High vs Low Dose Proton Pump Inhibitor (PPI) related Mortality in Hospitalized Coronavirus Disease-19 (COVID-19): A Retrospective Cohort Study

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Abstract

***Introduction**: The role of proton pump inhibitor (PPI) in Coronavirus Disease-19 (COVID-19) is still debatable. PPI is commonly used to prevent or treat upper gastrointestinal bleeding and/or dyspeptic symptoms. However, previous studies showed that PPI may lead to adverse outcomes in COVID-19 patients, thus the dose of PPI may play an important role. This study aimed to compare the risk of mortality between high vs low dose PPI in hospitalized COVID-19 patients.*
***Methods**: We performed retrospective cohort study from two COVID-19 referral centers in Jakarta between June 2021 and September 2021. We included hospitalized COVID-19 patients, moderate-critically ill cases, who had been given intravenous PPI for more than 7 days. We defined high dose PPI for omeprazole >40 mg/day or pantoprazole >40 mg/day, and low dose PPI for omeprazole ≤40 mg/day or pantoprazole ≤40 mg/day.*
***Results**: Of the total 365 patients (median age[Q1–Q3] 55 [45–64] years old), 216 subjects were given high dose PPI. Subjects with high dose PPI had a significantly higher mortality rate than the low dose PPI according to bivariate analysis (54.2% vs 26.1%; p<0.001), but quite similar length of stay (median[Q1–Q3] 12.5 [9–16] vs 13 [9–18] days). After conducting a multivariate analysis to control the confounders, we found that high dose PPI still led to higher mortality (aOR 3.04; 95%CI 1.22–7.60; p=0.017).*
***Conclusion**: High dose PPI may increase risk of mortality in hospitalized COVID-19 patients.*

***Keywords:** Coronavirus Disease-19, proton pump inhibitor, mortality*

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Perbandingan Penggunaan Penghambat Pompa Proton Dosis Tinggi dan Rendah terhadap Mortalitas pada Pasien Coronavirus Disease-19 (COVID-19) yang Menjalani Rawat Inap: Studi Kohort Retrospektif

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Abstrak

***Pendahuluan**: Peran obat penghambat pompa proton (PPP) pada Coronavirus Disease-19 (COVID-19) masih kontroversial. PPP sering digunakan untuk mencegah atau mengobati perdarahan saluran cerna atas dan/atau gejala dispepsia. Akan tetapi, berbagai studi pendahulu menunjukkan bahwa penggunaan PPP dapat menyebabkan luaran klinis buruk pada pasien COVID-19 sehingga pemberian dosis PPP secara tepat dapat menjadi solusi. Studi ini bertujuan untuk membandingkan risiko kematian antara PPP dosis tinggi dan rendah pada pasien COVID-19 yang menjalani rawat inap.*
***Metode**: Penelitian ini merupakan studi kohort retrospektif dari dua sentra rujukan COVID-19 di Jakarta selama Juni-September 2021. Studi ini melibatkan pasien COVID-19 rawat inap, derajat sedang-kritis, yang mendapatkan obat PPP intravena selama lebih dari 7 hari. PPP dosis tinggi didefinisikan bila pasien mendapatkan omeprazol >40 mg/hari atau pantoprazol >40 mg/hari, dan PPP dosis rendah untuk omeprazol ≤40 mg/hari atau pantoprazol ≤40 mg/hari.*
***Hasil**: Dari 365 pasien (median usia 55, Q1–Q3 45¬–64 tahun), sebanyak 216 subyek mendapatkan PPP dosis tinggi. Berdasarkan analisis bivariat, kelompok PPP dosis tinggi memiliki risiko mortalitas yang lebih tinggi dibandingkan PPP dosis rendah (54,2% vs 26,1; p<0,001), tetapi keduanya memiliki lama rawat inap yang tidak berbeda bermakna (median[Q1–Q3] 12,5 [9–16] vs 13 [9–18] hari). Setelah dilakukan analisis multivariat untuk mengontrol variabel perancu, ditemukan bahwa PPP dosis tinggi secara independen berhubungan dengan angka mortalitas yang lebih tinggi (aOR 3,04; IK95% 1,22–7,60; p=0,017).*
***Kesimpulan**: Pemberian PPP dosis tinggi dapat meningkatkan risiko kematian yang lebih tinggi pada pasien COVID-19 yang menjalani rawat inap.*

***Kata kunci**: Coronavirus Disease-19, penghambat pompa proton, mortalitas*

Introduction

Since declared as a pandemic in March 2020 by the World Health Organization (WHO), Coronavirus Disease-19 (COVID-19) is still the major healthcare problem worldwide until today. However, there is no definitive treatment for COVID-19, especially for hospitalized patients. Only a few of antiviral and low dose corticosteroids that showed benefit in COVID-19 thus far.[1]

In hospital care setting, patients with COVID19 are usually given proton pump inhibitor (PPI) in order to prevent or treat gastrointestinal bleeding and/or dyspeptic symptoms. It is one of the most frequently used drugs in hospital care administered in various dosages for different durations of therapy.[2] However, the use of routine PPI in COVID19 is still controversial. PPI is a strong acid inhibitor that may inhibit viral clearance in gut, including SARS-CoV2 virus that causes infection in gastrointestinal tract via fecal-oral transmission. In previous studies, PPI can also increase the risk of secondary bacterial pneumonia and acute respiratory distress syndrome (ARDS) in short term.

Several meta-analyses may support the link of PPI and poor outcomes in COVID-19 patients. Li GF, et al[3] found that the risk of SARS-COV2 infection was not associated in current or past PPI users compared to non-users. However, the current or regular PPI users were more likely to have severe outcome than non-users (pooled OR 1.67; 95%CI 1.19–2.33; p=0.003; I^2=63%). Another meta-analy-

sis of retrospective cohort studies by Kim HB, et al[4] also revealed that current or previous uses of PPI, but not histamine-2 receptor antagonist (H2RA), can increase poor outcomes in COVID-19 (HR 1.52, 95%CI 1.20–1.95), but not the incidence of COVID-19. Recent publication by Kamal F, et al[5] also showed that PPI use was associated with an increased risk of severe disease (OR 1.79; 95%CI 1.25–2.57; I^2=0%) and mortality (pooled OR 2.12; 95%CI 1.29–3.51; I^2=16%). However, all authors found substantial heterogeneity among the studies and some uncontrolled confounders may influence the results.

Ongoing debate is increasing related to the dose of PPI for inpatient COVID-19 therapy. Some experts argue that PPI is still needed as gastrointestinal bleeding prophylaxis agent in hospitalized patients with severe COVID-19, especially those with steroid and anticoagulant therapies, or to ameliorate dyspeptic symptoms and improve oral intake, that are also important during hospital care. Early study from Almario CV, et al[6] showed that twice daily PPI use had higher risk to get positive COVID-19 test compared to once daily or less (aOR 3.67; 95%CI 2.93–4.60 vs aOR 2.15; 95%CI 1.90–2.44). We consider that high dose of PPI, but not low dose, may lead to poor outcomes in COVID-19 patients. However, there is no evidence to support that hypothesis. Therefore, this study aimed to investigate the impact of low vs high dose of PPI to the outcome of hospitalized COVID-19 patients.

Methods

Study Design and Participants

This is a retrospective cohort study using electronic medical record in two COVID-19 referral centers in Jakarta, Indonesia: (i) Pertamina Jaya Hospital, one of COVID-19 referral hospital under Indonesian Healthcare Corporation group, and (ii) Wisma Haji Pondok Gede Field Hospital. Subjects were patients aged ≥18 years old with RT-PCR confirmed COVID-19 that hospitalized from June 2021 to September 2021. This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Research Ethical Commission Pertamina Jaya Hospital (Protocol No.001/EC/RSPJ/2022-S0).

Case Definition and Protocols

Only moderate, severe, or critical cases were included in our study. We classified the severity of COVID-19 according to the National definition as follows: (i) moderate cases: patients with clinical signs of pneumonia (fever, cough, dyspnea, increase of respiratory rate), but did not meet the criteria of severe COVID-19; (ii) severe cases: clinical sign of pneumonia with one of severe signs including respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 <93% on room air at sea level; (iii) critically-ill cases: patients with acute respiratory distress syndrome (ARDS), septic and septic shock, and/or dependent to life-support treatment such as mechanical ventilator or vasopressor drugs.

All subjects were treated with the same treatment protocol. Upon admission, patients underwent vital sign monitoring, complete blood test, electrocardiogram, and pulmonary imaging using X-ray or CT-scan. We performed routine blood test at the baseline including hematology, blood gas analysis, kidney and liver function test, electrolytes, blood glucose, C-reactive protein (CRP), and D-dimer levels.

Patients were treated with standard antiviral remdesivir 200 mg for 5–7 days and/or favipiravir with loading dose of 1600 mg b.i.d. followed by 600 mg b.i.d. for 7 days. We defined corticosteroids as low dose: dexamethasone 6 mg/day or equal, and high dose methylprednisolone ≥62.5 mg/day or equal. Other important treatments were anticoagulants (prophylaxis or therapeutic dose), intravenous vitamin C 1000 mg/day, oral vitamin D 5000 IU/day, and other symptomatic drugs. There were only two kinds of PPI that were used in our center, and we defined low dose PPI if the patients used omeprazole ≤40 mg/day or pantoprazole ≤40 mg/day, and high dose PPI for omeprazole >40 mg/day or pantoprazole >40 mg/day.

Inclusion and Exclusion Criteria

Our inclusion criteria were: (i) adults aged ≥18 years old; (ii) RT-PCR confirmed COVID-19 that met criteria of moderate, severe, or critical illness; (iii) used intravenous PPI from the beginning of hospitalization for more than 7 consecutive days. Our exclusion criteria were: (i) patients who died less than 7 days of hospitalization; (ii) patients who were referred to another center, (iii) gastrointestinal bleeding on admission that required high dose of PPI since the beginning of hospitalization;

(iv) incomplete data.

Outcomes

Our primary outcome was mortality during hospitalization, and the secondary outcome was length of hospitalization.

Statistical Analysis

We compared the mortality rate between high and low dose PPI group using bivariate test Chi-square, then followed by multivariate logistic test to control for the confounders. Our potential confounders were onset of symptoms, upper gastrointestinal bleeding, comorbidities (obesity, hypertension, type 2 diabetes mellitus, cerebrocardiovascular disease, and chronic kidney disease), several laboratory parameters on admission (hemoglobin, platelet, creatinine, CRP, D-dimer levels, and PaO_2/FiO_2 ratio), antivirals (remdesivir or favipiravir), and the dose of corticosteroid and anticoagulant. Meanwhile, the comparison of length of stay between the two groups was analyzed using independent-T test or Mann-Whitney test according to the data distribution. All the data was analyzed using IBM SPSS® version 25.

Results

Between June 2021 and September 2021, 1,076 patients with COVID-19 were selected from the database; however, after screened for aged ≥18 y.o. and excluded for pregnancy, death on arrival, mild cases, hospitalized <7 days, and referred to other centers in which the outcomes cannot be measured, we obtained 365 subjects from two referral hospital. Flowchart of subject selection was shown in Figure 1.

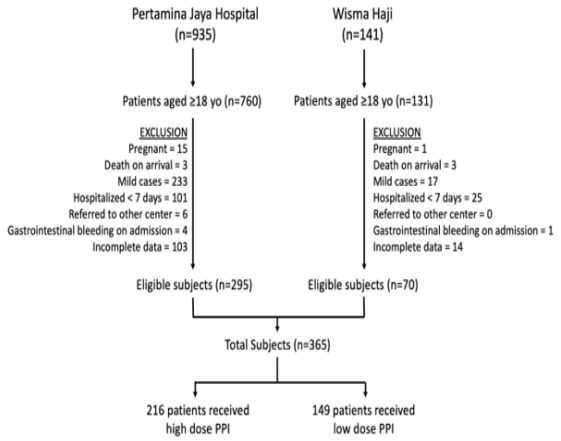

Figure 1. Flowchart of Subjects Selection

Baseline characteristics are shown in Table 1 and presented according to PPI dose group. The mean of age, gender, and onset of the symptoms were not different between the two groups. However, high dose PPI group had more severe cases on admission, more cases of type 2 diabetes mellitus, cerebrocardiovascular, and chronic kidney disease as comorbidities. The high dose PPI group also had higher CRP and D-dimer levels, and more severe pulmonary imaging on admission. Most subjects from both groups were given favipiravir as the antiviral treatment, but remdesivir was higher in high dose PPI group. High dose corticosteroid and therapeutic dose anticoagulant were more likely given in the high dose PPI group, than in the low dose group which was treated with low dose corticosteroid and prophylactic dose anticoagulant.

High dose PPI group had more mortality cases than low dose PPI group did in bivariate analysis (54.2% vs 26.1%). However, there was no statistical difference between the two groups for the length of hospital stays. After controlling for confounders in logistic regression analysis (Table 2), we found that the high dose PPI had higher mortality than low dose PPI groups did (aOR 3.04; 95%CI 1.22–7.60; p=0.017).

Discussion

This study found that high dose PPI is associated with higher mortality according to bivariate and multivariate analysis. However, it did not associate with the length of hospital stay.

Several biological mechanisms may explain these findings. PPI irreversibly inhibits its proton pump in parietal gastric cells that significantly reduce gastric acid. This hypochloremia condition may decrease protective effect of gastric acid and increase the survival rate of SARS-CoV2 virus in stomach until they reach enterocytes.[7] Low gastric acid also can modify gut microbiomes which facilitates secondary intestinal infection.[8] Furthermore, a previous study had reported that PPI may impair the activities of neutrophils, cytotoxic T-lymphocytes, and natural killer cells that contributes to increased risk of infection, such as pneumonia.[9] To ensure that subjects were adequately exposed to the risk factor, we only included patients that had been given PPI for more than 7 days. However, this study did not analyze viral clearance rates and secondary

Table 1. Baseline Characteristics

	All (n=365)	High Dose PPI (n=216)	Low Dose PPI (n=149)	p*
Age [median (Q1 - Q3)] [years]	55 (45 - 64)	58 (49 - 67)	52 (37,5 - 59)	<0.001**
≥60 y.o., n (%)	128 (35.1)	95 (44)	33 (22.1)	
Sex, male (%)	181 (49.6)	72 (48.3)	109 (50.5)	0.688
Onset of symptoms (days)*	5 (4 - 7)	5 (4 - 7)	5 (3 - 6)	0.001**
Previous used of PPI, n (%)	114 (31.2)	70 (32,4)	44 (29,5)	0.560
History of PUD, GERD, or upper GI tumor, n (%)	88 (24.1)	54 (25)	34 (22,8)	0.632
Upper GI bleeding, n (%)	64 (17.5)	48 (22.2)	16 (10,7)	0.005**
Comorbidities, n (%)				
Obesity	95 (26)	56 (25.9)	39 (26.2)	0.958
Hypertension	187 (51.2)	116 (53.7)	71 (47.7)	0.256
Type 2 diabetes mellitus	158 (43.3)	121 (56)	37 (24.8)	<0.001**
Cerebrocardiovascular disease	110 (30.1)	82 (38)	28 (18.8)	<0.001**
Chronic kidney disease	73 (20.0)	49 (22.7)	24 (16.1)	0.123
Others	53 (14.5)	34 (15.7)	19 (12.8)	0.426
Laboratory test+ [median (Q1 - Q3)]				
Hemoglobin (g/dL)	11.2 (10.2–12.5)	10.9 (10.2–12.1)	11.9 (10.8–13.2)	<0.001**
Leucocytes (per dL)	6,600 (4,750–10,050)	6,200 (4,600–9,475)	7,200 (4,950–10,100)	0.135
Platelet (per dL)	185 (147.5–275)	175.5 (144–252.7)	201 (152.5–301)	0.016**
Ureum (mg/dL)	68 (55–86)	69.5 (55.3–87.6)	65 (52–81.5)	0.044**
Creatinine (mg/dL)	1.0 (0.8–1.3)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	0.060
AST (U/L)	49 (37–63)	50.5 (37.5–67.0)	46 (35–59.5)	0.027**
ALT(U/L)	54 (38–66)	53 (37–66.7)	55 (39–66)	0.810
PaO_2/FiO_2 ratio	254 (154–300.5)	202 (124.3–286.5)	279 (250.5–309)	<0.001**
Random blood glucose (mg/dL)	181 (139–244)	200 (145–255)	155 (130.5–201.5)	<0.001**
C-reactive protein	70 (44–101)	95 (71.25–122)	45 (34–60)	<0.001**
D-dimer	880 (650–1,315)	1,100 (900–1,800)	650 (510–800)	<0.001**
Treatment				
Remdesivir	77 (21.1)	63 (29.2)	14 (9.4)	<0.001**
Favipiravir	288 (78.9)	153 (70.8)	135 (90.6)	
Low dose steroid	192 (52.6)	54 (25.0)	138 (92.6)	<0.001**
High dose steroid	173 (47.4)	162 (75.0)	11 (7.4)	
Prophylactic dose anticoagulant	200 (54.8)	60 (27.8)	140 (94)	<0.001**
Therapeutic dose anticoagulant	165 (45.2)	156 (72.2)	9 (6)	
Outcomes				
Deaths, n (%)	156 (42.7)	117 (54.2)	39 (26.1)	<0.001**
Length of stays [median (Q1–Q3)] [days]	13 (9–17)	12.5 (9–16)	13 (9–18)	0.339

** The data was analyzed using Chi-square for categorical variables or Mann-Whitney for numerical variables*
***p<0.05 was considered as statistically significant*
+Data were obtained on admission
GERD, gastroesophageal reflux disease; GI, gastrointestinal; PPI, proton pump inhibitors; PUD, peptic ulcer disease.

Table 2. Multivariate Analysis Using Multiple Logistic Regression*

	aOR	95%CI	p
High dose PPI	3.04	1.22–7.60	0.017

**After adjusted for onset of symptoms, cerebrocardiovascular disease, PaO_2/FiO_2 ratio, C-reactive protein levels*

infection, and therefore was unable to prove these biological plausibilities.

Previous observational studies may strengthen our findings. A retrospective study from Ramachandran P, et al[10] (n=295) found that pre-hospital PPI users had 2.3 higher mortality rate and 2.3 higher incidence of acute respiratory distress syndrome (ARDS) than non-users. However, another retrospective study from Zhang XY, et al[11] (n=154) also did not find any difference of viral clearance rate (HR 1.575; 95%CI 0.993–2.499) and length of stay (HR 1.064; 95CK 0.651–1.740) in PPI users compared to non-users. Data from Korean nationwide cohort study[12] showed that COVID-19 patients who used PPI for the last 30 days had poorer clinical outcomes, such as higher ICU admission rate, the need of mechanical ventilation, and even death, than non-users (aOR 1.79; 95%CI 1.3–3.1). Another study from Luxenburger H, et al[13] found that PPI users had a higher incidence of ARDS (48.4% vs 12.2%; p=0.02) and secondary infection (48.4% vs 20.0%; p<0.001) that contributed to higher death rates (19.4% vs 5.6%; p=0.01).

Our study demonstrated a good temporal relationship that PPI had given before the outcome presented. High dose PPI was typically given for upper gastrointestinal bleeding, but should be tapered after 48–72 hours, therefore prolonged high PPI may result to poor outcome.[14] Our study has controlled several major confounders, such as gastrointestinal bleeding, steroid and anticoagulant, and COVID-19 severity markers including CRP and D-dimer levels. In our study, severe and critical cases of COVID-19 were more likely to be given a higher dose of steroid and anticoagulant, therefore higher PPI was also administered. These data were obtained in Jakarta between June 2021 and September 2021 during the second peak of COVID-19 wave in Indonesia where the country was dominated by Delta variants with very high mortality rates.

On the other hand, our study also has some limitations, including wide confidence interval that may indicate uncertainty in the target population. Some potential confounders that may influence the results were still not controlled in this study, such as the level of severity (moderate, severe, and critical) including mechanical ventilation, the use of nasogastric tube, and some important treatment such as tocilizumab, intravenous immunoglobulin, and plasma convalescent that may influence the outcome.[3,4,15] In addition, we only used simple category dose of steroid and anticoagulant dose in our analysis. This study does not investigate total duration of PPI used that may play role on the outcome.

Nevertheless, this study gives additional evidence that supports dose-relationship about PPI and poor outcome of COVID-19. In clinical practice, routine PPI especially at high dose should be considered carefully. This study only investigated the outcome after a minimum of 7 days of PPI, thus could not be generalized for short-term hospitalization cases.

Conclusion

In hospitalized COVID-19 patients, the use of high dose PPI may increase the risk of mortality compared to the low dose PPI. Therefore, physicians should consider the risk-benefit and appropriate dose of PPI in COVID-19 patients.

Conflicts of Interest

None

Acknowledgment

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