Proton pump inhibitors use prior to COVID-19 hospitalization is associated with higher C lostridioides difficile infection rate

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Abstract:

Background: There are uncertainties regarding associations of prior proton pump inhibitor (PPI) use with susceptibility for COVID-19 and risks associated with SARS-CoV-2 infection. We aimed to evaluate associations of prior PPI use with outcomes in hospitalized Patients with COVID-19.

Research design and methods: We have retrospectively evaluated a total of 5959 consecutively hospitalized Patients with COVID-19 from a tertiary-level institution in period 3/2020-6/2021. Associations of prior PPI use with outcomes of in-hospital mortality, mechanical-ventilation, intensive-care unit stay, venous-thromboembolism, arterial-thrombosis, major-bleeding, bacteremia, and Clostridioides-difficile infection (Cdiff) were evaluated in an entire and case-matched cohorts.

Results: Among 5959 evaluated patients, there were 1967 (33%) PPI users. In an entire cohort, prior PPI use was associated with higher in-hospital mortality and higher occurrence of Cdiff. Association of prior PPI use with mortality diminished, whereas association with Cdiff persisted after multivariable adjustments. In a matched cohort prior PPI use was associated only with higher risk of CDiff but not other outcomes in line with multivariable analysis.

Conclusions: Although prior PPI use might not have significant impact on clinical course and mortality of SARS-CoV-2 infection, it may predispose development of complications like higher occurrence of Cdiff, and thus substantially impact the course of treatment.

Keywords: SARS-CoV-2; prognosis; pantoprazole; complications; diarrhea

1. Introduction

Proton pump inhibitors (PPI) are commonly prescribed drugs for management or prevention of gastrointestinal disorders and are taken without clear indication in up to 70% of users [1]. Prior to COVID-19 pandemic, PPI use had been associated with higher risks of nosocomial pneumonias, enteric infections and bacterial overgrowth [2,3].

There are uncertainties regarding associations of prior proton pump inhibitor (PPI) use and susceptibility for COVID-19, higher disease severity and higher mortality due to limited and inconsistent findings reported in the literature [4-7]. In fact, comorbid conditions associated with prior PPI use, but not PPI use itself, might predispose patients for worse clinical outcomes [5,7]. Associations of prior PPI use with a number of other clinically relevant outcomes in hospitalized Patients with COVID-19 are unknown.

2. Aim

We aimed to evaluate whether prior PPI use might be associated with higher incidence of in-hospital mortality and other unwanted outcomes by evaluating large tertiary institution registry of hospitalized Patients with COVID-19. We hypothesized that prior PPI use is associated with higher rates of unwanted clinical outcomes.

3. Methods

3.1. Patients and methods

We have retrospectively analyzed a cohort of 5959 consecutive hospitalized Patients with COVID-19 treated in the University hospital Dubrava, Zagreb, Croatia in period from 3/2020 to 6/2021. During the study period hospital was completely repurposed to serve as a regional referral center for most severe Patients with COVID-19 and those with other medical conditions that were concomitantly SARS-CoV-2 positive. All patients were confirmed COVID-19 cases with either PCR or antigen test in presence of compatible symptoms. Patients were treated in line with

contemporary guidelines with majority of patients receiving oxygen supplementation, corticosteroids and low molecular weight heparins of various intensity. Demographic information, prior PPI exposure, comorbidities, COVID-19 symptom severity, laboratory and clinical information were obtained by evaluation of written and electronic medical records and are a part of hospital Registry project (registered on the ClinicalTrials.gov website, identifier NCT05151094, registration date December 9, 2021). Prior PPI exposure was considered to be present if patients recorded PPI use at the time of hospital admission in their medical documentation. COVID-19 severity at the time of hospital admission was defined by the World health organization (WHO) criteria as mild (without evidence of hypoxia or pneumonia), moderate (pneumonia without hypoxia), severe (pneumonia requiring oxygen support) and critical (developing respiratory failure, ARDS, sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury) [8]. Comorbidities were evaluated as individual conditions and cumulatively using the Charlson comorbidity index (CCI). The Eastern Cooperative Oncology Group (ECOG) scale was used to define functional status of patients on admission.

Clinical outcomes of interest were evaluated during hospitalization and included in-hospital mortality of any cause, need for mechanical ventilation and intensive care unit (ICU) admission, occurrence of venous thromboembolic (VTE) and arterial thrombotic events confirmed by objective imaging and laboratory measures, occurrence of major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria, occurrence of bacteremia defined as positive blood cultures with exclusion of cases judged as contamination, and occurrence of confirmed Clostridioides difficile (C. diff.) infection. All C. diff. positive patients were uniformly diagnosed by ECDC criteria and were required to have diarrheal stools or toxic megacolon and a positive laboratory assay for C. difficile toxin A and/or B in stools or a toxin-producing C. diff. organism detected in stool via culture or positive PCR result. C. diff. positive patients were treated by attending physicians according to the institutional guidelines and with supervision of hospital infectious diseases specialist.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the University Hospital Dubrava Review Board (Nm: 2021/2503-04, Date: 01.04.2021).

3.2. Statistical methods

Normality of distribution of numerical variables was analyzed using the Kolmogorov-Smirnov test. Neither of investigated variables had normal distribution and they were presented as median and interquartile range (IQR) and were compared between PPI non-users and users using the Mann Whitney U test. Categorical variables were presented as frequencies and percentages and were compared between PPI non-users and users using the Chi squared test. Logistic regression was used to adjust the association of PPI use with clinically meaningful parameters (age, sex, severity of COVID-19 on admission, CCI, ECOG functional status) [9]. In addition, case-control matching procedure was performed to extract a cohort of 2502 patients (1251 PPI users and 1251 PPI non-users) who were 1:1 exact matched regarding age, sex, CCI and WHO defined COVID-19 severity on admission for additional comparisons. To improve robustness of these analysis, additional 1:1 propensity score matching was performed based on same variables and matching caliper placed at 0.2 times standard deviation of the propensity score [10]. All analyses were performed using the MedCalc statistical program version 20.114 (MedCalc Software Ltd, Ostend, Belgium). Two-sided P values <0.05 were considered statistically significant.

Sample size consideration: all consecutive patients treated in a given period were included (convenience sample). Due to large number (5959 patients) of comprehensively evaluated patients from a hospital registry no formal power analyses were performed.

4. Results

4.1. Patients' characteristics

Among 5959 evaluated patients, there were 1967 (33%) PPI users. Median age of an entire cohort was 72 years, IQR (62-81). There were 3346 (56.2%) males and 2613 (43.8%) females. COVID-19 severity on admission was mild in 560 (9.4%), moderate in 286 (4.8%), severe in 4202 (70.5%) and critical in 911 (15.3%) patients. Median CCI was 4 points, IQR (3-6).

4.2. Evaluation of an entire cohort

Clinical characteristics at the time of hospital admission of an entire cohort stratified according to the prior PPI use are shown in Table 1. In comparison to non-users, PPI users were significantly older, more frequently of female sex, more frequently had severe and less frequently critical intensity of COVID-19 symptoms on admission, had shorter duration of symptoms, worse functional status, higher cumulative comorbidity burden, more frequently had arterial hypertension, diabetes mellitus, hyperlipoproteinemia, atrial fibrillation, chronic kidney disease, active malignancy, dementia, used antibiotics at the time of hospital admission, lower C-reactive protein P(CRP), lower white blood cell count (WBC), lower ferritin, higher D-dimers, lower hemoglobin, lower platelets, higher interleukin 6 and higher procalcitonin ($P<0.05$ for all analyses).

As shown in Figure 1A, prior PPI use was associated with higher in-hospital mortality (OR 1.46, 95% CI (1.33-1.67), $P<0.001$) and higher occurrence of C. diff. infection (OR 1.66, 95% CI (1.26-2.21), $P<0.001$), whereas there was no significant association with mechanical ventilation, ICU stay, VTE, arterial thrombosis, major bleeding and bacteremia in unadjusted analyses ($P>0.05$ for all analyses).

As shown in Table 2, in multivariable analyses adjusted for clinically relevant parameters, association of prior PPI use with mortality diminished, whereas association of prior PPI use with

C. difficile infection persisted independently of older age, more severe COVID-19 and antibiotic use.

In the multivariate model presented in Table 2, PPI use demonstrated adjusted OR of 1.39, 95% (1.04-1.88) and antibiotics use adjusted OR of 2.01, 95% CI (1.51-2.67) for development of C. difficile infection. Significant interaction between PPI and antibiotic use and C. difficile infection occurrence existed (P<0.001). Concomitant use of both PPI and antibiotics, only antibiotics use, only PPI use and use of neither at the time of hospital admission resulted in C. diff. rates of 6.5%, 4.6%, 3.5% and 2.3%, respectively. The occurrence of C. diff. infection showed no significant association with in-hospital mortality (30.9% vs 34.1% for C. diff. infection vs others, respectively, P=0.349).

4.3. Evaluation of a case-control matched cohort

We further evaluated associations of prior PPI use with clinical outcomes in a case-matched cohort of patients consisting of 1251 PPI users and 1251 matched non-PPI users (1:1 exact matched regarding age, sex, CCI and WHO COVID-19 severity on admission). Median age of a matched cohort was 76 years, IQR (67-83). There were 51.6% males and 48.4% females. A total of 83.1% of patients had severe and 10.5% had critical COVID-19 on admission. Median CCI was 5 points, IQR (3-6).

As shown in Figure 1B, in-hospital mortality, mechanical ventilation, ICU stay, VTE, arterial thrombosis, major bleeding and bacterial sepsis rates were similar between prior PPI users and non-users in a matched cohort of patients (P>0.05 for all analyses). However, association with higher rate of C. diff. infection persisted (OR 1.5, 95% CI (1.02-2.22), P=0.041) in line with prior analyses.

We further corroborated our analyses with additional analysis of a propensity score matched cohort, obtaining same conclusion that prior PPI use remained associated with higher rate of C. diff. infection (OR 1.71, 95% CI (1.21-2.44), P=0.003).

5. Discussion

Although prior PPI use might not have significant impact on clinical course and mortality of SARS-CoV-2 infection among hospitalized Patients with COVID-19, it may predispose development of complications like higher occurrence of C. diff. infection, and thus substantially impact the course of treatment.

There are several points we would like to emphasize. Patients with prior PPI exposure were older and significantly more burdened with comorbidities. Unadjusted association of prior PPI use with higher in-hospital mortality diminished after clinically relevant adjustments, finding further corroborated in a matched cohort of patients, supporting the view that PPI-related comorbid conditions might be responsible for increased mortality observed with PPI use in a number of studies [5]. However, other clinically relevant outcomes were similarly frequent among patients with and without prior PPI exposure with the exception of C. diff. infection. PPI use is a recognized risk factor for occurrence of recurrent C. diff. infections out the context of SARS-CoV-2 infection [11,12]. Nevertheless, current COVID-19 studies are focused on hospitalization and mortality rates among PPI users and do not recognize the risk of C. diff. infection as a relevant clinical problem. C. diff. infections may substantially debilitate affected patients, have immediate as well as long-lasting epidemiological implications, and require active pharmacotherapy. Hospital acquired C. diff. infection is of special concern due to higher likelihood of severe or recurrent infection in comparison to community acquired infection. This might be especially important for tertiary institutions with high rate of referral from other hospitals and admission of patients from nursing homes. Due to absence of clinical trials, many guidelines do not provide recommendations for addressing PPI management, although PPI use is a potentially modifiable risk factor [11]. Our study is first to report current association and highlight the fact that clinical course of hospitalized Patients with COVID-19 might be substantially affected by prior PPI use

through development of unwanted complications non-related to the course of SARS-CoV-2 infection itself.

Main limitations of our study are single center experience and retrospective study design. Only PPI and antibiotics use at the time of hospital admission were analyzed. Due to registry-level data we had no access to information regarding PPI subtype, duration of treatment and indications for PPI use prior to and at the time of hospital admission, nor regarding specific antibiotic subtypes used prior to and at the time of admission. PPI use during hospitalization was almost uniform due to very high rates of corticosteroid treatment in severe and critical Patients with COVID-19 and we had no access to reliable information on antibiotic use during hospitalization. We also did not make a distinction between community acquired and hospital acquired C. difficile infection due to high rates of referral from other hospitals and admission of patients from nursing homes. Nevertheless, our study is based on a large dataset of uniformly treated, mostly severe and critical Patients with COVID-19, who are predominantly of old age and highly burdened with comorbidities. It is representative of a tertiary center institution and provides unique insights into risks associated with prior PPI use in this context.

6. Conclusions:

Although prior PPI use might not have significant impact on clinical course and mortality of SARS-CoV-2 infection among hospitalized Patients with COVID-19, it may predispose development of complications like higher occurrence of C. diff. infection, and thus substantially impact the course of treatment.

7. Expert opinion:

Vaccination program and emergence of Omicron SARS-CoV2 variant reduced the number of Patients with COVID-19 presenting with severe and critical form of the disease, and improved

clinical course of hospitalized patients with severe disease [13]. Nevertheless, vaccine hesitancy, waning effects of vaccination and inadequate immunization in immunocompromised groups of patients result in constant presence of patients with severe and critical COVID-19. PPIs are widely prescribed drugs with unsurpassed efficacy in treatment of peptic ulcer disease, gastroesophageal reflux disease, Zollinger-Ellison syndrome, Helicobacter pylori infection and prevention of nonsteroid anti-inflammatory drugs associated ulcers. Rareness of clinically important drug-drug interaction (with the exception of clopidrogel, methotrexate and HIV protease inhibitors) and favorable safety profile also contribute to their widespread use. Long-term PPI use has been associated with several safety concerns, including increased risk of gastrointestinal complications (C. diff. and other enteric infections, microscopic colitis, atrophic gastritis, malabsorption of minerals and vitamins), chronic kidney disease and drug-induced lupus. It is unclear at the moment may chronic PPI use result in increased risk of COVID-19 and consequently increased risk of death associated with SARS-CoV-2 infection. As our currently presented data suggest, PPI associated comorbid conditions but not PPI use per se may be responsible for increased mortality among hospitalized Patients with COVID-19 who were mostly elderly, with mostly severe and critical COVID-19 presentation, and with variety of acute and chronic comorbid conditions. Despite prior PPI use not affecting clinical course of COVID-19 disease itself, it significantly affects already strained hospital bed network in the pandemic conditions through propensity for C. diff. infection. Increased occurrence of C. diff. infection both prolongs the hospital stay and required therapies in affected patients, and complicates the organization of the hospital bed network due to necessary epidemiological measures [14]. It remains a question is this complication truly (and in what extent) preventable. Controlled use of not only PPIs, but also other concomitant therapies (antibiotics, other immunosuppressive therapies, etc.), as well as strict adherence to epidemiological measures may help in reducing C. diff. infection risk.

8. References

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Table 1: Patients' characteristics in an entire cohort and matched cohort of patients, stratified according to proton pump inhibitor (PPI) use in chronic therapy.

	No PPI (3992 pts)	**PPI** (1967 pts)	**P value**
Age (years), median and IQR	71 (60-81)	75 (66-83)	**<0.001 ***
Sex			**<0.001 ***
Male	2329 (58.3%)	1017 (51.7%)	
Female	1663 (41.7%)	950 (48.3%)	
COVID-19 severity			**0.011 ***
Mild	384 (9.6%)	176 (8.9%)	
Moderate	180 (4.5%)	106 (5.4%)	
Severe	2780 (69.6%)	1422 (72.3%)	
Critical	648 (16.2%)	263 (13.4%)	
ECOG status, median and IQR	2 (1-3)	3 (2-4)	**<0.001 ***
Duration of symptoms, median and IQR	6 (2-10)	4 (1-9)	**<0.001 ***
CCI, median and IQR	4 (2-5)	5 (4-7)	**<0.001 ***
Arterial hypertension	2534 (63.5%)	1515 (77%)	**<0.001 ***
Diabetes mellitus	1069 (26.8%)	687 (34.9%)	**<0.001 ***
Hyperlipoproteinemia	713 (17.9%)	624 (31.7%)	**<0.001 ***
Obesity	1187 (29.7%)	552 (28.1%)	0.182
Atrial fibrillation	541 (13.6%)	464 (23.6%)	**<0.001 ***
Chronic kidney disease	298 (7.5%)	376 (19.1%)	**<0.001 ***
Active malignancy	288 (7.2%)	283 (14.4%)	**<0.001 ***
Dementia	623 (15.6%)	436 (22.2%)	**<0.001 ***

Antibiotic use	1006 (25.2%)	773 (39.3%)	**<0.001 ***
CRP (mg/L), median and IQR	91.7 (43-155.1)	79.1 (33.3-137.3)	**<0.001 ***
Ferritin (µg/L), median and IQR	820 (437-1502)	682 (343-1280)	**<0.001 ***
D-dimers (mg/L FEU), median and IQR	1.26 (0.67-3.19)	1.5 (0.79-3.55)	**<0.001 ***
WBC ($x10^9$/L), median and IQR	8 (5.8-11.3)	7.7 (5.5-11)	**0.002 ***
Absolute neutrophils ($x10^9$/L), median and IQR	6.4 (4.3-9.5)	6.2 (4.1-9.2)	**0.005 ***
Absolute lymphocytes ($x10^9$/L), median and IQR	0.8 (0.58-1.19)	0.8 (0.5-1.2)	0.087
Hemoglobin (g/L), median and IQR	132 (119-143)	121 (106-136)	**<0.001 ***
RDW (%)	13.8 (13.2-14.7)	14.5 (13.7-15.8)	**<0.001 ***
Platelets ($x10^9$/L), median and IQR	225 (158-299)	214 (154-291)	**<0.001 ***
IL-6 (pg/mL), median and IQR	43.4 (13.8-99.1)	47.9 (21.6-119.6)	**0.023 ***
Procalcitonin (ng/mL), median and IQR	0.21 (0.08-0.7)	0.23 (0.09-0.85)	**0.022 ***

*Statistically significant at level P<0.05

Abbreviations: PPI=proton pump inhibitors, IQR=interquartile range, CCI=Charlson comorbidity index, COVID-19=Coronavirus disease 2019, ECOG=Eastern Cooperative Oncology group functional status, CRP=C reactive protein, WBC=white blood cell count, RDW=red blood cell distribution width, IL=interleukin.

Table 2: Logistic regression models evaluating adjusted associations of proton pump inhibitor use in chronic therapy with clinical outcomes during hospitalization for acute COVID-19.

	In-hospital mortality	Mechanical ventilation	ICU	VTE	Arterial thrombosis	Major bleeding	Bacteremia	C. difficile
PPI use	P=0.901 OR=0.99 (0.86-1.14)	P=0.772 OR=0.98 (0.84-1.14)	P=0.704 OR=1.03 (0.89-1.18)	P=0.984 OR=1 (0.79-1.28)	P=0.161 OR=1.19 (0.93-1.51)	P=0.503 OR=1.11 (0.81-1.53)	P=0.611 OR=0.95 (0.78-1.15)	**P=0.029 *** OR=1.39 (1.03-1.88)
Age (years)	**P<0.001 *** OR=1.03 (1.02-1.03)	**P<0.001 *** OR=0.98 (0.98-0.99)	**P<0.001 *** OR=0.98 (0.97-0.98)	P=0.668 OR=1 (0.99-1.01)	P=0.838 OR=1 (0.99-1.01)	P=0.244 OR=0.99 (0.98-1.01)	**P<0.001 *** OR=0.98 (0.98-0.99)	**P<0.001 *** OR=1.03 (1.01-1.04)
Male sex	**P<0.001 *** OR=1.54 (1.35-1.76)	**P<0.001 *** OR=1.74 (1.5-2.01)	**P<0.001 *** OR=1.68 (1.47-1.92)	**P=0.020 *** OR=0.77 (0.62-0.96)	P=0.442 OR=1.09 (0.87-1.38)	P=0.239 OR=1.2 (0.89-1.63)	**P<0.001 *** OR=1.59 (1.32-1.9)	P=0.640 OR=0.93 (0.7-1.25)
Charlson comorbidity index	**P<0.001 *** OR=1.16 (1.12-1.19)	P=0.664 OR=1.01 (0.97-1.04)	P=0.529 OR=1.01 (0.98-1.04)	**P=0.049 *** OR=0.94 (0.89-1)	**P<0.001 *** OR=1.12 (1.07-1.18)	**P=0.031 *** OR=1.07 (1.01-1.14)	P=0.305 OR=1.02 (0.98-1.07)	P=0.486 OR=1.02 (0.96-1.09)
Severe or critical COVID-19	**P<0.001 *** OR=19.65 (13.08-29.51)	P=0.997 -	**P<0.001 *** OR=9.4 (6.5-13.61)	**P<0.001 *** OR=2.22 (1.48-3.33)	**P<0.001 *** OR=0.61 (0.45-0.81)	P=0.623 OR=1.12 (0.71-1.78)	**P<0.001 *** OR=4.64 (3.02-7.13)	**P=0.029 *** OR=1.82 (1.06-3.12)
ECOG	**P<0.001 *** OR=1.75 (1.65-1.86)	**P<0.001 *** OR=1.29 (1.21-1.38)	**P<0.001 *** OR=1.3 (1.23-1.38)	P=0.846 OR=0.99 (0.9-1.09)	**P=0.003 *** OR=1.18 (1.06-1.31)	**P=0.012 *** OR=1.19 (1.04-1.37)	**P<0.001 *** OR=1.17 (1.08-1.26)	P=0.384 OR=0.94 (0.83-1.08)
Antibiotic use	P=0.424 OR=0.95 (0.82-1.08)	P=0.479 OR=0.95 (0.81-1.1)	P=0.584 OR=0.96 (0.84-1.1)	P=0.141 OR=1.19 (0.94-1.49)	P=0.513 OR=0.92 (0.72-1.18)	P=0.702 OR=1.06 (0.78-1.46)	P=0.279 OR=0.9 (0.75-1.09)	**P<0.001 *** OR=2.01 (1.51-2.68)

*Statistically significant at level P<0.05 / Abbreviations: ICU=intensive care unit, VTE=venous thromboembolism, C.=Clostridioides PPI=proton pump inhibitors, COVID-19=Coronavirus disease 2019, ECOG=Eastern Cooperative Oncology Group functional status

Figure 1: Associations of prior proton pump inhibitor use with clinical outcomes of in-hospital mortality, mechanical ventilation (MV), intensive care unit (ICU) stay, venous thromboembolism (VTE), arterial thrombosis (art. thr.), major bleeding, occurrence of bacteremia and occurrence of Clostridioides difficile infection (C. diff.) in **A)** an entire cohort and **B)** matched cohort of patients.