2 infection; however, current PPI usage was associated with worse outcomes of COVID-19 in a Korean nationwide cohort study with propensity score matching. Notably, the short-term current use of PPIs (<1 month) conferred a significantly increased risk of worse clinical outcomes of COVID-19. Our findings provide an improved understanding of the relationship of COVID-19 and PPIs and suggest that clinicians should be aware of the increased risks of these agents in patients with COVID-19. Guidance on the usage of PPIs in COVID-19 is urgently required considering the wide use of these agents worldwide. We expect that this study will help improve the control and management of the novel virus infection.

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