



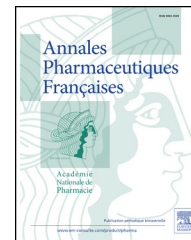
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ORIGINAL ARTICLE

What is the role of proton pump inhibitors consumption on the clinical presentation and severity of COVID-19 infection?

Quel est le rôle de la consommation d'inhibiteurs de la pompe à protons sur la présentation clinique et la gravité de l'infection au COVID-19 ?

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HIGHLIGHTS

- The COVID-19 severity scores (qCSI) were significantly higher in PPI users compared to non-users, in population with no comorbidity (Charlson Comorbidity Index = 0).
- Mortality rate wasn't significantly different between PPI-users and non-users.
- All three types of COVID-19 symptoms investigated in this study (flu-like, respiratory and gastrointestinal) manifested more in PPI users than non-users.

KEYWORDS

COVID-19 severity;
COVID-19 symptoms;
Proton pump

Summary

Objective. – Proton pump inhibitors (PPI) are among the most prescribed drugs worldwide; therefore, assessing their effect on COVID-19 infection symptoms and severity is of great importance. This study was designed to evaluate the role of previous PPI consumption on the clinical presentation and severity of COVID-19.

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inhibitors;
Predictor;
Mortality

Patients and methods. – All adult COVID-19 patients were eligible in this observational cross-sectional study. The patients' demographic and clinical data, history of PPI consumption, and comorbid disease were recorded. Charlson comorbidity index (CCI) and quick COVID-19 severity index (qCSI) score were calculated for each patient. IBM SPSS version 25 was used for statistical analysis.

Results. – Totally 670 patients completed the study (PPI users = 121). The average severity (qCSI) score of PPI user patients with comorbidity score of zero was significantly higher than non-users (P -value = 0.001). Mortality rate was 6.6% and 3.8% in PPI-users and non-users respectively (P -value = 0.117). PPI users were significantly more symptomatic compared to non-users (P -value = 0.001).

Conclusion. – We found that PPI users were meaningfully more symptomatic and had a higher severity (qCSI) score. Rational prescription of PPIs should be considered by physicians during and after the pandemic.

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MOTS CLÉS

Gravité du COVID-19 ;
Symptômes du
COVID-19 ;
Les inhibiteurs de la
pompe à protons ;
Prédicteur ;
Mortalité

Résumé

Objectif. – Les inhibiteurs de la pompe à protons (IPP) sont parmi les médicaments les plus prescrits dans le monde; par conséquent, l'évaluation de leur effet sur la gravité et les résultats de l'infection au COVID-19 est d'une grande importance. Cette étude a été conçue pour évaluer le rôle de la consommation d'IPP sur la gravité et les manifestations cliniques du COVID-19.

Patients et méthodes. – Tous les patients adultes atteints de COVID-19 étaient éligibles dans cette étude transversale observationnelle. Les données démographiques et cliniques des patients, les antécédents de consommation d'IPP et les maladies comorbides ont été enregistrés. L'indice de comorbidité de Charlson (CCI) et le score rapide de l'indice de gravité du COVID-19 (qCSI) ont été calculés pour chaque patient. IBM SPSS version 25 a été utilisé pour l'analyse statistique.

Résultats. – Au total, 670 patients ont terminé l'étude (utilisateurs d'IPP = 121). Le score moyen de sévérité (qCSI) des patients utilisateurs d'IPP avec un score de comorbidité de zéro était significativement plus élevé que les non-utilisateurs (valeur $p=0,001$). Le taux de mortalité était de 6,6 % et de 3,8 % chez les utilisateurs d'IPP et les non-utilisateurs respectivement (valeur $p=0,117$). Les utilisateurs d'IPP étaient significativement plus symptomatiques que les non-utilisateurs (valeur $p=0,001$).

Conclusion. – Nous avons constaté que les utilisateurs d'IPP avaient un score de gravité (qCSI) plus élevé et qu'ils étaient plus symptomatiques. Les médecins devraient tenir compte des risques et des avantages de la prescription d'IPP pendant et après la pandémie.

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Introduction

The world is struggling with a new pandemic caused by a new coronavirus which can cause Coronavirus disease 2019 (COVID-19) [1]. COVID-19 related Mortality rates are different in each nation [2]. Previous studies found that the old age [3], male sex [3], obesity [4], diabetes mellitus (DM) [3,4], immunodeficiency syndromes [5], chronic obstructive pulmonary disease (COPD) [3], and chronic kidney disease (CKD) [3] were significant predictors for severity of COVID-19 infection. Since the beginning of the pandemic, first cases reported in December 2019 in Wuhan-China [6], it has burdened a tremendous pressure on society, especially the health care units [7], thus making it necessary to explore the

possible factors that may influence the severity of COVID-19 infection.

COVID-19 is presented by several clinical manifestations, from pulmonary and flu-like to neurological and gastrointestinal manifestations. While a small portion of patients progresses to the highly lethal pneumonia, 20% of COVID-19 patients may present one or more gastrointestinal (GI) symptoms, such as diarrhea, vomiting, and abdominal pain.

Acid-related gastrointestinal (GI) diseases such as gastroesophageal reflux disease (GERD), esophagitis, and peptic ulcer disease (PUD) are among the most common GI diseases, with a prevalence of approximately 20% to 30% of adults in the United States [8,9].

Proton pump inhibitors (PPIs) are a potent acid-lowering agents and one of the first-line and most prescribed medications for GI disease described above [8,10,11].

When prescribing PPIs, physicians must consider confounding factors that influence PPIs efficacy and side effects, such as physiologic conditions, combination therapy, alcohol, smoking, sex, age, disease state, and diet [12]. A study on the Lebanese population reported a 71.4% PPIs overuse rate (59.2% overuse of indication, 22.1% overuse of duration, and 18.7% overuse of dosage). (12) By considering these factors, PPIs' adverse effects can be reduced.

PPIs' adverse effects on some conditions like bacterial gastroenteritis and pneumonia have long been proven [11].

Previous studies showed that the respiratory system and digestive tract are the main routes of the entrance of the COVID-19 virus into the body. And the persistent use of PPIs is related to an increased risk of viral infection during pandemics and high prevalence periods. The regular use of PPIs could decrease the natural gastric defense actions against ingested pathogens such as bacteria and viruses, , that could also change the microbial diversity of the gut [13].

Studies show different results concerning the effect of PPI drugs on COVID-19 outcomes. In a survey of the elderly (The elderly is defined as a person with age equal to or more than 65-years-old [14]), PPIs had a protective effect on COVID-19 clinical presentations [15]. In another study, the authors hypothesized PPIs' prophylactic and therapeutic role on COVID-19 [16].

On the other hand, some other studies associated PPIs consumption with poor COVID-19 outcomes by increasing mortality rate and severity of symptoms [17,18].

While the bulk of patients had mild symptoms, a smaller number of cases developed a more severe infection leading to hospital admission. The patients' severity score and mortality rate is different across the world, ranging between 0.5% to 10% [19,20].

Considering the challenging issues mentioned above, this study aims to investigate the possible relation between the regular consumption of the PPIs and the clinical manifestation and severity of COVID-19 infection.

Patients and methods

Data sources

Our study is a clinical observational and cross-sectional study. All the data used in this study was collected from patients with COVID-19 infection via in-person interviews (outpatient) or hospital data sheets (inpatient) from September 10th 2021, to January 18th 2022.

All the data including sex, age, body mass index (BMI), history of comorbidities and usage of the related medications, alcohol consumption, smoking, COVID-19 infection clinical presentations, hospitalization in ward or intensive care unit (ICU), respiratory rates, and O₂ saturation at the first visit, the maximum needed amount of O₂ flow, hospitalization outcome (well-being versus death), history of regular PPIs consumption (yes/no) and duration of PPIs consumption, were collected in a data-gathering sheet. All the data was gathered with patients' consent and were anonymized to guarantee patients' confidentiality. Ethics

committee approval was obtained for this study from the Iran University of Medical Sciences Ethics Committee for Clinical Researches.

Study population

Patients with positive SARS-CoV-2 PCR were enrolled in this study. We excluded uncooperative patients, the patients who had been under 18-years-old by the time of their first COVID-19 symptoms, and patients who used PPIs occasionally. The COVID-19 infection was confirmed by a qualitative Real-time reverse transcription-polymerase chain reaction (Real-time PCR) in Rasoul Akram hospital. The results were classified as negative or positive. Based on most hospitals' guidelines, the Real-time PCR- method is the gold standard to determine COVID-19 diagnosis [21].

Measurements

Charlson Comorbidity Index (CCI)

The patients' related comorbidity score and estimated 10-year survival were calculated for each patient based on age, history of myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular accident (CVA), transient ischemic attacks (TIA), dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, peptic ulcer disease (PUD), liver disease, diabetes mellitus (DM), chronic kidney disease (CKD), solid tumor, leukemia, lymphoma, and acquired immune deficiency syndrome (AIDS) via the Charlson comorbidity index (CCI) [22].

Patients were categorized into three groups based on their CCI score (0, 1, ≥ 2) to reduce the effect of their underlying condition on the results of our study.

PPI consumption

Based on the consumption of PPI drugs (Pantoprazole, Omeprazole, Rabeprazole, Esomeprazole, Lansoprazole), all patients were categorized into three groups:

- PPI non-users: patients with COVID-19 infection who had not been taking any types of PPIs before their infection;
- short-term PPI users: patients with COVID-19 infection who had been taking any type of PPIs during 12 weeks before their first COVID-19 presentation;
- long-term PPI users: patients with COVID-19 infection who had been taking any type of PPIs more than 12 weeks before their first COVID-19 presentation.

Each of these three CCI groups (CCI=0, CCI=1, CCI ≥ 2) were subcategorized into three subcategories based on their PPI consumption (PPI non-users, Short-term PPI users, and Long-term PPI users), making a total of nine subcategories (Fig. 1).

Quick COVID-19 Severity Index (qCSI)

The severity of COVID-19 infection was measured by the Quick COVID-19 Severity Index (qCSI) [23]. Patients' respiratory rate, O₂ saturation (SpO₂) and maximum received O₂ flow rate were collected, and after qCSI calculations, a severity score was assigned to them. Patients who expired

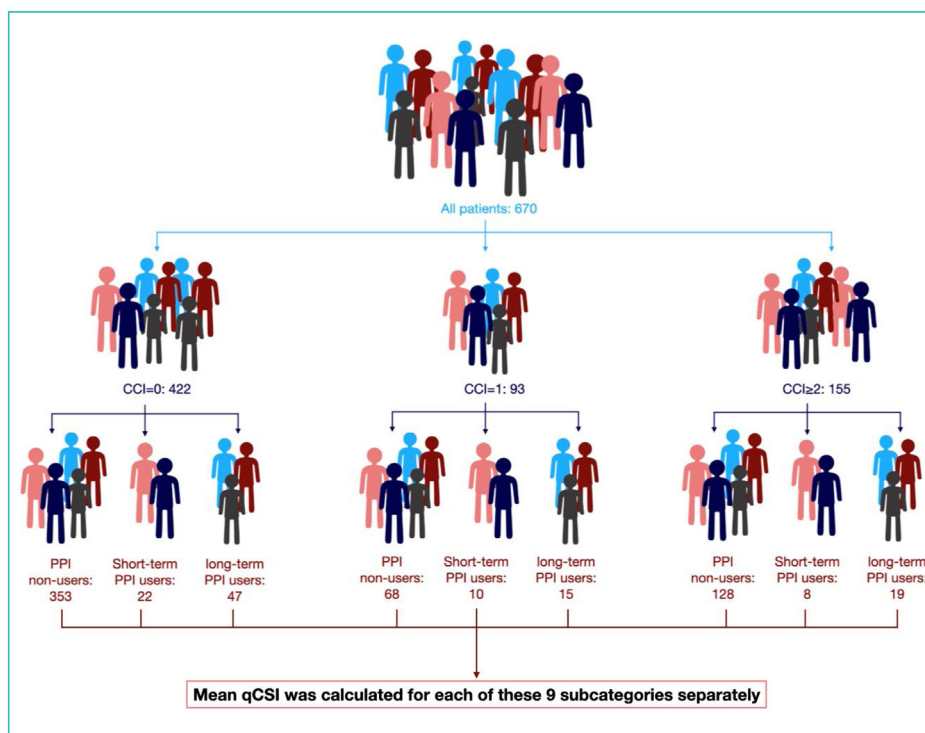


Figure 1. Our study population subcategorized into nine subcategories.
Notre population d'étude s'est subdivisée en neuf sous-catégories.

due to COVID-19 were given the worst severity score (qCSI score = 12) on this scoring system.

Based on the qCSI scoring system, patients were categorized into three risk groups: low risk ($0 \leq \text{qCSI} < 4$), medium-risk ($4 \leq \text{qCSI} < 8$), and high-risk ($8 \leq \text{qCSI} < 12$).

Patients' severity score based on qCSI was measured for patients in each group, then mean qCSI was calculated in each of the nine subcategories.

Clinical presentations

All clinical symptoms were categorized into three groups.

- Respiratory symptoms including dyspnea, coughing, chest pain, and positive image findings based on the chest (CT) scan (a Chest computed tomography (CT) scan was performed for all patients to confirm COVID-19 associated lung involvement regarding the CT-scan result [normal, ground-glass opacification, and consolidation] [24].);
- Flu-like symptoms including sneezing, anosmia or hyposmia, rhinorrhea, fatigue, malaise, fever, sore throat, myalgia or arthralgia, headaches, fever, and chills;
- Gastrointestinal symptoms including anorexia, epigastric fullness, weight loss, jaundice, diarrhea, dyspepsia, regurgitation, nausea, vomiting, dysgeusia, and a rise in liver biochemical tests (liver enzyme, Alkaline phosphatase, bilirubin).

Having at least one of the symptoms of each group was necessary to designate that symptom group to the patient.

Outcomes

The primary outcome of our study was to assess the possible relation between the severity of COVID-19 infection and history of previous PPI consumption (non-user, long-term, and short-term user) in COVID-19 patients.

The secondary outcome was the assessment of any association between PPI consumption and patients' symptoms and clinical presentation (respiratory symptoms, flu-like symptoms, and gastrointestinal symptoms).

Statistical analysis

IBM SPSS version 25 (SPSS Inc., Chicago, IL, US) was used for statistical analysis. Qualitative variables were described using absolute and relative frequency. Quantitative variables were described using mean and confidence intervals. The Kolmogorov – Smirnov test was used to assess the normality of data. Comparison of parametric quantitative normalized variables between two groups was performed using the independent sample T-Test and between several groups using analysis of variance (ANOVA). Quantitative non-parametric variables were compared between the two groups by the Mann–Whitney U test and between groups of more than two using the Kruskal Wallis test. The Chi-square test was used to compare the qualitative variables. Univariate and multivariate regression tests were used to predict the role of other confounding factors, in determining the severity of the disease.

All the tests performed; were two-tailed tests. *P*-values less than 0.05 were considered statistically significant.

Results

Totally 700 patients were enrolled in this study. Sixteen patients who have been under 18-years-old by the time of their first COVID-19 symptoms and 14 patients with a history of irregular PPI consumption or incomplete information were excluded from this study.

Finally, 670 patients between 18–90 years-old with a mean age of 44.23 ± 16.78 were included in this study. One hundred and twenty-one of the patients had a history of PPI consumption (40 (=6%) of the cases were short-term PPI users, 81(=12%) were long-term PPI users, and 549 (=82%) of the cases were non-users). Double-dose PPI consumption was seen in 17/121(=14.2%) of the patients, and they were all short-term users. Single-dose consumption was seen in 104/121(=85.8%) of the patients. The majority of our patients were female (=56.41%). PPI consumption was more in men and elderly patients (The elderly is defined as a person with an age equal to or more than 65-years-old (14)). Pantoprazole (=58.6%) was the most frequently prescribed PPI followed by Omeprazole (=29.7%), Rabeprazole (=4.9%), Esomeprazole (=4.1%) and lansoprazole (=2.4%).

Regarding the qCSI score, 546 Patients were considered low-risk ($0 \leq \text{qCSI} < 4$), 61 moderate-risk ($4 \leq \text{qCSI} < 8$), and 63 high-risk ($8 \leq \text{qCSI} \leq 12$). 86.9% of PPI non-users had a low severity (qCSI) score, 6.7% had a moderate severity (qCSI) score, and 6.4% had a high severity (qCSI) score.

These numbers in the same order were 52.5%, 20.0% and 27.5% for short-term PPI users and 59.3%, 19.8% and 21.0% for long-term PPI users (*P*-value = 0.001).

The average qCSI score of patients in all CCI categories (0, 1, ≥ 2) was lower in PPI non-users compared to PPI users; However, the difference was only significant among patients with CCI = 0 (*P*-value = 0.001) (Table 1).

The mean severity score in patients with CCI = 0 who had not been taking PPIs was 2.52; in the same category, the mean severity score for short-term PPI users and long-term PPI users was 5.75 and 4.25. *P*-value was significant for the association between PPI non-users and short-term PPI users (2.52 vs. 5.75; *P*-value = 0.001) and PPI non-users and long-term PPI users (2.52 vs. 4.25; *P*-value = 0.001) but was not significant between short-term and long-term users (*P*-value = 0.194) (Table 2).

One hundred nine patients with incomplete information about their COVID-19 clinical signs and symptoms were not considered for assessing the relationship between PPI consumption and different types of COVID-19 manifestations. The information collected from the remaining 561 patients revealed higher respiratory symptoms in PPI users than PPI non-users (29.3% in non-users vs. 50% in short-term users and 52.4% in long-term users). Occurrence of the flu-like symptoms (50.6% in non-users vs. 86.7% in short-term users and 81% in long-term users) and the gastrointestinal symptoms (21.8% in non-users vs. 53.3% in short-term users and 31.7% in long-term users) were also higher in PPI consumers (both long-term and short-term) compared to PPI non-users.

All three types of COVID-19 symptoms (respiratory symptoms, flu-like symptoms, and gastrointestinal

symptoms) emerged in greater proportions in PPI users (both long and short-term users) compared to PPI non-users (*P*-value = 0.001), but the results were not significant for the difference between short-term and long-term consumers (*P*-value = 0.71 for the respiratory symptoms, 0.712 for the flu-like symptoms and 0.84 for the GI symptoms) (Table 3).

Regarding the results of univariate and multivariate regression analysis, the elderly (*P*-value = 0.020) and patients who consumed PPIs (meaningful for pantoprazole) (*P*-value = 0.001) and NSAIDs (*P*-value = 0.022) had significantly higher COVID-19 infection severity score (qCSI) (Table 4).

Discussion

In our observational cross-sectional study, PPIs consumption was more in men and older patients and Pantoprazole was the most frequently prescribed PPI (=58.6%). We found that the average qCSI score of patients in all CCI categories (0, 1, ≥ 2) was lower in PPI non-users compared to PPI users (for both short- and long-term PPI users). However, the difference was only significant among patients with CCI = 0 (*P*-value = 0.001). In other CCI categories (1, ≥ 2), both short- and long-term PPI users had higher qCSI scores compared to the PPI non-users, but the differences were not statistically significant. The average qCSI score of short-term PPI user patients was non-significantly higher compared to the long-term PPI users. It seems that all the double dose PPI users were among short-term users with the higher severity scores).

All the three types of COVID-19 symptoms in our study (respiratory symptoms, flu-like symptoms, and gastrointestinal symptoms) emerged in greater proportions in PPI users (both long and short-term users) compared to PPI non-users (*P*-value = 0.001). We found that gastrointestinal and flu-like presentations were much more common in short-term users compared to long-term and non-PPI users. The reason was not apparent to us, but all double-dose PPI users were in this group. Double dose PPIs are prescribed for gastroesophageal reflux disease, especially extra-esophageal manifestation and refractory acid-related disorders; therefore, it may be related to the more severe baseline GI disease which PPIs were prescribed for it.

Mortality rate was 6.6% and 3.8% in PPI-users and non-users respectively (*P*-value = 0.117). The result was similar to the other studies, however the mortality rate difference between PPI users and non-users was not significant.

PPIs are one of the most popular medications used to treat and prevent acid-related gastrointestinal diseases. However, extensive consumption of PPIs has led to emerging evidence of short-term and long-term harmful effects, including increased risk of kidney, liver, and cardiovascular disease, dementia, enteroendocrine tumors of the gastrointestinal tract, defenselessness to respiratory and gastrointestinal infections, and reduced absorption of nutrients [25].

Cost-benefit of PPI drug regimens, therapeutic response, and adverse effects, besides the pharmacokinetics and pharmacogenomics of PPIs, should be considered in all nations, especially in the high-dose and long-term prescription of PPIs [26].

Table 1 Comparison between demographic, clinical data and qCSI in each PPI consumption groups.
Comparaison entre les données démographiques, cliniques et le qCSI dans chaque groupe de consommation d'IPP.

Variables	Proton pump inhibitors consumption						P-value	
	Non-users, n = 549		Short-term users, n = 40		Long-term users, n = 81			
	Count	%	Count	%	Count	%		
Sex	Female	329	59.90	17	42.50	32	39.50	0.001
	Male	220	40.10	23	57.50	49	60.50	
Age groups	< 65	484	88.20	31	77.50	63	77.80	0.01
	≥ 65	65	11.80	9	22.50	18	22.20	
Opioids	No	541	98.50	39	97.50	77	95.10	0.102
	Yes	8	1.50	1	2.50	4	4.90	
BMI groups	< 30	488	88.90	38	95.00	77	95.10	0.124
	≥ 30	61	11.10	2	5.00	4	4.90	
Smoking	No	449	81.80	32	80.00	62	76.50	0.524
	Yes	100	18.20	8	20.00	19	23.50	
Alcohol	No	462	84.20	32	80.00	64	79.00	0.434
	Yes	87	15.80	8	20.00	17	21.00	
Charlson comorbidity index (CCI)	0	353	64.30	22	55.00	47	58.00	0.149
	1	68	12.40	10	25.00	15	18.50	
	≥ 2	128	23.30	8	20.00	19	23.50	
NSAID consumption	No	536	97.60	39	97.50	76	93.80	0.155
	Yes	13	2.40	1	2.50	5	6.20	
ASA consumption	No	540	98.40	40	100.00	81	100.00	0.366
	Yes	9	1.60	0	0.00	0	0.00	
Metformin consumption	No	505	92.00	35	87.50	77	95.10	0.342
	Yes	44	8.00	5	12.50	4	4.90	
Statins consumption	No	539	98.20	40	100.00	79	97.50	0.624
	Yes	10	1.80	0	0.00	2	2.50	
Levothyroxine consumption	No	538	98.00	40	100.00	77	95.10	0.153
	Yes	11	2.00	0	0.00	4	4.90	
Steroids consumption	No	540	98.40	39	97.50	79	97.50	0.82
	Yes	9	1.60	1	2.50	2	2.50	
H2 blockers consumption	No	468	85.20	30	75.00	63	77.80	0.072
	Yes	81	14.80	10	25.00	18	22.20	
qCSI	0 ≤ < 4	477	86.90	21	52.50	48	59.30	0.001
	4 ≤ < 8	37	6.70	8	20.00	16	19.80	
	8 ≤ < 12	35	6.40	11	27.50	17	21.00	
Mortality	Alive	528	96.20	39	97.50	74	91.40	0.117
	Dead	21	3.80	1	2.50	7	8.60	

Table 2 Severity score assessment regarding PPI consumption in each of the nine subcategories.
Évaluation du score de sévérité concernant la consommation d'IPP dans chacune des neuf sous-catégories.

Charlson comorbidity index (CCI)	PPI consumption	Severity Score (qCSI)		Number	P-value
		Mean	Std. deviation		
0	1. Non-users	2.52	2.504	342	Sig = 0.005
	2. Short-term users	5.75	4.683	16	
	3. Long-term users	4.25	3.745	36	
	Total	2.81	2.853	394	
1	1. Non-users	2.24	1.75	67	Sig = 0.722
	2. Short-term users	3.71	3.94	7	
	3. Long-term users	3.83	4.98	12	
	Total	2.58	2.68	86	
≥ 2	1. Non-users	2.63	2.517	126	Sig = 0.623
	2. Short-term users	4.67	4.355	6	
	3. Long-term users	4.75	3.659	12	
	Total	2.90	2.861	144	

Table 3 Manifestation of clinical symptoms of COVID-19 infection in each PPI user groups.
Manifestation des symptômes cliniques de l'infection par COVID-19 dans chaque groupe d'utilisateurs d'IPP.

		Respiratory symptoms				Flu-like symptoms				GI Symptoms			
		No		Yes		No		Yes		No		Yes	
		Count	Row %	Count	Row %	Count	Row %	Count	Row %	Count	Row %	Count	Row %
PPI consumption	1. Non-users	331	70.7%	137	29.3%	231	49.4%	237	50.6%	366	78.2%	102	21.8%
	2. Short-term users	15	50.0%	15	50.0%	4	13.3%	26	86.7%	14	46.7%	16	53.3%
	3. Long-term users	30	47.6%	33	52.4%	12	19.0%	51	81.0%	43	68.3%	20	31.7%
P-value	1–2	0.001				0.001				0.001			
	1–3	0.001				0.001				0.001			
	2–3	0.71				0.712				0.84			

Table 4 Univariate and multivariate analysis of variables related to the COVID-19 severity score.
Analyse univariée et multivariée des variables liées au score de sévérité COVID-19.

Variables		(Univariate analysis)			(Multivariate analysis)		
		Unadjusted OR	95%CI	P-value	Adjusted OR	95%CI	P-value
Age (years)		0.036	0.045_0.162	0.001	0.092	0.044_0.160	0.002
Age groups (year)	≤25	0.514	–0.388_1.416	0.263	0.551	–0.30_1.48	0.217
	25–35	Reference			Reference		
	35–45	–0.929	–0.058_–1.800	0.037	–0.881	–1.71_–0.04	0.039
	45–55	–2.072	–0.70_–3.44	0.003	–1.960	–3.22_–0.5	0.004
	55–65	–1.913	–0.016_–3.81	0.048	–1.552	–3.49_0.26	0.099
	65≤	–3.514	–6.15_0.009	0.016	–3.041	–5.60_–0.47	0.020
Sex	Female	Reference			–		
	Male	0.445	–0.012_0.902	0.103	–		
BMI (kg/m ²)		–0.002	–0.074_0.070	0.696	–		
BMI groups (kg/m ²)	≤30	Reference			–		
	30≤	–0.172	–0.854_1.198	0.742	–		
Blood group	O	Reference			–		
	A	0.273	–0.33_0.738	0.458	–		
	B	0.303	–1.03_0.158	0.149	–		
	AB	0.350	–0.305_1.06	0.276	–		
Charlson comorbidity index (CCI)	0	Reference			–		
	1	–0.247	–0.885_0.392	0.228	–		
	2	0.106	–0.42_0.637	0.723	–		
Smoking		0.418	–0.179_1.016	0.211	–		
Alcohol		0.345	–0.967_0.276	0.257	–		
Opioids		0.905	–0.686_2.497	0.265	–		
PPI consumption	Non-users	Reference			–		
	Short-term users	2.343	1.348_3.338	0.001	2.376	1.41_3.34	0.001
	Long-term users	1.281	0.599_1.964	0.001	1.305	0.64_1.96	0.001
Pantoprazole		2.549	2.32_2.77	0.001	2.311	1.65_2.96	0.001
Omeprazole		2.795	2.56_3.02	0.001	0.599	–0.30_1.50	0.193
Lansoprazole		2.816	2.59_3.03	0.001	0.858	–2.32_4.04	0.597
Esomeprazole		2.824	2.60_3.04	0.001	–0.312	–2.78_2.16	0.804
Rabeprazole		2.818	2.59_3.03	0.001	0.734	–1.5_2.99	0.525
NSAID		1.53	0.222_2.855	0.022	1.53	0.222_2.855	0.022
ASA		–0.945	–2.849_0.960	0.330	–		
Metformin		0.461	–0.351_1.273	0.266	–		
Statin		0.437	–1.217_2.091	0.604	–		
Levothyroxine		1.411	–0.068_2.890	0.062	–		
Steroid		–0.327	–1.981_1.327	0.698	–		

During the COVID-19 pandemic, several studies were done to find a potential causative, susceptibility, prognostic, or preventive effect of PPIs on COVID-19. One study showed that PPI consumption is related to more severe COVID-19 infection and worse clinical consequences. The main mechanisms for this role are unclear. Our study demonstrated the same results [27].

A recent meta-analysis demonstrated that PPI consumption might be related to a worse clinical outcome in COVID-19 patients. Still, they could not find any association between PPIs use and susceptibility to the infection. Our study also demonstrated the same results [28].

Another meta-analysis found indistinct results about PPIs consumption safety throughout the COVID-19 pandemic. The authors believed that recent PPIs consumption might be related to a higher risk of COVID-19 infection and hospitalization. Still, these consequences are probably associated with the confounding factors leading to PPIs consumption rather than PPIs consumption itself. In this study, no association was found for severe outcomes. The results from the meta-analysis indicated no impact of current PPI consumption on COVID-19 consequences [29].

One other meta-analysis demonstrated that PPI use was not related to higher risk of infection and mortality in COVID-19 patients, but they found an association between PPI usage and higher risk of development to the more severe presentation and secondary infection. Our study demonstrated the same results. The authors suggested further studies to clarify the association between PPI consumption and COVID-19 infection and consequences [20].

Some studies revealed that PPI consumption is related to more severe clinical presentations and COVID-19 infection related mortality [17,18,28,30–32]. As we discovered in our study, regular short-term or long-term PPI consumption in patients with no other comorbidities (CCI=0) could be associated with more severe patterns of COVID-19 and presented more symptoms.

The results of other studies were inconclusive, with no significant relationship between PPI consumption and poor COVID-19 clinical outcome, and they suggested larger surveys [33,34].

The association between higher gastric pH and more gastric colonization of microbiomes has been proven in many studies [35] many studies suggest that higher viral loads can lead to more symptomatic and severe COVID-19 infection [17,31,36–38]. It seems that a higher load of COVID-19 virus can induce a stronger cytokine storm, more colonization of the virus, and thus more severe presentation of COVID-19 [17,31]. Our results were consonant with these studies.

Previous studies found that comorbidity factors like age, history of MI, CHF, peripheral vascular disease, CVA, TIA, dementia, COPD, connective tissue disease, PUD, liver disease, DM, CKD, solid tumor, leukemia, lymphoma, and acquired immunodeficiency syndrome (AIDS) are strong risk factors for the severe presentation of COVID-19; and this effect is unlikely to be changed by PPIs consumption [19,22,39,40] It may be a reason for insignificance of the

effect of PPI consumption on COVID-19 severity in patients with CCI ≥ 1 in our study.

Strength and limitation

Using CCI to segregate our patients based on their comorbidity factors to reduce the effect of their underlying conditions on the outcome of our investigation is one of the strengths of our study. The second strength is the exclusion of occasional PPI users in this study. The third one was logistic regression analysis and considering other confounding factors.

This study has some limitations. First, PPI consumption data was recorded based on patients' given history instead of prescription notes. Collecting subjective clinical data like dysgeusia, anorexia, sore throat, and muscle/joint aches that were recorded just based on patients' given history is another limitation of our work.

The third limitation is inadequate data about the exact quantitative dose of consumed PPI; therefore, we missed the cumulative dose effect of PPI consumption and COVID-19 severity and symptoms. Finally, our PCR kits had a false-positive rate of 7% rate for COVID-19 infection.

Conclusion

We discovered that PPI consumers without any comorbidity (CCI=0) had a higher COVID-19 severity score based on the qCSI scoring system and PPI users were significantly more symptomatic than PPI non-consumers.

Having a significant burden on the health care system, physicians should consider the risks and benefits of prescribing PPIs during and after the pandemic.

Widespread strategies should be considered to upturn reasonable prescription of PPIs and reduce over-use of PPIs, especially in high-risk populations.

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Author contribution

All authors had access to the data and a role in data gathering and writing the manuscript.

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Disclosure of interest

The authors declare that they have no competing interest.

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