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Research Article

Use of Proton-Pump Inhibitor Is Not Associated with Adverse Clinical Outcomes in COVID-19 Patients: A Territory-Wide Cohort Study

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Background. Evidence regarding the use of proton-pump inhibitors (PPIs) in COVID-19 patients remains elusive. *Aim*. To examine the potential effects of PPI use on the clinical outcomes of COVID-19 patients in a territory-wide cohort. *Methods*. A retrospective cohort study was performed using data from a territory-wide database in Hong Kong. Patients diagnosed with COVID-19 from 23 January 2020 to 1 January 2021 were identified by virological results. The primary endpoint was a composite of intensive care unit admission, use of invasive mechanical ventilation, and/or death. PPI users were identified by PPI use within 12 months prior to their diagnosis of COVID-19. *Results*. We identified 8,675 COVID-19 patients (mean age 46 years, 49% male, 97.6% of all reported cases in Hong Kong), of which 579 (6.7%) patients had used PPI. PPI users were found to be older, more likely to have comorbidities, concomitant medications and unfavourable laboratory parameters than nonusers. Of the 8,675 COVID-19 patients, 500 (5.8%) developed the primary endpoint. After propensity score (PS) balancing for patients' demographics, comorbidities, laboratory parameters, and use of medications, PPI use was not found to be associated with the development of primary endpoint in PS weighting (weighted hazard ratio (HR) 1.10, 95% confidence interval (CI) 0.82–1.46, $P = 0.529$), and PS matching analysis (weighted HR 0.79, 95% CI 0.56–1.13, $P = 0.198$). Consistent nonassociation was observed after multivariable adjustment (adjusted HR 0.84, 95% CI 0.67–1.06, $P = 0.142$), and in subgroups of current and past PPI users. *Conclusion*. PPI use is not found to be associated with adverse clinical outcomes in COVID-19 patients. The result remains robust after PS weighting, PS matching, and multivariable adjustment.

1. Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 238 million people and caused over 4.8 million deaths worldwide as of 13 October 2021 [1]. COVID-19 is a heterogeneous disease with a case-fatality ratio that varies substantially among different patient populations. Identified risk factors for adverse clinical outcomes include advanced age, preexisting cardiovascular disease, diabetes mellitus, chronic kidney disease, and liver injury [2–5]. In addition, various prediction models on the risk of hospital admission, adverse clinical outcomes, and mortality have been developed and published [6–8].

Proton-pump inhibitor (PPI) is an acid suppression therapy commonly used worldwide to treat gastrooesophageal reflux disease and peptic ulcers. As gastric acid can inhibit swallowed infectious microorganisms and prevent them from entering the intestine, PPI may alter its users' susceptibility to enteric pathogens [9]. Indeed, it was observed in an American online survey that the use of PPI increases the risks of contracting COVID-19 among community-dwelling people [10], whereas a separate Korean nationwide study suggested that PPI use does not increase users' susceptibility to SARS-CoV-2 infection. This Korean study, however, suggested that PPI use is correlated with worse clinical outcomes of COVID-19 [11]. Moreover, PPI treatment may even be a risk factor for the development of secondary infections among patients with an existing SARS-CoV-2 infection [12]. In contrast, the use of famotidine, a histamine-2 receptor antagonist (H2RA), is reported to be associated with a lower risk of clinical deterioration in COVID-19 patients [13]. In a case series, famotidine use is also correlated with improved patient-reported outcomes on symptoms among nonhospitalised COVID-19 patients [14]. Nonetheless, the association between famotidine use and better clinical outcomes for COVID-19 patients was not observed in a similar territory-wide study conducted in Hong Kong, after adjusting for patients' concomitant medications and laboratory parameters [15]. The contradictory findings in the aforementioned studies reflect the between-study heterogeneity and different sources of bias that had driven the effect estimates. In particular, most previous studies on the association between PPI use and severe clinical outcomes of COVID-19 involved a small sample size and did not adjust for important confounding factors, as shown in a meta-analysis [16]. Given the rapidly growing number of COVID-19 cases and the widespread use of PPI globally, this study is aimed at examine the impact of PPI use on clinical outcomes of COVID-19 using robust methodology to identify and adjust for different sources of confounders.

2. Materials and Methods

2.1. Study Design and Data Source. A territory-wide retrospective cohort study was conducted using data from the Clinical Data Analysis and Reporting System (CDARS) under the management of the Hospital Authority, Hong Kong [17]. CDARS is an electronic healthcare database that covers patients' demographic, death, diagnoses, procedures, drug prescription and dispensing history, and laboratory results of all public hospitals and clinics in Hong Kong [18]. The Hospital Authority is the sole public healthcare provider in Hong Kong and accounts for over 90% of all healthcare services provided to the Hong Kong population. All suspected and confirmed cases of COVID-19 are reported to the Department of Health, and all were hospitalised under the care of the Hospital Authority. SARS-CoV-2 reverse transcription polymerase chain reaction tests were performed on symptomatic patients presenting to outpatient clinics and hospitals, as well as on asymptomatic close contacts of infected patients and inbound travellers. All data are anonymised in CDARS to ensure confidentiality. Territory-wide epidemiological studies of various infectious diseases were previously conducted using CDARS [3, 19–21]. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding was used in CDARS. The use of ICD-9-CM codes in CDARS to identify medical conditions has been found to be 99% accurate when referenced to clinical, laboratory, imaging, and endoscopy results from the electronic medical records [22].

2.2. Subjects. Consecutive laboratory-confirmed COVID-19 patients between 23 January 2020 and 1 January 2021 were identified by virological results (Supplementary Table 1). The baseline date was defined as the date of diagnosis of COVID-19 by virological results. Patients were followed from the baseline date to the earliest of the following: (i) discharge from hospital, (ii) the last follow-up date (*i.e.*, 1 January 2021), (iii) admission to the intensive care unit (ICU), (iv) use of invasive mechanical ventilation (IMV), or (v) death. PPI users were defined as patients who had used PPI within 12 months before baseline date (i.e., the diagnosis of COVID-19) to prevent immortal time bias introduced when treatment status is determined by a prescription issued or received at some point during follow-up of their hospitalisation [23]. The study protocol was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (reference number: 2020.074); informed consent was waived due to the study's retrospective nature and the use of anonymised clinical data.

2.3. Clinical Evaluation. All COVID-19 patients in the study were admitted to medical wards or ICU with isolation facilities. Initial investigations included a complete blood count (with a differential count), clotting profile (prothrombin time, activated partial-thromboplastin time, international normalised ratio), and serum biochemical measurements (electrolytes, renal and liver biochemistries, C-reactive protein and lactate dehydrogenase, glucose, and procalcitonin). These laboratory assessments and chest radiography were performed regularly as clinically indicated. A reverse transcription polymerase chain reaction (RT-PCR) assay was used to detect a conserved region in the E gene of SARS-CoV and SARS-CoV-2 as well as other bat-associated SARS-related viruses (*Sarbecovirus*) as screening [24]. All positive samples were sent out to the Public Health

Laboratory Services Branch Centre for Health Protection, Department of Health, for confirmation by real-time RT-PCR targeting at SAR-CoV-2-specific RNA-dependent-RNA-polymerase gene region. Microbiological workup including sputum and blood bacterial culture, nasopharyngeal aspirate for respiratory viruses and atypical pathogens, and urine for *Streptococcus pneumoniae* and *Legionella* antigen tests were performed as appropriate. Details on clinical management of COVID-19 patients are described in the Supplementary methods (available here).

2.4. Data Collection. Data were retrieved from CDARS on 2 January 2021. Demographic data including patients' gender and age at the time of diagnosis were captured. Dates of registered death were captured and ascertained in CDARS using data from Hong Kong Death Registry. In addition, data concerning the use of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) prescribed within 12 months before the baseline date were collected. Similarly, at baseline, haematological and virological parameters, liver and renal biochemistries, and other relevant laboratory parameters were also collected. Thereafter, serial laboratory parameters, as well as SARS-CoV-2 viral assays, were collected until the last follow-up date. Data on relevant diagnoses, procedures, concomitant medications, and exposure to antivirals, antibiotics and antifungals, corticosteroids, interferon beta, and immunoglobulin before baseline and during follow-up were retrieved.

2.5. Definitions. The primary endpoint was a composite endpoint of ICU admission, use of IMV, and/or death. The secondary endpoints were ICU admission, use of IMV, and death, respectively. The use of PPI, H2RAs, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) were defined as use within 12 months before the baseline date (*i.e.,* the diagnosis of COVID-19). Among PPI users, the cumulative days of the use of PPI within 12 months before the diagnosis of COVID-19 were categorised into <30 days, 30-89 days, 90-179 days, and ≥180 days. In a subgroup analysis, current PPI users were defined as patients who used PPIs within 1 month prior to their diagnosis of COVID-19; past PPI users were defined as patients who used PPIs 1 to 12 months prior to their diagnosis of COVID-19 [11]. On sensitivity analysis, short-term new NSAID users were defined as patients who began using NASID within 1 month prior to their COVID-19 diagnosis. New users of PPI were defined as patients who began using PPI within 12 months prior to their COVID-19 diagnosis, without any exposure to PPI between 12 and 36 months prior to their COVID-19 diagnosis. Details on definitions of comorbidities are described in the Supplementary methods (available here).

2.6. Statistical Analysis. Data were analysed using Statistical Product and Service Solutions (SPSS) version 25.0 (SPSS, Inc., Chicago, Illinois), SAS (9.4; SAS Institute Inc., Cary, NC), and R software (4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed in mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were presented as numbers (percentage). Qualitative and quantitative differences between subgroups were compared by the Chi-square test or Fisher's exact tests for categorical parameters and Student's t-test or Mann–Whitney test for continuous parameters, as appropriate.

Differences in baseline clinical characteristics were observed between PPI users and nonusers (Tables 1 and 2). Propensity score (PS), the conditional probability of receiving PPI, was estimated to control for 23 confounders and reduce selection bias (Table 2) [25, 26]. PS weighting and 1 : 3 PS matching were used to balance patients' baseline clinical characteristics. The balance of baseline clinical characteristics between PPI users and nonusers was assessed by absolute standardised mean difference (ASMD), where an ASMD of below 0.2 indicated a good balance [27, 28]. Before estimating PS, missing data were imputed by multiple imputation. Details on PS estimation and multiple imputation are described in the Supplementary methods (available here).

Hazard ratios and adjusted hazard ratios (aHRs) with 95% confidence interval (CI) of PPI use on the primary endpoint were estimated by Cox proportional hazards regression. Weighted Cox proportional hazards regression was used in PS weighting and matching analysis. Details of modelling are described in the Supplementary methods (available here). All statistical tests were two-sided. Statistical significance was taken as $P < 0.05$. Subgroup analyses on current and past PPI users were performed. As patients who received short-term NSAID for early pneumonia symptoms may start PPI simultaneously, sensitivity analysis was performed after excluding short-term new NSAID users to minimise protopathic bias, *i.e.*, reverse causation bias [11, 29]. Another sensitivity analysis was performed on new PPI users who began using PPI within 12 months prior to the diagnosis of COVID-19. In addition, patients who used H2RA within 12 months prior to the diagnosis of COVID-19 were analysed as active control on the risk of adverse clinical outcomes of COVID-19 in a sensitivity analysis after excluding all PPI users.

3. Results

3.1. Demographic Characteristics. We identified 8,675 COVID-19 patients between 23 January 2020 and 1 January 2021 which represented 97.6% of all patients who reported to the Department of Health during the study period. Among these patients, their mean age was 45.8 ± 19.9 years; 48.5% were male; 579 (6.7%) patients had used PPI before their diagnosis of COVID-19 (516 pantoprazole, 46 lansoprazole, 15 esomeprazole, and 2 dexlansoprazole) (Table 1). Compared to PPI nonusers, PPI users were older, more likely to have diabetes mellitus, malignant tumours, and cardiovascular, digestive, nervous system, respiratory, and kidney diseases. PPI users had worse renal and liver functions, and higher C-reactive protein and LDH; they also had higher neutrophil counts, and lower lymphocyte and platelet counts compared to PPI nonusers. More PPI users received H2RAs, NSAIDs, aspirin, corticosteroids, antibiotics, antifungals, and antiviral treatment for COVID-19 as compared to PPI nonusers (Table 1).

Table 1: Baseline clinical characteristics of patients with SARS-CoV-2 infection/COVID-19 who were or were not PPI users before multiple imputation.

Clinical characteristics	All $N = 8,675$	PPI nonuser $N = 8,096$	PPI user $N = 579$	P value
Age (years)	45.8 ± 19.9	44.5 ± 19.4	64.3 ± 16.7	<0.001
Male gender (n, %)	4,207 (48.5)	3,915 (48.4)	292 (50.4)	0.335
Comorbidities (n , %)				
Cardiovascular diseases	2,139 (24.7)	1,758 (21.7)	381 (65.8)	<0.001
Hypertension	2,030 (23.4)	1,669 (20.6)	361 (62.3)	<0.001
Ischemic heart disease	226 (2.6)	106 (1.3)	120 (20.7)	<0.001
Cardiac dysrhythmias	243 (2.8)	172 (2.1)	71 (12.3)	<0.001
Heart failure	69 (0.8)	32 (0.4)	37 (6.4)	<0.001
Digestive diseases	831 (9.6)	673 (8.3)	158 (27.3)	<0.001
Peptic ulcer	107 (1.2)	61 (0.8)	46 (7.9)	<0.001
Chronic liver disease	494 (5.7)	439 (5.4)	55 (9.5)	<0.001
Liver failure, cirrhosis, or cirrhotic complications	45 (0.5)	29 (0.4)	16 (2.8)	<0.001
Biliary disease	116 (1.3)	73 (0.9)	43 (7.4)	<0.001
Gastrointestinal haemorrhage	220 (2.5)	153 (1.9)	67 (11.6)	<0.001
Diabetes mellitus	1,348 (15.5)	1,104 (13.6)	244 (42.1)	<0.001
Malignant tumour	263 (3.0)	201 (2.5)	62 (10.7)	<0.001
Nervous system diseases	308 (3.6)	228 (2.8)	80 (13.8)	<0.001
Cerebrovascular events	216 (2.5)	153 (1.9)	63 (10.9)	<0.001
Other nervous system diseases [†]	137 (1.6)	104 (1.3)	33 (5.7)	<0.001
Respiratory disease [‡]	307 (3.5)	247 (3.1)	60 (10.4)	<0.001
Kidney disease	150 (1.7)	90 (1.1)	60 (10.4)	<0.001
Human immunodeficiency virus infection	12 (0.1)	12 (0.1)	0 (0)	1.000
Nosocomial infection	224 (2.6)	185 (2.3)	39 (6.7)	<0.001
Laboratory results				
Creatinine (μmol/L)	69 (58-83)	68 (57-82)	75 (63-100)	<0.001
Urea (mmol/L)	4.3 ± 2.3	4.2 ± 2.0	5.9 ± 4.7	<0.001
Sodium (mmol/L)	138.3 ± 3.1	138.3 ± 3.0	137.8 ± 3.9	0.001
Potassium (mmol/L)	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.5	0.385
Albumin (g/L)	40.6 ± 5.0	40.8 ± 4.8	37.4 ± 6.0	<0.001
Alanine aminotransferase (U/L)	23 (16 − 36)	23 (16 − 36)	23 (16 − 36)	0.691
Total bilirubin (μmol/L)	8.6 ± 6.1	8.6 ± 5.6	9.6 ± 10.3	0.021
Lactate dehydrogenase (U/L)	213.4 ± 84.1	211.7 ± 82.6	236.3 ± 99.0	<0.001
C-reactive protein (mg/dL)	1.6 ± 3.2	1.5 ± 3.1	3.0 ± 4.7	<0.001
International normalised ratio	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.4	0.026
Haemoglobin (g/dL)	13.6 ± 1.6	13.7 ± 1.6	12.8 ± 1.9	<0.001
WCC ($\times 10^9$/L)	5.7 ± 2.2	5.7 ± 2.2	5.9 ± 2.4	0.138
WCC $<3.5 \times 10^9$/L (n, %)	840 (10.0)	784 (10.0)	56 (9.7)	0.806
Lymphocyte ($\times 10^9$/L)	1.4 ± 0.8	1.5 ± 0.8	1.2 ± 0.6	<0.001
Lymphocyte $<1 \times 10^9$/L (n, %)	2,308 (27.5)	2,074 (26.6)	234 (40.5)	<0.001
Neutrophil ($\times 10^9$/L)	3.6 ± 1.9	3.6 ± 1.8	4.0 ± 2.2	<0.001
Neutrophil-lymphocyte ratio	3.2 ± 3.1	3.1 ± 2.8	4.5 ± 5.8	<0.001
Platelet ($\times 10^9$/L)	224.5 ± 75.7	225.8 ± 75.4	206.0 ± 76.9	<0.001
Platelet $<150 \times 10^9$/L (n, %)	1,135 (13.5)	992 (12.7)	143 (24.7)	<0.001
SpO_2 (%)	97.7 ± 2.2	97.7 ± 1.8	17.1 ± 4.4	0.001
Respiratory rate (/min)	16.0 ± 3.7	16.0 ± 3.7	16.2 ± 4.7	0.142

Table 1: Continued.

Clinical characteristics	All $N = 8,675$	PPI nonuser $N = 8,096$	PPI user $N = 579$	P value
Treatment before baseline (n , %)				
H2RA	1,027 (11.8)	843 (10.4)	184 (31.8)	<0.001
NSAID	774 (8.9)	547 (6.8)	227 (39.2)	<0.001
Aspirin	432 (5.0)	236 (2.9)	196 (33.9)	<0.001
Other antiplatelets [§]	95 (1.1)	33 (0.4)	62 (10.7)	<0.001
Anticoagulants	180 (2.1)	111 (1.4)	69 (11.9)	<0.001
Antihypertensive drugs [¶]	1,554 (17.9)	1,214 (15.0)	340 (58.7)	<0.001
Statins	1,052 (12.1)	780 (9.6)	272 (47.0)	<0.001
Treatment during follow-up (n , %)				
Antiviral treatment				
Ribavirin	1,878 (21.6)	1,713 (21.2)	165 (28.5)	<0.001
Lopinavir-ritonavir	1,814 (20.9)	1,662 (20.5)	152 (26.3)	0.001
Interferon beta	2,947 (34.0)	2,638 (32.6)	309 (53.4)	<0.001
Oseltamivir	81 (0.9)	76 (0.9)	5 (0.9)	0.856
Ganciclovir	0 (0)	0 (0)	0 (0)	—
Aciclovir/famciclovir/valaciclovir	9 (0.1)	8 (0.1)	1 (0.2)	0.463
Antibiotic treatment	2,626 (30.3)	2,321 (28.7)	305 (52.7)	<0.001
Antifungal treatment	8 (0.1)	4 (0.05)	4 (0.7)	0.001
Corticosteroid	1,180 (13.6)	993 (12.3)	187 (32.3)	<0.001
(i) Dexamethasone	1,087 (12.5)	920 (11.4)	167 (28.8)	<0.001
(ii) Hydrocortisone	97 (1.1)	78 (1.0)	19 (3.3)	<0.001
(iii) Prednisolone	58 (0.7)	43 (0.5)	15 (2.6)	<0.001
(iv) Methylprednisolone	5 (0.1)	5 (0.1)	0 (0)	1.000
Intravenous immunoglobulin therapy	4 (0.05)	3 (0.04)	1 (0.2)	0.241
Clinical outcomes in 60 days *(n, %)*				
Primary endpoint	500 (5.8)	398 (4.9)	102 (17.6)	<0.001
(i) Death	144 (1.7)	97 (1.2)	47 (8.1)	<0.001
(ii) Intensive care unit admission	407 (4.7)	338 (4.2)	69 (11.9)	<0.001
(iii) Invasive mechanical ventilation	181 (2.1)	148 (1.8)	33 (5.7)	<0.001
Follow-up duration (days)	11 (7-16)	11 (7-16)	12 (7-18)	0.001

All comorbidities were represented as binary parameters. Categorical variables were presented as number (percentage). Creatinine, alanine aminotransferase, and follow-up duration were expressed in median (interquartile range), whereas other continuous variables were expressed in mean ± standard deviation. Qualitative and quantitative differences between subgroups were analysed by Chi-square or Fisher's exact tests for categorical parameters and Student's t -test or Mann–Whitney U test for continuous parameters, as appropriate. [†]Other nervous system disease was defined by ICD-9-CM diagnosis codes for inflammatory diseases of the central nervous system (ICD-9-CM codes: 320-327), hereditary and degenerative diseases of the central nervous system (ICD-9-CM codes: 330-337), and other disorders of the central nervous system (ICD-9-CM codes: 340-345). [‡]Respiratory system disease was defined by ICD-9-CM diagnosis codes for pneumonia other than SARS-related pneumonia (ICD-9-CM codes: 480-487·0) in previous 3 months, chronic obstructive pulmonary disease and allied conditions (ICD-9-CM codes: 490-496), pneumoconioses and other lung diseases due to external agents (ICD-9-CM codes: 500-508) in previous 3 months, and other diseases of respiratory system (ICD-9-CM codes: 510-519) in previous 3 months. [§]Other antiplatelet included clopidogrel, dipyridamole, eptifibatide, and ticagrelor. [¶]Antihypertensive drugs included angiotensin-converting-enzyme inhibitors, angiotensin receptor beta blockers, calcium channel blockers, and thiazide diuretics. H2RA: H2 receptor antagonist; NSAID: nonsteroidal anti-inflammatory drug; PPI: proton-pump inhibitor; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: peripheral oxygen saturation; WCC: white cell counts.

3.2. Events. Among the 8,675 COVID-19 patients followed, 500 (5.8%) developed the primary endpoint, *i.e.*, adverse clinical outcomes including ICU admission, use of IMV, and/or death; 407 (4.7%) were admitted to ICU, 181 (2.1%) used IMV, and 144 (1.7%) died.

3.3. PPI Use and Clinical Outcomes after PS Weighting. IPTW by PS resulted in greater similarity of distributions of the 23 clinical characteristics between PPI users and nonusers and reduced all ASMDs to below 0.2 (Supplementary Figures 1A-1B). Table 2 shows the result in 1 of the 20 imputed data sets; consistent patterns were obtained across other imputed data sets.

After PS weighting, PPI use was found not to be associated with adverse clinical outcomes (weighted HR 1.11, 95% CI 0.83–1.47, $P = 0.482$). Likewise, PPI use was found not to be associated with ICU admission, use of IMV, and death (Table 3). In one of the imputed PS-weighted cohort, 102 out of 579 (17.6%) PPI users and 72 out of 474 (15.2%) nonusers developed adverse clinical outcomes, respectively:

Table 2: Baseline clinical characteristics and balancing diagnositcs before and after propensity score weighting and matching between patients with SARS-CoV-2 infection/COVID-19 who were proton-pump inhibitor (PPI) users and nonusers for a single multiple imputation data set.

Clinical characteristics	Before propensity score weighting/matching			After propensity score weighting			After propensity score matching		
	PPI nonuser $N = 8,096$	PPI user $N = 579$	ASMD	PPI nonuser $N = 474$	PPI user $N = 579$	ASMD†	PPI nonuser‡ $N = 395$	PPI user $N = 395$	ASMD †
Age (years)	44.5 ± 19.4	64.3 ± 16.7	1.19	61.7 ± 18.4	64.3 ± 16.7	0.16	62.3 ± 16.9	60.2 ± 16.9	0.12
Male gender (*n*, %)	3,915 (48.4)	292 (50.4)	0.04	246 (51.9)	292 (50.4)	0.03	194 (49.1)	189 (47.8)	0.02
Comorbidities (n , %)									
Cardiovascular diseases	1,758 (21.7)	381 (65.8)	0.93	284 (60.0)	381 (65.8)	0.13	234 (59.2)	217 (54.9)	0.09
Digestive diseases	673 (8.3)	158 (27.3)	0.43	109 (23.0)	158 (27.3)	0.10	93 (23.5)	93 (23.5)	0.003
Diabetes mellitus	1,104 (13.6)	244 (42.1)	0.58	186 (39.3)	244 (42.1)	0.06	154 (39)	143 (36.2)	0.06
Malignant tumour	201 (2.5)	62 (10.7)	0.27	43 (9.1)	62 (10.7)	0.06	42 (10.6)	37 (9.4)	0.05
Nervous system diseases	228 (2.8)	80 (13.8)	0.32	61 (12.9)	80 (13.8)	0.03	49 (12.4)	45 (11.4)	0.03
Respiratory disease	247 (3.1)	60 (10.4)	0.24	35 (7.4)	60 (10.4)	0.10	28 (7.1)	33 (8.4)	0.05
Kidney disease	90 (1.1)	60 (10.4)	0.30	31 (6.5)	60 (10.4)	0.13	26 (6.6)	22 (5.6)	0.04
Nosocomial infection	185 (2.3)	39 (6.7)	0.18	29 (6.1)	39 (6.7)	0.03	25 (6.3)	23 (5.8)	0.02
Laboratory results									
Creatinine (μmol/L)	68 (57-82)	75 (63-100)	0.23	74 (61-91)	75 (63-99)	0.11	72 (61-92)	72 (60-89)	0.02
Albumin (g/L)	40.9 ± 4.8	37.4 ± 6.0	0.58	38.2 ± 5.8	37.4 ± 6.0	0.13	38.2 ± 5.8	38.4 ± 5.4	0.05
ALT (U/L)	23 (16-35)	23 (16-36)	0.05	23 (16-36)	23 (16-35)	0.14	23 (16-37)	24 (16-37)	0.04
Total bilirubin (μmol/L)	8.6 ± 5.6	9.5 ± 10.3	0.09	8.6 ± 5.0	9.5 ± 10.3	0.09	8.4 ± 4.4	8.7 ± 4.9	0.03
LDH (U/L)	211.3 ± 81.8	235.9 ± 98.7	0.26	235.4 ± 100.3	235.9 ± 98.7	0.005	239 ± 108.1	228.7 ± 96.4	0.11
C-reactive protein (mg/dL)	1.4 ± 3.0	3.0 ± 4.7	0.34	2.6 ± 4.0	3.0 ± 4.7	0.10	2.7 ± 4.3	2.4 ± 3.9	0.08
Haemoglobin (g/dL)	13.7 ± 1.6	12.8 ± 1.9	0.46	13.1 ± 1.8	12.8 ± 1.9	0.15	13.0 ± 1.8	13.1 ± 1.6	0.06
White cell counts ($\times 10^9$/L)	5.7 ± 2.2	5.9 ± 2.4	0.05	5.7 ± 2.2	5.9 ± 2.4	0.07	5.7 ± 2.3	5.7 ± 1.8	0.02
Lymphocyte ($\times 10^9$/L)	1.5 ± 0.8	1.2 ± 0.6	0.51	1.3 ± 0.7	1.2 ± 0.6	0.11	1.3 ± 0.9	1.2 ± 0.6	0.04
Neutrophil ($\times 10^9$/L)	3.6 ± 1.8	4.0 ± 2.2	0.17	3.8 ± 1.9	4.0 ± 2.2	0.08	3.8 ± 2.0	3.7 ± 1.7	0.04
Platelet ($\times 10^9$/L)	226.6 ± 75.6	206.2 ± 76.9	0.27	209.6 ± 76.7	206.2 ± 76.9	0.05	208.9 ± 76.9	211.4 ± 74.8	0.03
SpO_2 (%)	97.9 ± 1.8	97.1 ± 4.1	0.18	97.4 ± 2.4	97.1 ± 4.1	0.06	97.3 ± 2.3	97.4 ± 1.8	0.02
Respiratory rate (/min)	16.0 ± 4.0	16.2 ± 4.5	0.06	16.2 ± 4.5	16.2 ± 4.5	0.001	16.2 ± 3.9	16.3 ± 5.0	0.01
Concomitant drugs (n, %)									
H2RA	843 (10.4)	184 (31.8)	0.46	177 (37.4)	184 (31.8)	0.12	176 (44.6)	157 (39.7)	0.12
NSAID	547 (6.8)	227 (39.2)	0.66	191 (40.3)	227 (39.2)	0.02	181 (45.8)	164 (41.5)	0.11
Aspirin	236 (2.9)	196 (33.9)	0.65	124 (26.2)	196 (33.9)	0.16	99 (25.1)	79 (20.0)	0.14

PPI users were defined as patients who had any use of PPI within 12 months before the diagnosis of COVID-19. †An ASMD < 0.2 indicated good balance between PPI users and PPI nonusers. Parameters with ASMD ≥ 0.2 would be adjusted in the doubly robust model. ‡The number of COVID-19 patients in PPI non-user group was 912 patients after 1 : 3 propensity score matching; 53.9%, 23.0%, and 23.0% of PPI users were matched to 3, 2, and 1 PPI nonusers, respectively. ASMD: absolute standardised mean difference; PPI: proton-pump inhibitors; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2:peripheral oxygen saturation.

69 (11.9%), 33 (5.7%) and 47 (8.1%) of the PPI users were admitted to ICU, used IMV, and died, respectively; 49 (10.3%), 27 (5.7%) and 31 (6.5%) of PPI nonusers were admitted to ICU, used IMV, and died, respectively. The 7-, 28-, and 56-day cumulative incidence (95% CI) of adverse clinical outcomes in PPI users were 12.1% (9.6%–15.1%), 24.3% (19.4%–30.2%), and 29.5% (22.6%–37.9%), respectively; the 7, 28, and 56-day cumulative incidence (95% CI) of adverse clinical outcomes in PPI nonusers were 7.3% (5.7%–9.3%), 23.2% (18.1%–29.5%), and 27.9% (21.5%–35.8%), respectively (log-rank test, $P = 0.386$) (Figure 1(a)). Among 579 PPI users, 183 (31.6%), 59 (10.2%), 75 (13.0%), and 262 (45.3%) had used PPI for <30 days, 30-89 days, 90-179 days, and ≥180 days, respectively. PPI use

Table 3: Cox proportional hazard regression on association between use of proton-pump inhibitors (PPIs) with the development of primary endpoint (a composite endpoint of intensive care unit admission, use of invasive mechanical ventilation, and death) in patients with SARS-CoV-2 infection/COVID-19 after propensity score weighting and matching.

PPI use on adverse clinical outcomes	PS weighting model		PS matching model	
Main analysis	Weighted HR (95% CI)	*P* value	Weighted HR (95% CI)	*P* value
Composite endpoint	1.10 (0.82–1.46)	0.529	0.79 (0.56–1.13)	0.198
ICU admission	1.11 (0.79–1.57)	0.540	0.91 (0.60–1.38)	0.655
Use of invasive mechanical ventilation	0.97 (0.61–1.54)	0.882	0.66 (0.36–1.22)	0.184
Death	1.06 (0.67––1.65)	0.812	0.63 (0.35–1.13)	0.122
Subgroup analysis on current PPI user †	Weighted HR (95% CI)	*P* value	Weighted HR (95% CI)	*P* value
Composite endpoint	1.13 (0.82–1.55)	0.460	0.82 (0.55–1.24)	0.355
ICU admission	1.18 (0.80–1.72)	0.406	0.99 (0.60–1.62)	0.963
Use of invasive mechanical ventilation	0.98 (0.57–1.69)	0.937	0.70 (0.34–1.45)	0.335
Death	1.02 (0.61–1.70)	0.939	0.54 (0.27–1.08)	0.083
Subgroup analysis on past PPI user †	Weighted HR (95% CI)	*P* value	Weighted HR (95% CI)	*P* value
Composite endpoint	1.06 (0.68–1.66)	0.798	0.71 (0.38–1.31)	0.270
ICU admission	1.15 (0.70–1.89)	0.589	0.81 (0.41–1.59)	0.538
Use of invasive mechanical ventilation	1.13 (0.57–2.25)	0.726	0.73 (0.27–1.97)	0.532
Death	0.90 (0.41–1.99)	0.803	0.62 (0.18–2.10)	0.443
Sensitivity analysis ‡	Weighted HR (95% CI)	*P* value	Weighted HR (95% CI)	*P* value
Composite endpoint	1.11 (0.83–1.49)	0.469	0.74 (0.52–1.06)	0.099
ICU admission	1.13 (0.79–1.60)	0.502	0.86 (0.57–1.31)	0.483
Use of invasive mechanical ventilation	1.02 (0.64–1.65)	0.919	0.70 (0.38–1.30)	0.258
Death	1.09 (0.69–1.72)	0.699	0.58 (0.31–1.07)	0.082

Parameters with absolute standardised mean difference ≥0.2 were adjusted in the doubly robust model. † Current PPI user ($N = 341$) was defined as patient who had used PPI within 1 month before the diagnosis of COVID-19, while past PPI user ($N = 238$) was defined as patient who had used PPI between 1 month and 12 months before the diagnosis of COVID-19. ‡ Short-term new nonsteroidal anti-inflammatory drug (NSAID) users who newly started NSAID within 1 month before COVID-19 diagnosis were excluded in the sensitivity analysis. CI: confidence interval; HR: hazard ratio; PPI: proton-pump inhibitor; PS: propensity score; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

was not associated with adverse clinical outcomes regardless of cumulative days of use before COVID-19 diagnosis (Supplementary Table 4). Subgroup analyses on current and past PPI users showed comparable results (Supplementary Tables 5 and 6, Table 3).

3.4. PPI Use and Clinical Outcomes after PS Matching. PS matching led to greater similarity in distributions of the 23 clinical characteristics between PPI users and non-users and reduced all ASMDs to <0.2 (Table 2 and Supplementary Figure 1C). Among 579 PPI users, 395 (68.2%) were matched to at least 1 PPI nonuser; 54.2%, 18.5%, and 27.3% were matched to 3, 2, and 1 PPI nonuser, respectively. Consistent patterns were also observed across other imputed data sets. Compared to PPI users who were matched to PPI nonusers, PPI users who were not matched were older, more likely to have co-morbidities, had worse liver and renal function, and higher C-reactive protein and LDH, had higher neutrophil counts, and had lower lymphocyte and platelet counts (Supplementary Table 3).

After PS matching, PPI use was found not to be associated with adverse clinical outcomes (weighted HR 0.81, 95% CI 0.57–1.14, $P = 0.228$). Specifically, PPI use was found not to be associated with ICU admission, use of IMV, and death (Table 2). In one of the imputed PS-matched cohort, 51 of 395 (12.9%) PPI users and 58 of 395 (14.7%) nonusers developed adverse clinical outcomes, respectively; 40 (10.1%), 14 (3.5%) and 17 (4.3%) of PPI users were admitted to ICU admission, used IMV, and died, respectively; whereas 40 (10.1%), 24 (6.1%), and 25 (6.3%) of PPI nonusers were admitted to ICU, used IMV, and died, respectively. The 7-, 28-, and 56-day cumulative incidence (95% CI) of adverse clinical outcomes in PPI users were 9.3% (6.7%–12.7%), 19.1% (13.6%–26.4%), and 22.9% (15.0%–34.2%), respectively; the 7-, 28-, and 56-day cumulative incidence (95% CI) of adverse clinical outcomes in PPI nonusers were 7.9% (6.1%–10.1%), 23.7% (19.0%–29.5%), and 26.3% (20.6%–33.1%), respectively (log-rank test, $P = 0.168$) (Figure 1(b)). Subgroup analyses on current and past PPI users showed comparable results (Supplementary Tables 5 and 6, Table 3).

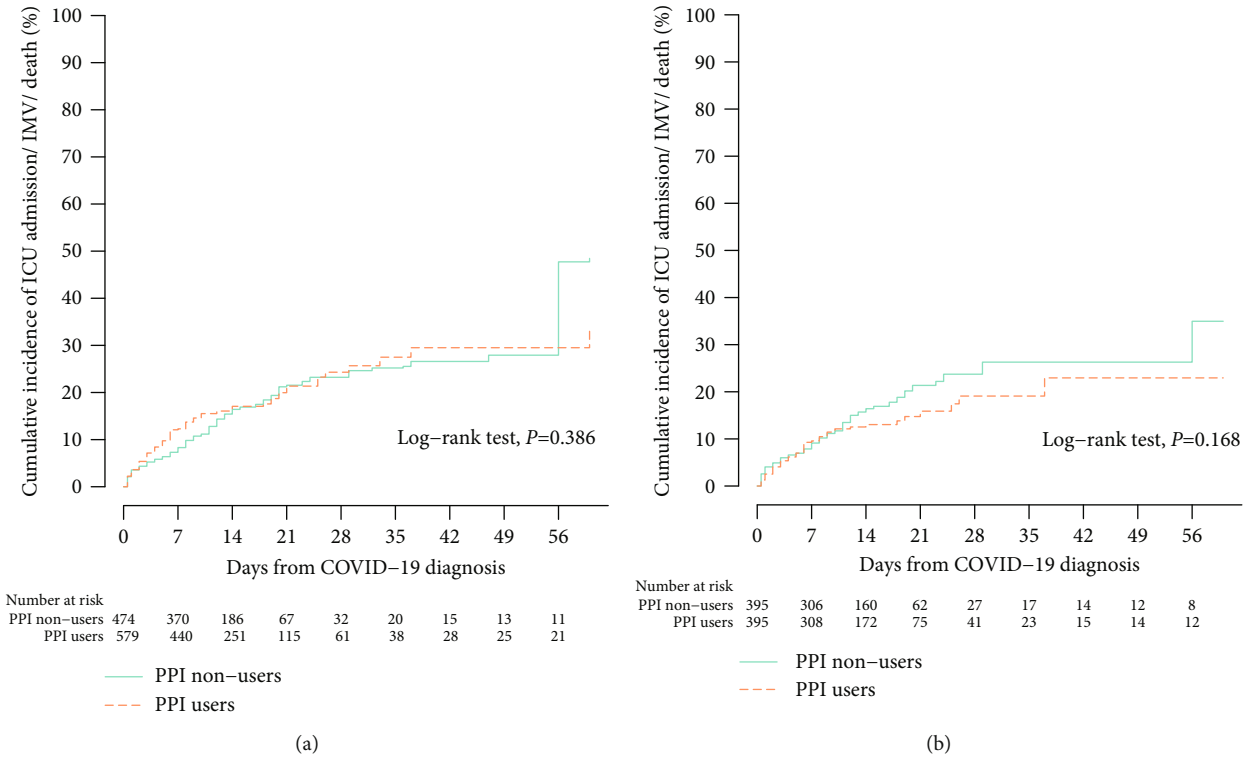

Figure 1: Cumulative incidence of primary endpoint (a composite endpoint of intensive care unit admission, use of invasive mechanical ventilation, and death) in patients with SARS-CoV-2 infection/COVID-19 who were and were not PPI users after (a) propensity score weighting and (b) propensity score matching in a single multiple imputation data set. COVID-19: coronavirus disease 2019; PPI: proton-pump inhibitor; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

3.5. PPI Use and Clinical Outcomes before PS Balancing. The development of adverse clinical outcomes was more common in PPI users relative to nonusers (Table 1). On univariate analysis, the use of PPI was found to be associated with a higher risk of adverse clinical outcomes of COVID-19 (HR 3.36, 95% CI 2.71-4.18, $P < 0.001$). Moreover, the use of H2RAs, NSAIDs, aspirin, age, gender, preexisting comorbidities, and baseline laboratory parameters were found to be associated with adverse clinical outcomes (Table 4). However, after adjusting for patients' age, gender, comorbidities, and baseline laboratory parameters, the use of PPI (aHR 0.84, 95% CI 0.67-1.06, $P = 0.142$) was not found to be associated with adverse clinical outcomes of COVID-19. Other factors, such as advanced age, male gender, preexisting circulatory system disease, diabetes mellitus, respiratory disease, chronic kidney disease, elevated levels of alanine aminotransferase, LDH, C-reactive protein, and respiratory rate, and lower albumin and platelet counts were found to be associated with a heightened risk of adverse clinical outcomes on multivariable analysis (Table 4). Subgroup analyses on current and past PPI users showed comparable results (Supplementary Table 7).

3.6. Sensitivity Analysis. After excluding short-term new NSAID users, 566 PPI users and 8,018 nonusers were included in a sensitivity analysis. PS weighting and matching led to greater similarity in distributions of the 23 clinical characteristics between PPI users and non-users and reduced all ASMDs to <0.2. The result was comparable to the main analysis (Supplementary Table 8 & Table 3). After excluding the prevalent PPI users, 269 PPI new users and 8,096 PPI nonusers were included in another sensitivity analysis (Supplementary Table 9). New use of PPI was found not to be associated with adverse clinical outcomes of COVID-19 (Supplementary Table 10). In the sensitivity analysis on H2RA users as an active control, the use of H2RA was also found not to be associated with adverse clinical outcomes of COVID-19 (Supplementary Tables 10-11).

4. Discussion

In this study, the use of PPI in COVID-19 patients and its relationship with adverse clinical outcomes were examined in a territory-wide cohort in Hong Kong. Based on the data collected, PPI use was found not to be associated with adverse clinical outcomes including admission to ICU, use of IMV, and death. Furthermore, the result remains robust after PS weighting, PS matching, and multivariable adjustment.

Gastrointestinal symptoms including vomiting, diarrhoea, or nausea have been reported in COVID-19 patients [16]. Studies have shown that angiotensin-converting enzyme-2, the SARS-CoV-2 host receptor, is expressed in gastrointestinal epithelial cells and may potentially cause gastrointestinal infection [30]. This supposition is further

Table 4: Univariate and multivariable analyses with Cox proportional hazards regression on factors associated with the development of primary endpoint (a composite endpoint of intensive care unit admission, use of invasive mechanical ventilation, and death) in patients with SARS-CoV-2 infection/COVID-19 after multiple imputation and before propensity score balancing.

Parameters	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
PPI use	3.36 (2.71–4.18)	<0.001	0.84 (0.67–1.06)	0.142
H2RA use	2.61 (2.14–3.19)	<0.001		
NSAID use	1.32 (1.00–1.73)	0.049		
Aspirin use	4.35 (3.48–5.43)	<0.001		
Age (years)	1.07 (1.06–1.07)	<0.001	1.03 (1.02–1.04)	<0.001
Male gender	1.76 (1.47––2.11)	<0.001	1.29 (1.07–1.56)	0.009
Circulatory system disease	8.33 (6.83–10.16)	<0.001	1.38 (1.08–1.76)	0.009
Digestive system disease	2.90 (2.36–3.55)	<0.001		
Diabetes mellitus	12.84 (10.61–15.53)	<0.001	3.58 (2.87–4.46)	<0.001
Malignant tumour	3.50 (2.61–4.68)	<0.001		
Nervous system disease	3.77 (2.92–4.88)	<0.001		
Respiratory disease	5.60 (4.43––7.07)	<0.001	2.21 (1.73–2.82)	<0.001
Chronic kidney disease	7.55 (5.74–9.93)	<0.001	1.37 (1.03––1.84)	0.031
Creatinine	1.003 (1.002–1.003)	<0.001		
Albumin	0.86 (0.85–0.87)	<0.001	0.98 (0.96–0.99)	0.007
Alanine aminotransferase	1.001 (1.001–1.002)	<0.001	1.001 (1.000–1.002)	0.001
Total bilirubin	1.02 (1.01–1.02)	<0.001		
LDH	1.006 (1.006–1.006)	<0.001	1.004 (1.003–1.004)	<0.001
C-reactive protein	1.16 (1.15–1.17)	<0.001	1.06 (1.05–1.08)	<0.001
Haemoglobin	0.84 (0.80–0.89)	<0.001		
Neutrophil to lymphocyte ratio	1.08 (1.07–1.08)	<0.001		
Platelet	0.993 (0.991–0.994)	<0.001	0.997 (0.995–0.998)	<0.001
SpO_2	0.95 (0.94–0.96)	<0.001		
Respiratory rate	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.04)	0.010

PPI, H2RA, NSAID, and aspirin user referred to PPI, H2RA, NSAID, and aspirin use within 12 months before the diagnosis of COVID-19. Patients were followed from the date of COVID-19 diagnosis to the date of discharge, the last follow-up date (1 January 2021), date of intensive care unit admission, date of use of invasive mechanical ventilation, or date of death, whichever came first. aHR: adjusted hazard ratio; CI: confidence interval; H2RA: H2 receptor antagonist; LDH: lactate dehydrogenase; NSAID: nonsteroidal anti-inflammatory drug; PPI: proton-pump inhibitor; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: peripheral oxygen saturation.

supported by the detection of SARS-CoV-2 RNA in faecal tests, and by the alterations of gut microbiome during the disease course of COVID-19 [31, 32]. As PPI reduces gastric acid production, it may account for gastrointestinal infection if more SARS-CoV-2 enters the lower gastrointestinal tract.

A recent Korean nationwide study by Lee et al. reported the clinical outcomes of 364 and 188 COVID-19 patients with current and past use of PPI, respectively [11]. The study found that current PPI use within 30 days prior to the onset of COVID-19 was associated with a 79% increase in the risk of developing severe clinical outcomes of COVID-19, whereas the same association was not seen in patients with past use of PPI. Following Lee et al.'s study, a meta-analysis published as a letter in an academic journal also showed that current or regular use of PPI was associated with severe clinical outcomes of COVID-19. However, it is important to note that there was evidence of substantial between-study heterogeneity that impaired the validity of the results [29]. Additionally, most of the studies in the meta-analysis involved a relatively small population of PPI users and did not adjust for confounders; therefore, the effect estimates were more susceptible to confounding and selection biases [33].

Interestingly, a recent PS-matched territory-wide study conducted in Hong Kong by Zhou et al. concluded that PPI use was associated with worse clinical outcomes of COVID-19 [34]. However, the authors did not explicitly define "PPI users" in their study. As the authors also included medications used after COVID-19 infection in their PS matching analysis, one may interpret that the definition of "PPI users" contemplates those who used PPI at the time of or after their COVID-19 diagnosis and during hospitalisation. The inclusion of patients' clinical data after contracting COVID-19 is also reflected by the unexpectedly high prevalence of prior comorbidities of respiratory diseases (98%) and gastrointestinal diseases (97%) in their data. It is plausible that in certain cases, COVID-19-induced respiratory and gastrointestinal symptoms were inadvertently considered as preexisting comorbidities. As PPI may be prescribed to critically ill patients requiring intensive care

for stress ulcer prophylaxis, the association between PPI use and severe clinical outcomes of COVID-19 may be inevitably influenced by protopathic bias, or reverse causation bias, if patients who used PPI after their diagnosis of COVID-19 were included as PPI users in the studies. Reverse causation bias has been raised previously as a source of overestimated association in studies on the use of PPI and the risk of pneumonia [29].

As outlined in the sections above, our findings were different from Lee et al.'s and Zhou et al.'s studies. One possible explanation lies in the substantial clinical characteristic differences between PPI users and nonusers. For instance, whereas Lee et al.'s study captured less comprehensive data at the patient level, our study incorporated more comprehensive patient-level data such as patients' comorbidities, laboratory parameters, and concomitant medications. The inclusion of more complete patient parameters enabled more precise adjustments for confounders on the adverse clinical outcomes of COVID-19 through PS weighting, PS matching, and multivariable analysis. In our study, COVID-19 patients who used PPI were indeed found to be at greater risk of developing adverse clinical outcomes on univariate analysis, probably due to the fact that those patients are prone to more risk factors (namely older age and more comorbidities) for adverse clinical outcomes at the time of their COVID-19 diagnosis (Table 1). Therefore, a fairer comparison between PPI users and nonusers on clinical outcomes could only be drawn after balancing for these confounding factors using stringent statistical approaches, namely, PS weighting, PS matching, and multivariable adjustment. Moreover, PPI users were defined in our study as COVID-19 patients who used PPI before their COVID-19 diagnosis to minimise the reverse causation bias. Sensitivity analysis that excluded patients who started recent and short-term use of NSAID as a possible treatment for early pneumonia symptoms also showed comparable results to that of the main analysis.

The strength of our study includes a territory-wide cohort that covers 97.6% of all COVID-19 patients in Hong Kong with detailed patient-level clinical data. Notwithstanding, our study has a number of limitations. Firstly, missing data on laboratory parameters might lead to biases as in other observational studies. These biases, however, can partially be compensated by our extensive cohort size. Missing data were uncommon for routine laboratory parameters that are checked as part of our clinical practice. However, less routine laboratory parameters, such as the international normalised ratio, may not be checked for each patient due to minor variations in clinical practice in different hospitals. Multiple imputation with 20 imputed data sets was used to reduce the possible selection bias due to missing data [35]. Secondly, COVID-19 patients who used and did not use PPI might have been different in terms of the baseline clinical characteristics (*e.g.*, age and gender) such that our study might be subjected to confounding as in other observational studies. We were not able to accurately identify patients with diseases associated with PPI use included gastroesophageal reflux disease, *Helicobacter pylori* infection, Barrett's oesophagus, achalasia, and stricture. Barrett's oesophagus is uncommon in Hong Kong [36]. The prevalence of *Helicobacter pylori* infection is over 50% in Eastern Asia including Hong Kong [37]. The information on body mass index was not available in most of the patients, while the information on the presence of radiographic chest infiltrates was not available. Due to the difference in clinical characteristics, some older PPI users (mean age: 74 years) with more comorbidities were not able to be matched with PPI nonusers in the PS matching analysis (Supplementary Table 3). This may limit the generalizability of the result to these older patients with comorbidities. Thus, in addition to PS matching, we also applied PS weighting and multivariable adjustment on important clinical characteristics aiming to include all PPI users in the cohort. Thirdly, PPI may be purchased by patients without a prescription. Thus, the use of PPI prior to hospitalisation might go unreported in certain patients. Fourth, ascertainment bias may affect the reliability of the study due to inaccurate entry of certain diagnosis codes for comorbidities, namely diabetes mellitus and cardiovascular disease. Nonetheless, every endeavour was made to minimise such bias by including laboratory and medication data for certain diagnoses (diabetes mellitus and hypertension). The use of ICD-9-CM codes in CDARS to identify medical conditions has also been found to be 99% accurate when referenced to clinical, laboratory, imaging, and endoscopy results from the electronic medical records [22].

In conclusion, PPI use was found not to be associated with adverse clinical outcomes in a territory-wide cohort of COVID-19 patients. The results remained robust in PS weighting, PS matching, and multivariable adjustment analysis. Despite the ongoing pandemic with millions of COVID-19-related casualties, this study's findings do not favour withholding PPI use.

Abbreviations

aHR: Adjusted hazard ratio
ASMD: Absolute standardised mean difference
CDARS: Clinical Data Analysis and Reporting System
COVID-19: Coronavirus disease 2019
H2RAs: Histamine-2 receptor antagonists
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
ICU: Intensive care unit
IMV: Invasive mechanical ventilation
LDH: Lactate dehydrogenase
NSAIDs: Nonsteroidal anti-inflammatory drugs
PPIs: Proton-pump inhibitors
PS: Propensity score
RT-PCR: Reverse transcription polymerase chain reaction
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Data Availability

The data that support the findings of this study are available from the Hospital Authority, Hong Kong. Restrictions apply

to the availability of these data, which were used under license for this study. Data are available with the permission of the Hospital Authority, Hong Kong.

Conflicts of Interest

Terry Yip has served as an advisory committee member and a speaker for Gilead Sciences. Francis Chan has served as a consultant to Eisai, Pfizer, Takeda, and Otsuka and has been paid lecture fees by Eisai, Pfizer, AstraZeneca, and Takeda. Grace Lui has served as an advisory committee member for Gilead, Merck and GSK, speaker for Gilead and Merck and received research grant from Gilead, Merck, and GSK. Vincent Wong has served as an advisory committee member for 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Janssen, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, TARGET-NASH and Terns; and speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences, and Merck. He has also received a research grant from Gilead Sciences. Henry Chan is an advisor for AbbVie, Aptorum, Arbutus, Hepion, Intellia, Janssen, Gilead, GSK, GRAIL, Medimmune, Merck, Roche, Vaccitech, VenatoRx, Vir Biotechnology and speaker for Mylan, Gilead, and Roche. Sunny Wong is an advisor for Aptorum, Claves, an dGroken Biosciences and has received speaker fees or travel support from Janssen, AstraZeneca, Ferring, Menarini, Gilead, and Chong Lap. Joyce Mak has received grants from Janssen, the Hong Kong College of Physicians, and the Hong Kong Society of Gastroenterology. Siew Ng has served as an advisory committee member for Pfizer, Ferring, Janssen, and Abbvie and speaker for Ferring, Tillotts, Menarini, Janssen, Abbvie, and Takeda. She has received research grants from Olympus, Ferring, and Abbvie. David Hui has served as an advisory committee member for Roche.

Authors' Contributions

All authors were responsible for the study concept and design. Grace Wong, Terry Yip, and Grace Lui were responsible for the acquisition and analysis of data, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for the interpretation of data, the drafting, and critical revision of the manuscript for important intellectual content. All authors approved the final version of the article, including the authorship list. TCF Yip and FKL Chan should be considered joint first author.

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Supplementary Materials

Supplementary Table 1: list of diagnosis codes and/or virological assays to define coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Supplementary Table 2. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes for comorbidities. Supplementary Table 3: baseline clinical characteristics between proton-pump inhibitor (PPI) users with SARS-CoV-2 infection/COVID-19 who found and did not find propensity score matched PPI nonusers for a single multiple imputation data set. Supplementary Table 4: Cox proportional hazard regression on association between different cumulative days of use of PPIs with the development of primary endpoint (a composite endpoint of intensive care unit (ICU) admission, use of invasive mechanical ventilation, and death) in patients with SARS-CoV-2 infection/COVID-19 after propensity score weighting. Supplementary Table 5: baseline clinical characteristics and balancing diagnoitics before and after propensity score weighting and matching between patients with SARS-CoV-2 infection/COVID-19 who were current PPI user and nonuser for a single multiple imputation data set. Supplementary Table 6: baseline clinical characteristics and balancing diagnostics before and after propensity score weighting and matching between patients with SARS-CoV-2 infection/COVID-19 who were past PPI user and nonuser for a single multiple imputation data set. Supplementary Table 7: univariate and multivariable analyses with Cox proportional hazard regression on factors associated with the development of primary endpoint (a composite endpoint of intensive care unit admission, use of invasive mechanical ventilation, and death) in patients with SARS-CoV-2 infection/COVID-19 after multiple imputation and before propensity score balancing. Supplementary Table 8: Baseline clinical characteristics and balancing diagnostics before and after propensity score weighting and matching between patients with SARS-CoV-2 infection/COVID-19 who were PPI user and nonuser for a single multiple imputation data set in sensitivity analysis after excluding short-term new NSAID users. Supplementary Table 9: baseline clinical characteristics and balancing diagnostics before and after propensity score weighting and matching between patients with SARS-CoV-2 infection/COVID-19 who were PPI new user and nonuser for a single multiple imputation data set after excluding PPI prevalent users in 12-36 months prior COVID-19 diagnosis. Supplementary Table 10: Cox proportional hazard regression on association between use of PPIs with the development of primary endpoint (a composite endpoint of intensive care unit admission, use of invasive mechanical ventilation, and death) in patients with SARS-CoV-2 infection/COVID-19 after propensity score weighting and matching in new PPI users, and users of H2 receptor antagonist (H2RA) as active control. Supplementary Table 11: baseline clinical characteristics and balancing diagnostics before and after propensity score weighting and matching between patients with SARS-CoV-2 infection/COVID-19 who were H2RA user and nonuser for a single multiple imputation data set. Supplementary Figure 1: Propensity score of two groups of patients who received and did not receive PPIs in a single imputation data set: (A) before propensity score weighting or matching, (B) after propensity score weighting, and (C) after propensity score matching. *(Supplementary Materials)*

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