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Proton pump inhibitors associated with severe COVID-19 among two-dose but not three-dose vaccine recipients

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Ethical approval: This study was approved by the Central Institutional Review Board of the Hospital Authority of Hong Kong (CIRB-2021-005-4) and the DH Ethics Committee (LM171/2021).

Informed consent: Informed consent was not needed, as all subjects were anonymized in the electronic healthcare database system.

Abstract

Background and Aim: Proton pump inhibitors (PPIs) may increase the risk of COVID-19 among non-vaccinated subjects via various mechanisms, including gut dysbiosis. We aimed to investigate whether PPIs also affect the clinical outcomes of COVID-19 among vaccine recipients.

Methods: This was a territory-wide cohort study of 3 272 286 vaccine recipients (aged ≥ 18 years) of ≥ 2 doses of either BNT162b2 or CoronaVac. Exclusion criteria included prior gastrointestinal surgery, immunocompromised status, and prior COVID-19. The primary outcome was COVID-19, and secondary outcomes included COVID-19-related hospitalization and severe infection (composite of intensive care unit admission, ventilatory support, and/or death). Covariates include age, sex, the Charlson Comorbidity Index, comorbidities, and concomitant medication use. Subjects were followed from index date (first dose of vaccination) until outcome occurrence, death, additional dose of vaccination, or March 31, 2022. Exposure was pre-vaccination PPI use (any prescription within 90 days before the index date). Propensity score (PS) matching and a Poisson regression model were used to estimate the adjusted incidence rate ratio (aIRR) of outcomes with PPI use.

Results: Among 439 154 PS-matched two-dose vaccine recipients (mean age: 65.3 years; male: 45.7%) with a median follow-up of 6.8 months (interquartile range: 2.6–7.9), PPI exposure was associated with a higher risk of COVID-19 (aIRR: 1.08; 95% confidence interval [95% CI]: 1.05–1.10), hospitalization (aIRR: 1.20; 95% CI: 1.08–1.33), and severe infection (aIRR: 1.57; 95% CI: 1.24–1.98). Among 188 360 PS-matched three-dose vaccine recipients (mean age: 62.5 years; male: 49.0%; median follow-up: 9.1 months [interquartile range: 8.0–10.9]), PPIs were associated with higher infection risk (aIRR: 1.11; 95% CI: 1.08–1.15) but not other outcomes.

Conclusions: Although PPI use was associated with a higher COVID-19 risk, severe infection was limited to two-dose but not three-dose vaccine recipients.

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Introduction

Vaccination is one of the most effective measures in preventing the severe clinical course and mortality of COVID-19.[1] Two vaccines of different platforms are available in Hong Kong: BNT162b2 (a mRNA vaccine) and CoronaVac (an inactivated virus vaccine). The efficacy of protection from symptomatic COVID-19 after two doses of BNT162B2[2] and CoronaVac[3] is 95% and 70%, respectively.

The gut microbiota contributes to COVID-19 susceptibility and its disease courses. Several mechanisms include the expression of the viral entry receptor angiotensin-converting enzyme 2 (ACE2), homeostasis of the immune system, and mediation of the "gut–lung axis." Furthermore, the gut microbiota has also been recognized to modulate the immune response to different kinds of vaccination.[4] Antibiotic-induced gut microbiota perturbation could impair antibody production and affinity among those with low pre-existing antibody titers against influenza virus.[5] Similarly, COVID-19 vaccine immunogenicity and efficacy may be impaired by antibiotic usage.[6,7]

Prior to the widespread rollout of vaccination programs, studies conducted in early 2020 have shown that proton pump inhibitors (PPIs) may increase the risk of COVID-19 and severe clinical outcomes with a dose–response relationship.[8–10] Postulated mechanisms include gut dysbiosis from potent gastric acid suppression, leading to a higher viral load in the gastrointestinal tract, resulting in cytokine storms,[11] and impairment of leukocyte functions.[12] Intuitively, gut dysbiosis induced by PPIs may also affect vaccine immunogenicity, similar to antibiotics. However, there are currently no studies investigating whether PPIs could increase the risk of COVID-19 and adverse clinical outcomes after vaccination. A differential effect may also exist depending on the number of vaccine doses administered and the vaccine platform (mRNA *vs* inactivated virus), requiring further investigation.

Therefore, we conducted a territory-wide cohort study on COVID-19 vaccine recipients to determine the effects of PPIs on the development of COVID-19 and associated clinical outcomes with stratification according to the number of vaccines and vaccine platform.

Methods

Data source and study design. A retrospective cohort study was conducted using an electronic medical record database, the Clinical Data Analysis and Reporting System (CDARS) from the Hospital Authority (including all individuals who ever used Hospital Authority [HA] services), linked with territory-wide vaccination records and COVID-19 confirmed case records from the Department of Health of Hong Kong SAR Government by anonymous unique patient identifiers. The Hospital Authority is the sole public healthcare provider for the local population of more than 7 million people. The CDARS contains all essential clinical information, including the patient's demographics, inpatient attendance, outpatient and emergency attendance, diagnosis, laboratory results, procedures, and prescription details. The CDARS used the International Classification of Diseases, Ninth Revision (ICD-9) for disease coding. A number of high-quality, territory-wide studies were conducted on COVID-19 using CDARS.[13–20]

Study population. Individuals aged at least 18 years who had received two or three doses of either the BNT162b2 or CoronaVac vaccine between February 23, 2021 (the commencement of the mass vaccination program in Hong Kong) and March 31, 2022, were included. Analyses were conducted separately for two sub-cohorts: (i) two-dose vaccine recipients (n = 3 272 286) and (ii) three-dose vaccine recipients (n = 1 570 469). Figure S1 shows the subject selection process. Patients with a history of gastrointestinal surgery, those who were immunocompromised (cancer, transplant, primary immunodeficiency, immune-related inflammatory disorders including rheumatoid arthritis, inflammatory bowel disease, and others, splenectomy, and end-stage renal disease/dialysis) before the first dose of vaccination, or those who had a history of COVID-19 before the second/third dose of vaccination, respectively, were excluded.

Patients were followed from the date of the first dose of vaccination (i.e. the index date) until the earliest of outcome occurrence, death, additional dose of vaccination, or study end date (March 31, 2022). Patients with outcomes between the first dose and the second/third dose of vaccination were excluded, respectively, from the second/third-dose recipient cohort. Infection due to both wild type and variants, including *omicron*, was included. Notably, the first *omicron* cluster was detected in December 2021 in Hong Kong. Mandatory hospitalization for infection was in effect until March 2022.

Exposures of interest. The primary exposure of interest was pre-vaccination use of PPIs (British National Formulary [BNF] 1.3.5), which included esomeprazole, omeprazole, rabeprazole, pantoprazole, lansoprazole, and dexlansoprazole. Pre-vaccination PPI users were defined as receiving any prescription of PPIs within 90 days before the first dose of vaccination. PPI never users were defined as those who did not receive any prescription of PPI from 90 days before the first dose of vaccination until the end of the follow-up period. Figure 1 shows the study time frame.

Outcomes of interest. The primary outcome of interest was COVID-19, defined as a positive polymerase chain reaction (PCR) test confirmed by the Department of Health. During the study period, it was mandatory by law that an individual who tested positive by direct antigen testing be confirmed by PCR test. Secondary outcomes were (i) COVID-19-related hospitalization, defined as hospital admission within 28 days after a positive PCR test; (ii) severe COVID-19, defined as a composite of intensive care unit (ICU) admission, ventilatory support (ICD-9 procedure codes: 39.65, 89.18, 93.90, 93.95, 93.96, 96.7, and 96.04), and/or COVID-19-related mortality (defined as all-cause mortality within 28 days after a positive PCR test); and (iii) COVID-19-related mortality.

Statistical analyses. R software (version 3.2.3) was used for all statistical analyses. Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR).

Covariates include age, sex, Charlson Comorbidity Index (CCI) score, vaccine platform (BNT162b2 and CoronaVac), presence of

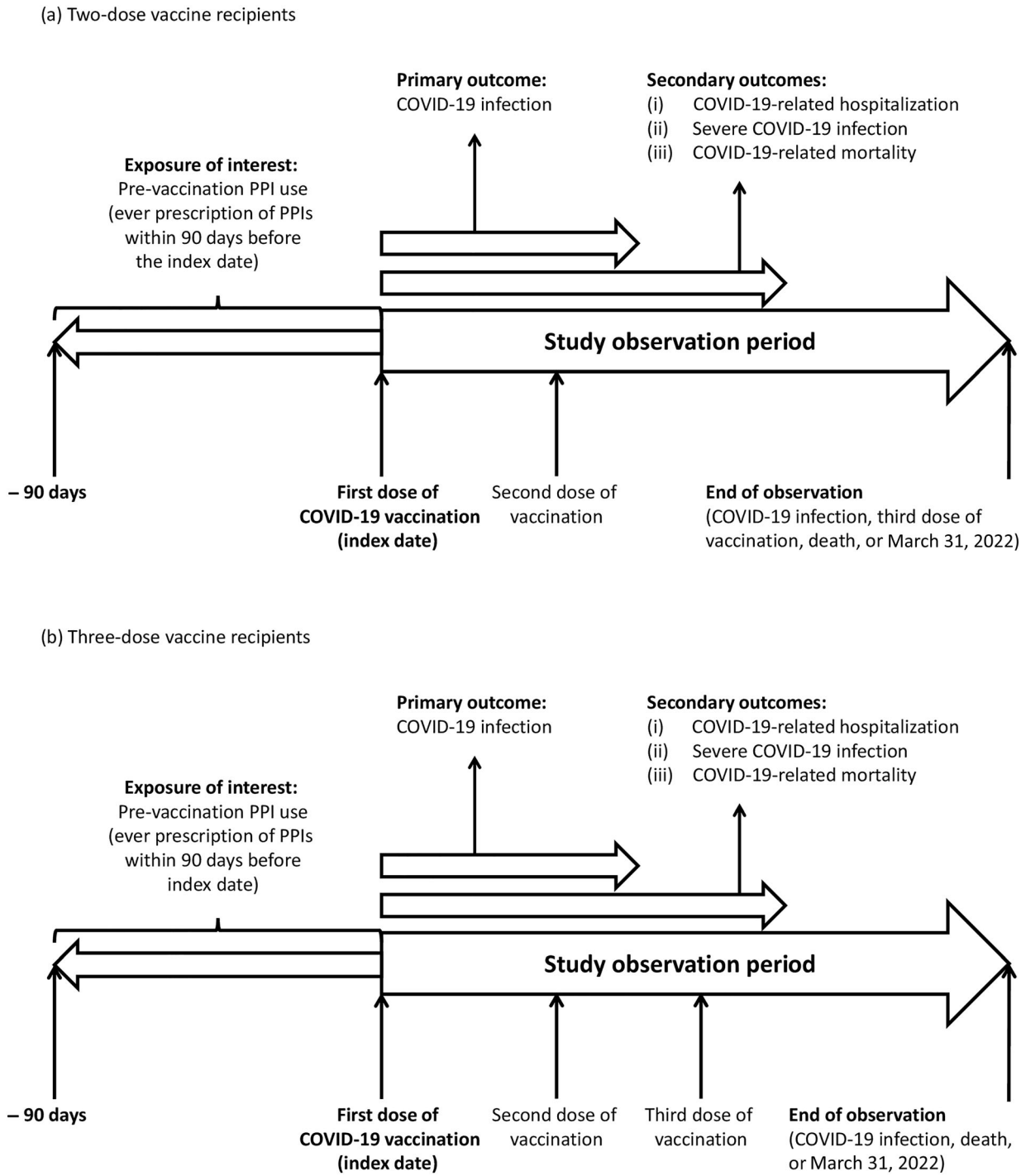

Figure 1 Study time frame. PPI, proton pump inhibitor.

comorbidities (hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, respiratory disease, obesity, smoking, alcohol use disorders, ulcers, moderate-to-severe liver disease,[21,22] and chronic renal failure), and medication use within the past 90 days (histamine 2 receptor antagonists [H2RAs],[9,23,24] angiotensin-converting enzyme inhibitors [ACEIs],[25] angiotensin receptor blockers, metformin, lipid-modifying drugs, antiplatelets, non-steroidal anti-inflammatory drugs, oral anticoagulants, oral corticosteroids, antidepressants, antibiotics, and antiviral drugs). Table S1 details the ICD-9 coding for the covariates.

Propensity score (PS) matching was conducted to minimize potential confounding between pre-vaccination PPI users and never users at a 1:1 ratio using the nearest-neighbor algorithm with a caliper of 0.2, where the PS was estimated using logistic regression

for the covariates listed above. A standardized mean difference (SMD) of 0.2 or less was considered negligible.[26] The PS was estimated by multivariable logistic regression based on the aforementioned covariates and represents the probability of prescribing PPIs to an individual given the covariates.

Poisson regression was used to estimate the adjusted incidence rate ratio (aIRR) of outcomes among pre-vaccination PPI users *versus* never users in the PS-matched cohort, with the log of follow-up time included as an offset in the model. Stratified analyses by age (< 60 and ≥ 60 years), sex, CCI categories (0 and ≥ 1), and vaccine platform were conducted.

The association between pre-vaccination cumulative PPI exposure and outcomes was estimated using Poisson regression adjusted for the covariates listed above (same as those included in the PS model). Cumulative PPI exposure in the past 90 days before the first dose of vaccination was categorized by cumulative duration (0 [PPI non-use], 1–30, and 31–90 days).

Sensitivity analyses were also conducted with a modified index date defined as the date of the second dose of vaccination for two-dose vaccine recipients and the date of the third dose of vaccination for three-dose vaccine recipients.

A two-sided P-value < 0.05 was defined as statistical significance.

Results

Patient characteristics

Two-dose vaccine recipients. Of the two-dose vaccine recipients, 439 154 (219 577 PPI users and 219 577 PPI non-users) were PS matched. The mean age was 65.6 years (SD: 15.8) in PPI non-users and 65.0 years (SD: 14.6) in PPI users. The median follow-up was 6.8 months (IQR: 2.6–7.9), and the median duration of pre-vaccination PPI use was 3.0 months (IQR: 1.0–3.0). There was a significant difference between PPI users and non-users in terms of baseline characteristics before PS matching (Table S1); however, there was no difference in most baseline characteristics, including age, sex, comorbidities, and concomitant medication usage, between the PS-matched groups with an SMD < 0.2 (Table 1), except for past H2RA use. To ensure the robustness of the effect estimates, all covariates were further

Table 1 Baseline characteristics between proton pump inhibitor users and non-users after propensity score matching

	Two-dose vaccine recipients			Three-dose vaccine recipients		
	PPI never users (n = 219 577)	Pre-vaccination PPI users (n = 219 577)	SMD	PPI never users (n = 94 180)	Pre-vaccination PPI users (n = 94 180)	SMD
Age, years, mean (SD)	65.59 (15.83)	65.04 (14.60)	0.036	62.58 (13.94)	62.45 (12.88)	0.010
Sex, male (%)	96 508 (44.0)	104 137 (47.4)	0.070	44 966 (47.7)	47 327 (50.3)	0.050
Charlson Comorbidity Index, mean (SD)	0.48 (0.76)	0.49 (0.83)	0.014	0.36 (0.64)	0.35 (0.67)	0.012
Vaccine platform—CoronaVac (%)	128 318 (58.4)	128 032 (58.3)	0.003	50 638 (53.8)	50 856 (54.0)	0.005
Comorbidities—no. (%)						
Hypertension	88 623 (40.4)	81 461 (37.1)	0.067	33 024 (35.1)	30 145 (32.0)	0.065
Diabetes mellitus	41 763 (19.0)	39 862 (18.2)	0.022	14 673 (15.6)	13 876 (14.7)	0.024
Dyslipidemia	54 711 (24.9)	51 164 (23.3)	0.038	21 934 (23.3)	20 233 (21.5)	0.043
Cardiovascular diseases	101 134 (46.1)	96 002 (43.7)	0.047	37 308 (39.6)	34 713 (36.9)	0.057
Respiratory diseases	9274 (4.2)	7886 (3.6)	0.033	2963 (3.1)	2477 (2.6)	0.031
Obesity diagnosis	14 861 (6.8)	13 087 (6.0)	0.033	6019 (6.4)	5327 (5.7)	0.031
Smoking	3378 (1.5)	3080 (1.4)	0.011	1334 (1.4)	1258 (1.3)	0.007
Alcohol use disorders	1371 (0.6)	1142 (0.5)	0.014	485 (0.5)	416 (0.4)	0.011
Ulcers	8171 (3.7)	8740 (4.0)	0.013	3568 (3.8)	3177 (3.4)	0.022
Moderate–severe liver disease	641 (0.3)	631 (0.3)	0.001	234 (0.2)	200 (0.2)	0.008
Chronic renal failure	4463 (2.0)	4054 (1.8)	0.014	1002 (1.1)	925 (1.0)	0.008
Medication use in the past 6 months—no. (%)						
ACEIs	30 491 (13.9)	32 349 (14.7)	0.024	11 177 (11.9)	11 600 (12.3)	0.014
ARBs	42 156 (19.2)	41 302 (18.8)	0.010	15 452 (16.4)	15 350 (16.3)	0.003
Metformin	41 802 (19.0)	41 382 (18.8)	0.005	15 706 (16.7)	15 426 (16.4)	0.008
Lipid-lowering agents	115 487 (52.6)	117 932 (53.7)	0.022	45 527 (48.3)	45 870 (48.7)	0.007
Antiplatelets	59 771 (27.2)	83 794 (38.2)	0.235	23 191 (24.6)	30 628 (32.5)	0.175
NSAIDs	58 207 (26.5)	61 055 (27.8)	0.029	30 971 (32.9)	30 988 (32.9)	< 0.001
Oral anticoagulants	10 289 (4.7)	9702 (4.4)	0.013	3259 (3.5)	2505 (2.7)	0.046
Steroids	3865 (1.8)	3562 (1.6)	0.011	1419 (1.5)	1181 (1.3)	0.022
Antidepressants	27 144 (12.4)	21 322 (9.7)	0.085	10 343 (11.0)	8219 (8.7)	0.076
Antibiotics	28 705 (13.1)	23 388 (10.7)	0.075	11 123 (11.8)	8931 (9.5)	0.076
Antiviral drugs	5908 (2.7)	4790 (2.2)	0.033	2543 (2.7)	2042 (2.2)	0.035
H2RAs	73 123 (33.3)	29 866 (13.6)	0.478	31 618 (33.6)	13 738 (14.6)	0.455

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; H2RAs, histamine 2 receptor antagonists; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SD, standard deviation; SMD, standardized mean difference.

adjusted for in the Poisson regression models in the subsequent analyses. Sensitivity analysis based on modified index dates also showed similar results (Table S3).

Three-dose vaccine recipients. For the three-dose vaccine recipients, 188 360 subjects (94 180 PPI users and 94 180 PPI non-users) were PS matched. The mean age was 62.6 years (SD: 13.9) in PPI non-users and 62.5 years (SD: 12.9) in PPI users. The median follow-up was 9.1 months (IQR: 8.0–10.9), and the median duration of pre-vaccination PPI use was 2.7 months (IQR: 0.8–3.0). The difference in baseline characteristics between PPI users and non-users before PS matching (Table S1) no longer existed after PS matching with all SMD < 0.2 (Table 1), except for past H2RA use. To ensure the robustness of the effect estimates, all covariates were further adjusted for in the Poisson regression models in the subsequent analyses. Sensitivity analysis based on modified index dates also showed similar results (Table S3).

Association between pre-vaccination proton pump inhibitor use and COVID-19 outcomes

Two-dose vaccine recipients. Among the PS-matched two-dose vaccine recipients, 32 914 (7.5%) developed COVID-19. The median time from the index date to the development of infection was 6.4 months (IQR: 3.1–7.4). Pre-vaccination PPI use was associated with a higher risk of COVID-19 (aIRR: 1.08; 95% confidence interval [95% CI]: 1.05–1.10), COVID-19-related hospitalization (aIRR: 1.20; 95% CI: 1.08–1.33), and severe disease outcomes (composite of ICU admission/ventilatory support/death —aIRR: 1.57; 95% CI: 1.24–1.98) and death (aIRR: 1.55; 95% CI: 1.21–1.97) (Table 2). Sensitivity analysis based on modified index dates also showed similar results (Table S4).

While PPI use was associated with a similarly higher risk of COVID-19, regardless of duration or cumulative dose (Table 3), a biological gradient existed for severe COVID-19 and death. Compared with PPI non-use, the use of PPIs for 30 days or less was not significantly associated with a higher risk of severe

Table 2 Association between pre-vaccination proton pump inhibitor use and COVID-19 outcomes after vaccination with BNT162b2/CoronaVac among the propensity score-matched cohort

(a) Two-dose vaccine recipients

	Events	Person-days	No. of persons	Incidence rate (per 100 000 person-days)	Adjusted IRR (95% CI)
COVID-19					
Never users	16 007	37 370 151	219 577	42.83365	—
Pre-vaccination PPI users	16 907	37 607 313	219 577	44.95668	**1.075 (1.051–1.100)**
COVID-19-related hospitalization					
Never users	818	37 775 475	219 577	2.165426	—
Pre-vaccination PPI users	943	38 035 615	219 577	2.479255	**1.195 (1.078–1.325)**
Severe COVID-19 (ICU admission/ventilatory support/death)					
Never users	158	37 793 443	219 577	0.418062	—
Pre-vaccination PPI users	243	38 055 527	219 577	0.638541	**1.569 (1.244–1.978)**
COVID-19-related death					
Never users	145	37 793 812	219 577	0.383661	—
Pre-vaccination PPI users	222	38 056 074	219 577	0.58335	**1.545 (1.210–1.972)**

(b) Three-dose vaccine recipients

	Events	Person-days	No. of persons	Incidence rate (per 100 000 person-days)	Adjusted IRR (95% CI)
COVID-19					
Never users	6082	26 490 668	94 180	22.95903	—
Pre-vaccination PPI users	6625	26 602 743	94 180	24.90345	**1.114 (1.075–1.154)**
COVID-19-related hospitalization					
Never users	107	26 642 021	94 180	0.401621	—
Pre-vaccination PPI users	132	26 767 472	94 180	0.493136	1.213 (0.922–1.596)
Severe COVID-19 (ICU admission/ventilatory support/death)					
Never users	11	26 644 144	94 180	0.041285	—
Pre-vaccination PPI users	7	26 769 807	94 180	0.026149	0.789 (0.273–2.277)
COVID-19-related death					
Never users	7	26 644 210	94 180	0.026272	—
Pre-vaccination PPI users	6	26 769 831	94 180	0.022413	0.794 (0.225–2.809)

Those with significant *P*-values were bolded.

95% CI, 95% confidence interval; ICU, intensive care unit; IRR, incidence rate ratio; PPI, proton pump inhibitor.

Table 3 Association between pre-vaccination cumulative duration of proton pump inhibitor exposure and COVID-19, hospitalization, and severe COVID-19 among the whole cohort

Cumulative duration (within 90 days pre-vaccination)	Events	Person-days	Persons	Incidence rate (per 100 000 person-days)	IRR (95% CI) (crude)	IRR (95% CI) (adjusted)
(a) Two-dose recipients						
COVID-19						
0 days (non-users)	16 007	37 370 151	219 577	42.83365	—	—
1–30 days	5286	11 767 058	58 817	44.92202	**1.049 (1.017–1.082)**	**1.108 (1.073–1.145)**
31–90 days	11 621	25 840 255	160 760	44.97247	**1.05 (1.025–1.075)**	**1.058 (1.032–1.086)**
COVID-19 hospitalization						
0 days (non-users)	818	37 775 475	219 577	2.165426	—	—
1–30 days	170	11 911 796	58 817	1.427157	0.659 (0.559–0.777)	**1.238 (1.042–1.472)**
31–90 days	773	26 123 819	160 760	2.958985	**1.366 (1.239–1.508)**	**1.183 (1.059–1.322)**
Severe COVID-19						
0 days (non-users)	158	37 793 443	219 577	0.418062	—	—
1–30 days	21	11 916 487	58 817	0.176226	0.422 (0.267–0.665)	1.377 (0.864–2.195)
31–90 days	222	26 139 040	160 760	0.849304	**2.032 (1.657–2.491)**	**1.606 (1.26–2.047)**
COVID-19 mortality						
0 days (non-users)	145	37 793 812	219 577	0.383661	—	—
1–30 days	16	11 916 608	58 817	0.134266	0.35 (0.209–0.586)	1.223 (0.723–2.07)
31–90 days	206	26 139 466	160 760	0.78808	**2.054 (1.661–2.54)**	**1.604 (1.244–2.068)**
(b) Three-dose recipients						
COVID-19						
0 days (non-users)	6082	26 490 668	94 180	22.95903	—	—
1–30 days	2322	8 377 628	29 139	27.71668	**1.207 (1.151–1.266)**	**1.103 (1.05–1.159)**
31–90 days	4303	18 225 115	65 041	23.61028	1.028 (0.989–1.069)	**1.12 (1.075–1.167)**
COVID-19 hospitalization						
0 days (non-users)	107	26 642 021	94 180	0.401621	—	—
1–30 days	25	8 438 000	29 139	0.296279	0.738 (0.477–1.14)	1.042 (0.662–1.64)
31–90 days	107	18 329 472	65 041	0.583759	**1.454 (1.112–1.9)**	1.275 (0.948–1.713)
Severe COVID-19						
0 days (non-users)	11	26 644 144	94 180	0.041285	—	—
1–30 days	1	8 438 499	29 139	0.01185	0.287 (0.037–2.223)	0.678 (0.082–5.641)
31–90 days	6	18 331 308	65 041	0.032731	0.793 (0.293–2.144)	0.816 (0.265–2.513)
COVID-19 mortality						
0 days (non-users)	7	26 644 210	94 180	0.026272	—	—
1–30 days	1	8 438 499	29 139	0.01185	0.451 (0.055–3.666)	1.37 (0.145–12.954)
31–90 days	5	18 331 332	65 041	0.027276	1.038 (0.33–3.271)	0.716 (0.188–2.719)

Those with significant *P*-values were bolded.
95% CI, 95% confidence interval; IRR, incidence rate ratio.

COVID-19 or death. Use of PPIs for 31–91 days was associated with a higher risk of all these outcomes (severe outcomes—aIRR: 1.61 [95% CI: 1.26–2.05]; and death—aIRR: 1.60 [95% CI: 1.24–2.07]) (Table 3). Sensitivity analysis based on modified index dates also showed similar results (Table S5).

Three-dose vaccine recipients. Among the PS-matched three-dose vaccine recipients, 12 707 (6.7%) developed COVID-19. The median time from the index date to the development of infection was 9.0 months (IQR: 8.0–10.9), respectively. Pre-vaccination PPI use was associated with a higher risk of COVID-19 (aIRR: 1.11; 95% CI: 1.08–1.15) but not adverse disease outcomes, including hospitalization (aIRR: 1.21; 95% CI: 0.92–1.60) and severe disease (aIRR: 0.79; 95% CI: 0.27–2.28) (Table 2). Sensitivity analysis based on modified index dates also showed similar results (Table S4).

Proton pump inhibitor use was associated with a similarly higher risk of infection regardless of the duration of use (Table 3). However, a longer duration had no association with higher risks for all three secondary outcomes. Sensitivity analysis based on modified index dates also showed similar results (Table S5).

Stratified analysis. As PPIs did not have significant effects on adverse clinical outcomes of COVID-19 among three-dose vaccine recipients, stratified analyses were performed on two-dose vaccine recipients only.

Among two-dose vaccine recipients, the magnitude of the higher infection risk associated with PPI use was similar regardless of vaccine platform, age, sex, and CCI (Table 4). However, PPI use was associated with a higher risk of hospitalization (aIRR: 1.30; 95% CI: 1.15–1.47), severe outcomes (aIRR: 1.60; 95% CI: 1.25–2.05), and death (aIRR: 1.61; 95% CI: 1.24–2.09) in

Table 4 Stratified analysis on the association between pre-vaccination proton pump inhibitor use and COVID-19 outcomes among the propensity score-matched two-dose vaccine recipients

Pre-vaccination PPI use	Adjusted incidence rate ratio (95% CI)							
	BNT162b2	CoronaVac	Age < 60	Age ≥ 60	Male	Female	CCI 0	CCI ≥ 1
COVID-19	**1.07 (1.033–1.108)**	**1.077 (1.046–1.109)**	**1.063 (1.026–1.101)**	**1.065 (1.034–1.098)**	**1.052 (1.017–1.087)**	**1.097 (1.063–1.131)**	**1.084 (1.055–1.115)**	**1.05 (1.009–1.093)**
COVID-19-related hospitalization	1.007 (0.828–1.224)	**1.299 (1.15–1.467)**	1.226 (0.969–1.55)	**1.218 (1.084–1.369)**	**1.253 (1.086–1.447)**	1.143 (0.986–1.326)	1.046 (0.902–1.213)	**1.372 (1.187–1.587)**
Severe COVID-19	1.482 (0.763–2.875)	**1.60 (1.248–2.052)**	0.61 (0.211–1.763)	**1.645 (1.295–2.09)**	**1.734 (1.289–2.333)**	1.375 (0.943–2.006)	1.354 (0.931–1.97)	**1.797 (1.332–2.424)**
COVID-19-related mortality	1.187 (0.558–2.526)	**1.61 (1.243–2.086)**	0.801 (0.217–2.965)	**1.574 (1.226–2.02)**	**1.746 (1.284–2.376)**	1.303 (0.866–1.961)	1.347 (0.906–2.002)	**1.737 (1.269–2.377)**

Those with significant *P*-values were bolded.
95% CI, 95% confidence interval; CCI, Charlson Comorbidity Index; PPI, proton pump inhibitor.

CoronaVac (but not BNT162b2 recipients) and those aged ≥ 60 years (aIRR: 1.22, 95% CI: 1.08–1.37; aIRR: 1.65, 95% CI: 1.30–2.09; and aIRR: 1.57, 95% CI: 1.23–2.02 for the three secondary outcomes, respectively). The harmful effect of PPIs also appeared to be higher among those with CCI ≥ 1 compared with those with CCI 0. Sensitivity analysis based on modified index dates also showed similar results (Table S6).

Discussion

In this territory-wide cohort study involving > 300 000 PS-matched COVID-19 vaccine recipients, we showed that pre-vaccination PPI use was associated with a slightly higher risk of COVID-19 (8–11%) in two-dose or three-dose vaccine recipients. Nevertheless, PPI use was associated with a 20% and 57% higher risk of hospitalization and severe clinical outcomes among two-dose vaccine recipients, but not among three-dose vaccine recipients.

Proton pump inhibitors reduce the acidity of the stomach by their acid-suppressive effect, leading to impaired eradication of ingested pathogens (e.g. *Clostridium difficile*), altering their immunomodulatory and anti-inflammatory effects.[11] PPI users may have more SARS-CoV-2 virus colonization in the gastrointestinal tract and hence more severe disease due to cytokine storm as ACE2 receptors, points of entry for the SARS-CoV-2 virus, are also expressed in the gastrointestinal tract (so-called gut–lung axis).[27,28] Intragastric inoculation of the Middle East respiratory syndrome coronavirus in mice pretreated with PPIs has been shown to worsen epithelial damage in the small bowel, with subsequent development of respiratory infection.[29] PPIs also have negative effects on the immune system, including polymorphonuclear neutrophils, cytotoxic T cells, and natural killer activities.[9]

Furthermore, specifically on vaccine immunogenicity, PPIs alter the gut microbiota profile, including a lower diversity of microbiota and an increase in the relative abundance of certain oral bacteria, including *Enterococcus*, *Streptococcus*, *Staphylococcus*, and the pathogenic species *Escherichia coli*.[30] Prior clinical studies reported that antibiotic-induced gut dysbiosis and disturbance of bile acid homeostasis lead to impaired vaccine immunogenicity to influenza[5] and possibly COVID-19.[6] Several potential mechanisms by which microbiota modulate vaccine immune responses have been proposed, including (i) the production or regulating production of immunomodulatory molecules, immunomodulatory cytokines, immunomodulatory metabolites, and encoding epitopes that cross-react with vaccine-encoded epitopes[4]; (ii) Toll-like receptor 5-mediated sensing of flagellin produced by gut microbiota[31]; (iii) the regulating production of type I interferons by plasmacytoid dendritic cells, which in turn affects the conventional dendritic cells functioning on T cell priming[32]; and (iv) microbiota-derived short-chain fatty acids involved in B cell metabolism for antibody production and plasma cell differentiation.[4]

Given the high efficacy of two doses of BNT162b2 and CoronaVac (protection from symptomatic COVID-19 is 95%[2] and 70%,[3] respectively), it is not surprising that the effects of PPIs on increasing infection risk were only slightly elevated (6–8%) in two-dose or three-dose vaccine recipients. However, among two-dose vaccine recipients, PPIs were still associated with a 26% higher risk of hospitalization and a 61% higher risk of severe clinical outcomes. Paradoxically, among three-dose vaccine

recipients, the effects of PPIs on these adverse outcomes were not observed. It is well acknowledged that booster doses can further enhance antibody production[33,34] and reduce the severity of infection outcomes.[35] A higher antibody level to wild-type SARS-CoV-2 reduces COVID-19 risk even during times of *omicron* variant predominance.[36] Therefore, the negative impact of PPIs on adverse infection outcomes is likely negated by potent protection from the booster third dose of vaccination.

Subgroup analysis showed that PPI use was associated with a higher risk of adverse outcomes of COVID-19 in two-dose CoronaVac but not BNT162b2 recipients. A similar phenomenon was observed among older individuals and those with comorbidities, but not among younger age groups and those without comorbidities. BNT162b2 led to an approximately 10-fold higher level of neutralizing antibody than CoronaVac after two doses.[37] Vaccine effectiveness against infection progressively diminished, from 92% at 15–30 days to 47% at 121–180 days and 23% from day 211 onwards among BNT162b2 recipients.[38] This further corroborates our hypothesis that a higher humoral response induced by booster doses will offset the unfavorable effects of PPIs on vaccine immunogenicity. Healthy-entrant bias may also partly contribute to this finding. In order to be defined as third-dose vaccine recipients in this study, those subjects should not acquire infection after two doses of vaccines and therefore might be intrinsically less susceptible to COVID-19 and have a better response to COVID-19 vaccines.

To the best of our knowledge, this is the first study to demonstrate the potential undesirable effects of PPIs on COVID-19 and severe clinical outcomes among COVID-19 vaccine recipients. Prior research investigating the effects of PPIs on COVID-19 recruited mostly unvaccinated subjects.[39] A prior study has demonstrated a biological gradient of PPIs in increasing the risk of COVID-19 compared with PPI non-users (odds ratio of 2.15 and 3.67 for once daily and twice daily PPI use, respectively).[8] In a Korean study, PPI use was associated with a 79% higher risk of severe clinical outcomes of COVID-19 (including the requirement of oxygen therapy, ICU admission, invasive ventilation, or death).[9] Our results shed light on the potential interaction between gut microbiota and vaccine immunogenicity. It also highlights that individuals with pre-vaccination PPI use may have to consider an early booster dose in order to prevent adverse infection outcomes.

Several limitations of this study should be noted. First, residual/unmeasured confounding may still exist due to the observational study design. For example, smoking and alcohol use were derived from coding instead of a questionnaire survey. Nevertheless, the PS matching design rendered similar characteristics between PPI users and non-users so as to minimize potential bias (Table 1).

Second, the effect of genetic polymorphisms in cytochrome P450 2C19 on the metabolism of PPIs and hence COVID-19 outcomes could not be investigated,[40] although Asians are infrequently PPI extensive metabolizers. Third, PPIs are prescription drugs in Hong Kong, and there should not be over-the-counter use. However, we do not have data on the issue of the percentage of prescribed PPIs being taken from patients in the electronic healthcare database. Fourth, gut microbiota data were unavailable, and therefore, the postulation that PPIs impair vaccine immunogenicity and COVID-19 outcomes among two-dose vaccine recipients via gut microbiota as a mediator requires further studies. Fifth, prior asymptomatic infection before the index date could not be ruled out, and this study included PCR-confirmed positive cases only, which may overestimate the effects of PPI as asymptomatic infection could be missed. Furthermore, the fourth dose of vaccination was not available before the study end date in Hong Kong. Sixth, as the study end date was March 2022, the neutralizing antibody level of some subjects who received vaccination 1–2 years ago likely waned, and virus strains evolved from wild type to other variants during the study period. Some subjects might have received more than three doses of vaccines. Therefore, the study findings may not be applicable to contemporary clinical care. Nevertheless, our study findings may provide insights into future vaccine trials and developments, including potential pandemics of other novel infectious agents. Seventh, subgroup analysis may lead to underpower due to the small number of events. This also held for analyzing secondary outcomes among three-dose vaccine recipients. Eighth, the outcome of severe infection is clinically more important and relevant than infection per se, as the majority of individuals will get infection even with multiple doses of vaccines.

Conclusion

Although pre-vaccination PPI use was associated with a slightly higher risk of COVID-19, severe infection outcomes were limited to two-dose but not three-dose vaccine recipients. Further studies are warranted to investigate the interaction between gut microbiota and PPIs on COVID-19 vaccine immunogenicity and clinical outcomes.

Data availability statement. Data sharing will be available upon reasonable request.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Study subject selection flow diagram.
Table S1. ICD-9 coding for covariates.
Table S2. Baseline characteristics between proton pump inhibitor users and non-users before propensity score matching.
Table S3. Sensitivity analysis based on modified index date: baseline characteristics between proton pump inhibitor users and non-users after propensity score matching.
Table S4. Sensitivity analysis based on modified index date: association between pre-vaccination proton pump inhibitor use and COVID-19 outcomes after vaccination with BNT162b2/CoronaVac among the propensity-score matched cohort.

Table S5. Sensitivity analysis based on modified index date: association between pre-vaccination cumulative duration of proton pump inhibitor exposure and COVID-19, hospitalization and severe COVID-19 among the whole cohort.

Table S6. Sensitivity analysis based on modified index date: stratified analysis on the association between pre-vaccination proton pump inhibitor use and COVID-19 outcomes among the propensity score matched two-dose vaccine recipients.