Proton pump inhibitor therapy usage and associated hospitalization rates and critical care outcomes of COVID-19 patients

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Proton Pump Inhibitors (PPI) are one of the most prescribed medications in the United States. However, PPIs have been shown to increase the risk of enteric infections. Our study aims to evaluate the correlation between PPI and COVID-19 severity. We performed a retrospective cohort study on patients who tested positive for SARS-CoV-2 from March to August 2020. Patients were categorized based on PPI user status. Primary outcomes included need for hospital or ICU admission and 30-day mortality. Secondary outcomes looked to determine the severity of COVID-19 infection and effect of comorbid conditions. 2,594 patients were reviewed. The primary outcomes of our study found that neither active nor past PPI use was associated with increased hospital admission or 30-day mortality following completion of multivariate analysis. Additionally, there was no association between COVID-19 infection and the strength of PPI dosing (low, standard, high). However, the following covariates were independently and significantly associated with increased admission: age, male gender, diabetes, COPD, composite cardiovascular disease, kidney disease, and obesity. The following covariates were associated with increased mortality: age, male gender, COPD, and kidney disease. In conclusion, the high risk features and comorbidities of PPI users were found to have a stronger correlation to severe COVID-19 infection and poor outcomes as opposed to the use of PPI therapy.

SARS-CoV-2 or Coronavirus Disease 2019 (COVID-19) is a viral disease that has surmounted into a global pandemic immensely impacting healthcare in the United States (US) and around the world. As of March 2022, there are over 446 million worldwide cases of recorded COVID-19 infections with over 80 million in the US alone and millions of high-risk individuals who remain unvaccinated1. The clinical manifestations of COVID-19 vary widely; however, those with severe COVID-19 illness typically have significant respiratory compromise2–5. Several risk factors for both susceptibility of infection and clinical outcomes have been proposed, including age greater than 65, diabetes, coronary artery disease and chronic obstructive pulmonary disorder (COPD) placing individuals at increased risk6,7. Additionally, proton pump inhibitor (PPI) use has been identified as a possible risk factor for increased severity for COVID-19 infection, yet this association has not been extensively studied.

PPIs are one of the most common classes of medications prescribed in the US8. Their use however has been associated with increased risk of infections including pneumonia, Clostridium difficile and spontaneous bacterial peritonitis9–13. It is postulated that these infections may occur due to a decrease in gastric acid leading to a disruption of gut flora9. Studies evaluating the relationship between the severity of COVID-19 infection and PPI therapy are emerging, but the relationship is not well established. Therefore, our study aims to determine the association between the severity of COVID-19 infection and trends in PPI use.

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Methods

Study design. We performed a retrospective cohort study within St. Luke’s University Health Network (SLUHN), a 10-hospital network located in Eastern Pennsylvania. This study was approved by the SLUHN Institutional Review Board (IRB) and was performed in accordance with institutional guidelines and regulations. Charts of patients who underwent COVID-19 testing where reviewed and those who tested positive for SARS-CoV-2 through nasopharyngeal swab specimens and SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) testing from March 2020 to August 2020 met inclusion criteria. Patients who had repeated testing completed were only counted for once. Those who only had positive serological antibody testing, and not a positive RT-PCR, were excluded from the study. Charts were reviewed to determine patient’s history of PPI use (including esomeprazole, omeprazole, pantoprazole, lansoprazole, and rabeprazole).

Data collection. Data was collected through utilization and review of the electronic health record (EHR) system, and all variables were recorded in one data collection form. Information regarding PPI use was collected including type, current status (active use, past use, or no use; active users had been prescribed and taking PPIs within the last 30 days prior to admission while past users included those who had a history of usage within the last 31 to 365), strength (grouped as low, standard, and high; based off clinical guidelines published by the National Institute for Health and Care Excellence)\(^\text{14}\). Additional variables included critical care outcomes (including need for supplemental oxygen, ICU admission, mechanical ventilation, and 28-day mortality) were also collected.

Data analysis. Using SPSS version 27 to analyze our data (Armonk, NY: IBM Corp), we first compared patient demographic and clinical variables between our three patient groups (patients with active PPI use, patients with past PPI use, and patients with no PPI use). Next, we constructed direct multivariable logistic regression models to determine the independent effect of PPI usage on hospital admission within two weeks of COVID testing and 30-day mortality after adjusting for relevant patient covariates. Although we originally planned to model hospital discharge disposition as an additional outcome, there were insufficient subgroup samples for several categories, so we reported only descriptive information.

Prior to regression modeling, we conducted separate bivariate analyses (one-way analysis of variance for normally distributed continuous variables and chi square tests for categorical variables) to determine which covariates were best suited to multivariable modeling for each of our three outcomes at \(p < 0.20\). In addition to PPI usage, our potential covariates included age; gender; race (white versus non-white/other/did not answer due to small subgroup sizes for nonwhite racial groups); diabetes; chronic obstructive pulmonary disease (COPD); composite cardiovascular disease (heart failure, cardiomyopathy, and/or coronary artery disease); kidney disease; cancer; and obesity [defined as body mass index (BMI) > 30]. We were unable to include sickle cell anemia or organ transplantation due to limited samples sizes within each PPI group.

We also assessed for linearity in the logit for age and BMI as continuous covariates; both had acceptable values for all models. Based on examination of the normalized residuals, Cook’s D, and leverage statistics, the admissin model had 124/2,593 outliers (4.8%); the SNF residency model had 67/2,592 outliers (2.6%); and the 30-day mortality model had 61/1,757 outliers (3.5%); there were no influential data points for any of the models. Given these relatively small values, we retained all patients in our regression analyses.

To ascertain model goodness of fit, we reported the omnibus chi square statistic and the Hosmer-Lemeshow goodness-of-fit statistic. For each covariate, we present adjusted odds ratios (AOR), and 95% confidence intervals (CIs), with \(p < 0.05\) denoting statistical significance for covariates in the final models.

We further evaluated hospital-admitted patients based on their PPI usage by conducting separate chi square and Kruskal Wallis tests for the following categorical and skewed continuous outcomes, respectively: 1) COVID versus non-COVID reason for admission; 2) oxygen usage; 3) ICU admission; 4) hospital length of stay; and 5) distribution of comorbidities. Finally, we evaluated only active PPI users based on their PPI dosages by conducting separate chi square and Kruskal Wallis tests for the following outcomes: 1) hospital admission within two weeks of COVID testing; 2) oxygen usage; 3) ICU admission; 4) hospital length of stay; and 5) 30-day mortality. For these analyses, \(p < 0.05\) denotes statistical significance, with no adjustment for multiple comparisons.

Ethical approval and consent to participate. Ethics approval was obtained from the Institutional Review Board (IRB) before starting the study. No consent to participate was taken or needed (with approval from IRB) as study was retrospective in nature and based of the review of patient charts.

Results

A total of 2,594 patient charts were reviewed and included in the study sample. 1,312 subjects were female (50.5%) and 1,499 (57.7%) were white. The mean age was 52.6 years and the mean BMI was 30.7. 2,048 patients (78.9%) had no past or present history of PPI use. 448 individuals (17.3%) were active PPI users and 98 individuals (3.8%) had a history of PPI use. Key demographic and clinical characteristics of each individual group are listed in Table 1. Those in the active or prior PPI use group were associated with significantly higher rates of concurrent diabetes, COPD, composite cardiovascular disease (cardiomyopathy, congestive heart failure, and coronary artery disease), kidney disease, cancer, and obesity.

Bivariate comparisons were completed looking at hospital admission within two weeks of COVID testing as well as overall 30-day mortality and are listed in Table 2. Of 1,040 total admissions, 286 (27.5%) were active PPI users, 54 (5.2%) past PPI users, and 700 (67.3%) non-PPI users. Bivariate comparisons identified the following 10 covariates for inclusion in the multivariable regression model (\(p < 0.20\)): PPI usage, age, gender, race, diabetes, composite cardiovascular disease, COPD, kidney disease, cancer, and obesity. With regards to 30-day mortality,
Table 1. Patient demographic and clinical variables*. *Denominators differ for some variables due to missing data. **SD Standard deviation, COPD Chronic obstructive pulmonary disease. ***Cardiovascular disease is a composite of cardiomyopathy, congestive heart failure, and coronary artery disease. ****Defined as BMI > 30 kg/m². *****Based on separate one-way analysis of variance or chi square tests, as appropriate.

| Variable                  | Active PPI use (n = 448) | Past PPI use (n = 98) | No PPI use (n = 2,048) | p-value****** |
|---------------------------|--------------------------|-----------------------|------------------------|---------------|
| Age, years                | 65.0 ± 17.2              | 62.2 ± 18.6           | 49.5 ± 19.8            | <.0001        |
| Gender (n,%)              | 255 female (56.9%)       | 64 female (65.3%)     | 990 female (48.3%)     | <.0001        |
| Race (n,%)                | 309 white (69%)          | 57 white (58.2%)      | 1,129 white (55.1%)    | <.0001        |
| BMI, kg/m² (mean ± SD)**  | 30.9 ± 9.2               | 30.3 ± 6.6            | 30.7 ± 7.6             | .84           |
| Diabetes (n,%)            | 200 (44.6%)              | 46 (46.9%)            | 479 (23.4%)            | <.0001        |
| COPD* (n,%)               | 111 (24.8%)              | 21 (21.4%)            | 134 (6.5%)             | <.0001        |
| Cardiovascular disease*** (n,%) | 213 (47.5%) | 48 (49%)             | 297 (14.5%)            | <.0001        |
| Kidney disease (n,%)      | 153 (34.2%)              | 33 (33.7%)            | 222 (10.8%)            | <.0001        |
| Cancer (n,%)              | 93 (20.8%)               | 18 (18.4%)            | 136 (6.6%)             | <.0001        |
| Obesity**** (n,%)         | 249 (55.6%)              | 50 (51%)              | 681 (33.3%)            | <.0001        |
| Organ transplant (n,%)    | 1 (0.2%)                 | 0                    | 7 (0.3%)               | .79           |
| Sickle cell anemia (n,%)  | 7 (1.6%)                 | 3 (3.1%)              | 13 (0.6%)              | .01           |

Table 2. Unadjusted comparisons for hospital admission within two weeks of COVID testing and for overall 30-day mortality *. *Denominators differ for some variables due to missing data. **PPI Proton pump inhibitor, SD Standard deviation, COPD Chronic obstructive pulmonary disease. ***Cardiovascular disease is a composite of cardiomyopathy, congestive heart failure, and coronary artery disease. ****Defined as BMI > 30 kg/m². *****Based on separate one-way analysis of variance or chi square tests, as appropriate.
cells in the epithelium of the lungs, ACE-2 is also abundantly found on the enterocytes in the gastrointestinal tract via the angiotensin converting enzyme-2 (ACE-2) receptor. In addition to being found on viruses in extreme acidic or basic environments and stabilization in a neutral environment often created by infection based on prior data examining the use of PPIs and their associations with infection risk. Many hypotheses have been developed theorizing the potential effect of PPI therapy on severity of COVID-19 infection. Bivariate comparisons identified the following 10 covariates for inclusion in the multivariable regression model for Hospital Admission within Two Weeks of COVID Testing and 30-day mortality. *Omnibus chi-square p-value < .0001; Hosmer–Lemeshow goodness-of-fit p-value = .51 (For Hospital Admission within Two Weeks of COVID Testing) and p-value = .49 (For 30-Day Mortality). **AOR Adjusted odds ratio, CI Confidence interval, PPI Proton pump inhibitor, COPD Chronic obstructive pulmonary disease, BMI Body Mass Index. ***Cardiovascular disease is a composite of cardiomyopathy, congestive heart failure, and coronary artery disease. ****Obesity utilized for a Hospital Admission within 2 Weeks of COVID Testing and BMI utilized for 30-Day Morality; Defined as BMI > 30 kg/m2.

Table 3. Multivariable logistic regression for hospital admission within two weeks of COVID testing and 30-day mortality. *Omnibus chi-square p-value < .0001; Hosmer–Lemeshow goodness-of-fit p-value = .51 (For Hospital Admission within Two Weeks of COVID Testing) and p-value = .49 (For 30-Day Mortality). **AOR Adjusted odds ratio, CI Confidence interval, PPI Proton pump inhibitor, COPD Chronic obstructive pulmonary disease, BMI Body Mass Index. ***Cardiovascular disease is a composite of cardiomyopathy, congestive heart failure, and coronary artery disease. ****Obesity utilized for a Hospital Admission within 2 Weeks of COVID Testing and BMI utilized for 30-Day Morality; Defined as BMI > 30 kg/m2.

186 patients died in total: 56 (30.1%) active PPI users, 11 (5.9%) past PPI users, and 119 (64%) non-PPI users. Bivariate comparisons identified the following 10 covariates for inclusion in the multivariable regression model (p < 0.20): PPI usage, age, BMI, gender, race, diabetes, composite cardiovascular disease, COPD, kidney disease, and cancer. Multivariable regression results are displayed in Table 3. In the regression model, PPI use was not associated with hospital admissions or 30-day mortality. The model found the following variables significant: age, male gender, diabetes, COPD, composite cardiovascular disease, kidney disease and obesity. As further presented in Table 3, the following covariates were significantly associated with increased mortality: age, male gender, COPD and kidney disease.

Secondary outcomes for admitted patients based on their PPI use was evaluated and are listed in Table 4. Compared to past and nonusers, active PPI users had slightly higher median hospital length of stay (p = 0.02). Additionally, past PPI users had a higher percentage of ICU admissions (p = 0.03), while both active and past PPI users had higher percentages of diabetes, COPD, composite cardiovascular disease, kidney disease, cancer, and obesity (p < 0.006). For active and past PPI users (n = 546), pantoprazole was most frequently taken (316, 57.9%), followed by omeprazole (196, 35.9%); esomeprozole (19, 3.5%); lansoprazole (14, 2.6%); dexlansoprazole (5, 0.9%); and rabeprazole (2, 0.4%). Table 5 further presents secondary outcomes for active PPI users only based on dosage (low, standard, or high). None of the outcomes were significantly different.

Additionally, data was also collected on the use of histamine receptor antagonist (H2RA) within the study’s sample. For active and past PPI users taking H2RA medications (n = 206), famotidine was most frequently consumed (170, 82.5%), followed by ranitidine (34, 16.5%); and cimetidine (2, 1.0%). 55 patients were found to be taking H2RAs, but not PPIs. Unfortunately, due to this limited subgroup sample, analysis was unable to be performed to yield statistically significant results.

Discussion

Many hypotheses have been developed theorizing the potential effect of PPI therapy on severity of COVID-19 infection based on prior data examining the use of PPIs and their associations with infection risk. Previous studies such as, Moayyedi et al., have shown that PPI therapy is associated with increased risk of enteric infections, possibly secondary to suppression of gastric acid secretion. Additional studies have also proven inactivation of viruses in extreme acidic or basic environments and stabilization in a neutral environment often created by PPI and other forms of antacid medications. SAR-CoV2 has been shown to invade the body through the gastrointestinal tract via the angiotensin converting enzyme-2 (ACE-2) receptor. In addition to being found on cells in the epithelium of the lungs, ACE-2 is also abundantly found on the enterocytes in the gastrointestinal tract providing them with a point of invasion. Therefore, these findings have prompted theoretical concern that use off PPI therapy can place individuals not only at increased risk of COVID-19 infection but also of severe disease.

Our large, single network retrospective study examined the relationship between PPI therapy and the severity of COVID-19 infection. After adjusting for relevant patient demographics and clinical variables, neither active nor past PPI use significantly predicted hospital admission within two weeks of COVID testing or 30-day mortality. For patients admitted to the hospital, active PPI users had slightly higher median length of stay, and but both active and past PPI users had a greater frequency of comorbid conditions compared to non-users. Additionally, dosage of PPI therapy (low, standard, and high) was compared but was not found to be associated with hospital admission or 30-day mortality. For patients admitted to the hospital, active PPI users had slightly higher median length of stay, and both active and past PPI use significantly predicted hospital admission within two weeks of COVID testing or 30-day mortality. The model found the following variables significant: age, male gender, COPD, composite cardiovascular disease, kidney disease and obesity. As further presented in Table 3, the following covariates were significantly associated with increased mortality: age, male gender, COPD and kidney disease.

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with more frequent hospital admissions within two weeks of COVID testing, requirement for ICU admission, or increased length of hospital stay.

Recent literature has found conflicting results regarding the association between PPIs and COVID-19 outcomes. One of the first and largest studies evaluating the association was the Korean Nationwide Cohort Study completed by Lee et al. which involved a sample size of 234,427 patients. Overall, this study concluded that PPI use may not increase susceptibility to SARSCo-2 infection but placed individuals at increased risk of severe COVID-19 infection. Results of our studied differed in that there was no positive correlation between PPI use and COVID-19 severity, but rather significant correlations were seen with various comorbidities through completion of regression modeling. Although the Korean Cohort Study did make note of their sample's baseline characteristics and comorbidities and their strength lies in the study's large sample size, the study lacked insight into the potential confounding variables that they left unmeasured. In addition to completing a multi regression analysis to determine the independent effect of PPI usage, our study further aimed to look at the effect of age and comorbid conditions, including obesity or increased BMI, which are confirmed risk factors for COVID-19.

Table 4. Hospital-admitted patient outcomes based on PPI Use* (n = 1,040). *PPI Proton pump inhibitor, COPD Chronic obstructive pulmonary disease. **Denominators are reduced due to "N/A" responses for certain patients. ***Cardiovascular disease is a composite of cardiomyopathy, congestive heart failure, and coronary artery disease. ****Defined as BMI > 30 kg/m2. *****Based on separate chi square or Kruskal Wallis tests, as appropriate; "N/A" indicates insufficient sample sizes for statistical compari.

|                        | Active PPI use (n = 286) | Past PPI use (n = 54) | No PPI use (n = 700) | p-value***** |
|------------------------|--------------------------|-----------------------|----------------------|--------------|
| COVID-related admission (n,%) | 228/286 (79.7%)          | 40/53 (75.5%)         | 583/695 (83.9%)     | .11          |
| Length of stay (median, range) | 6 (1–45)                | 5 (1–56)              | 5 (1–91)             | .02          |
| ICU admission** (n,%) | 77/277 (27.8%)           | 20/48 (41.7%)         | 198/665 (30.2%)     | .03          |
| Oxygen use (n,%)   | Mechanical ventilation: 41 (14.3%) BPAP: 2 (0.7%) Supplemental: 173 (60.5%) None: 70 (24.5%) | Mechanical ventilation: 11 (20.4%) BPAP: 0 Supplemental: 29 (53.7%) None: 14 (25.9%) | Mechanical ventilation: 91 (13%) BPAP: 4 (0.6%) Supplemental: 435 (62.1%) None: 170 (24.3%) | .79          |
| Diabetes (n,%)              | 156 (54.5%)              | 31 (57.4%)            | 311 (44.4%)         | .006         |
| COPD* (n,%)                | 98 (34.3%)               | 15 (27.8%)            | 114 (16.3%)         | <.0001       |
| Cardiovascular disease*** (n,%) | 177 (61.9%)             | 39 (72.2%)            | 232 (33.1%)         | <.0001       |
| Kidney disease (n,%)       | 136 (47.6%)              | 25 (46.3%)            | 190 (27.1%)         | <.0001       |
| Cancer (n,%)               | 74 (25.8%)               | 12 (22.2%)            | 91 (13%)            | <.0001       |
| Obesity**** (n,%)          | 166 (58%)                | 26 (48.1%)            | 311 (44.4%)         | <.0001       |
| Organ Transplant (n,%)     | 8 (2.1%)                 | 8 (1.1%)              |                     | .23          |
| Sickle cell anemia (n,%)   | 1 (0.3%)                 | 0                     | 3 (0.4%)            | N/A          |

Table 5. Active PPI use: outcomes based on PPI dosage (n = 286)*. *PPI Proton pump inhibitor. **Based on separate chi square or Kruskal Wallis tests, as appropriate.
Use of PPI therapy has been shown to increase individuals risk of infection and has raised theoretical concern that it can lead to severe COVID-19 infection. Our data suggests that PPI therapy is not associated with an increased risk of severe COVID-19 infection. Although more data is necessary in order to include PPI use in risk stratification models for COVID-19, clinicians should recognize that based off our data that COVID-19 should not change their clinical management and prescription of PPI therapy.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. 16.
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Author contributions

B.S.: Acquisition of data, interpretation/analysis of data, draft and substantive revision of manuscript. S.M.: Conception Acquisition of data, interpretation/analysis of data, draft manuscript. S.C.: Acquisition of data, interpretation/analysis of data, draft manuscript. N.P.: Acquisition of data, interpretation/analysis of data, draft manuscript. M.A.: Acquisition of data, interpretation/analysis of data, drafting of manuscript. J.A.S.: Acquisition of data. J.S.: Interpretation of data, drafting of manuscript. Y.S.: Conception of study, substantive revision of manuscript, approval of the submitted version of manuscript. All the above authors agree to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

Competing interests

The authors declare no competing interests.
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