

The role of Proton Pump Inhibitors in COVID-19

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Abstract

The use of proton pump inhibitors (PPIs) has been associated with increased risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and severe outcomes. This may be because the gut is the most important immune organ in the body and the virus reach and replicate rapidly in the absence of gastric acid. Therefore, the use of PPIs as acid suppressant drugs may have negative impact on COVID-19. We aimed to identify the relationship between the use of PPIs with the incidence of Covid-19 and the severity of outcomes. This case-control study was conducted on 246 participant who were pretested for Covid-19 in Herat city, Afghanistan. We investigated the incidence rate and risk of severe clinical symptoms and outcomes (mechanical ventilation, intensive care unit (ICU) admission and requirement of oxygen therapy) in COVID-19 patients. The incidence of Covid-19 was insignificantly higher among PPI-users than non-users (OR 1.29, 95% CI 0.74 – 2.25). Moreover, the symptoms including respiratory, digestive and systemic complains, taste and smell disturbances and outcome of the disease were more severe in PPI users {OR (95% CI)}, 2.47 (0.71 – 8.63), 2.16 (0.97 – 4.84), 2.32 (1.01 – 5.31), 2.23 (1.05 – 4.72), 2.62 (1.23 – 5.45), 4.38 (2.01 – 9.51), 7.56 (2.93 – 19.61) and 5.99 (2.52 – 14.30) respectively. In Conclusion We found a significant increased risk of COVID-19 negative outcomes in PPIs users. Further studies with larger sample size are needed to find the exact role of PPIs use on COVID-19.

Keywords: Proton Pump Inhibitors, COVID-19, Risk factor, SARS CoV-2

INTRODUCTION

The Covid-19 pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been ceaselessly affecting different populations and territories (Aleem et al., 2022) since it was first reported in China in December 2019 (Lai et al., 2020). Considering the pandemic of Covid-19 and the necessity to find a drug for its treatment, some already approved drugs for other diseases are explored in order to repurpose (Aguila & Cua, 2020; Ray et al., 2020).

Proton pump inhibitors (PPIs) are one of the most widely prescribed group of drugs approved by Food and Drug Administration (FDA) for the treatment of gastric ulcers and gastroesophageal reflux disease (GERD) (Fock et al., 2008; Loffredo et al., 2021; Ray et al., 2020). However, they have been shown to have multiple therapeutic effects beside gastric

acid suppression (Ray et al., 2020), but they have been prescribed with no specific indication in almost 70% of cases and the use of PPIs for long time increases the negative impact and side effects of these drugs on human body (Marks, 2016).

Gastric acid has a protective effect that inactivate swallowed microorganisms including some viruses such as several rotavirus strains (Weiss & Clark, 1985), influenza virus (Hayase et al., 2002), norovirus (Prag et al., 2017) and Middle East respiratory syndrome coronavirus (MERS-CoV) (Zhou et al., 2017). As the SARS-CoV-2 can invade the body not only via respiratory system but also via gastrointestinal (GI) system (Trottein & Sokol, 2020; F. Xiao et al., 2020), the virus uses angiotensin converting enzyme-2 (ACE-2) receptor which is greatly expressed in the GI tract (Hamming et al., 2004) to enter and replicate in the enterocytes and cause GI

symptoms of the disease (Lamers et al., 2020; Sultan et al., 2020). Therefore, because the gut is the most important immune organ in the body and the virus reach to the gut and replicate rapidly (Dhar & Mohanty, 2020) in the absence of gastric acid and the use of PPIs as acid suppressant drugs may not only increase the GI symptoms of Covid-19 but also assist inflammation to distribute to other organs such as lungs (Gut-lung axis) (Almario et al., 2020; Trottein & Sokol, 2020). Moreover by decreasing the intraluminal environment pH, PPIs reduce the activity of ACE2, (Liu et al., 2010) a receptor which is used by SARS-CoV-2 for entry into human body (F. Xiao et al., 2020).

There are some data that shows PPIs can be used as antiviral drugs (Ray et al., 2020) and may be effective for the prophylaxis or even the treatment of covid-19 (Taştemur & Ataseven, 2020), but the data on effect of these drug on the risk of susceptibility to COVID-19 and the severity of infection are conflicting. Some studies indicate the relation of PPIs use with the higher susceptibility (Charpiat et al., 2020; Israelsen et al., 2021) and negative outcome of COVID-19 (Pranata et al., 2021; Ramachandran et al., 2022); while others not found any relation (Israelsen et al., 2021; Park et al., 2022; Zippi et al., 2021). Due to these contradictory reports, we tried to further investigate the potential link between the use of PPIs and COVID-19 in our society.

Study Design, Place and date: This case-control study was conducted in Herat, Afghanistan, from April 1 to December 29, 2021.

Sample size and sampling procedure: According to the accepted definition of the World Health Organization, each COVID-19 case is a positive PCR test individual. So, PCR positive reported patients were included in the case group and then the same age and gender patients were included in the control group. Using Epo Info software, with a confidence interval of 95% and a power of 90% by the Kelsey method, the calculated minimum required sample size was 90 participants for each case and control group.

Inclusion and exclusion criteria: Totally, 246 adult patients aged ≥ 18 years that were tested for SARS-CoV-2 RNA included for the analysis. Subjects were divided in cases (positive test) vs. controls (negative test) to examine the risk of infection with current PPIs use. Both hospitalized and ambulatory patients were included. Patients were excluded if they were less than 18 years old or had insufficient clinical documentation available for study.

Exposure: Individuals taking a PPI (lansoprazole, dexlansoprazole, esomeprazole, pantoprazole, rabeprazole, and omeprazole) for >1 month were classified as PPI-users and individuals taking a PPI for ≤ 1 month were classified as non-users.

Study outcomes: In this case-control study, the primary outcome of interest was a positive SARS-CoV-2 RNA test during the study period. Secondary outcomes were requirement of oxygen therapy, ICU admission, mechanical ventilation, and lastly, the composite of ICU admission with severe clinical outcomes of COVID-19 (administration of invasive ventilation or death).

Data collection: The data were collected through questionnaires. Informed consent of the enrolled patients was obtained. The collected data were including patients' age, gender, marital status, education, occupation, and income. As well as, data were included clinical manifestations such as the result of SARS-CoV-2 test, presence of respiratory, gastrointestinal, and systemic complaints, ageusia, anosmia, history of ICU admission, oxygen therapy, and mechanical ventilation.

Ethical approval: This research was approved by the Scientific Research Committee of the Faculty of Medicine, Herat University of Afghanistan (15 –27/09/2021).

Statistical analysis: IBM SPSS Statistic software (version 22) was used for statistical analysis of the data. Comparison of different socio-demographic between positive (case) and negative (control) described using chi-squared tests for the categorical variables and measures are presented as percentages. The P value <0.05 was considered statistically significant. Results are presented as odds ratio (OR) with 95% confidence intervals (95% CIs).

RESULTS

In this study, the data of 246 patients who were tested for SARS-CoV-2 RNA in Herat province from April 1 to December 29, 2021 were analyzed. The mean \pm SD age of the analytic population was 41.6 ± 16.9 years (range ≥ 18 years). Of the study population, 82 (56.2%) females and 64 (43.8%) males with positive results of SARS-CoV-2 test including the case group and the remaining 67 (67.0%) females and 33 (33.0%) men with negative SARS-CoV-2 test results were included in the control group, respectively. The highest incidence of COVID-19 was between age group of 18 – 29 years, which 44 (30.1%) of them were in the cases group and 31 (31.0%) of them were in the control group. Also, in the case group 85 (58.2%) were married, including 64 (44.4) were illiterate, and in the control group 69 (69.0%) were married, including 56 (56.0%) were illiterate (**Table 1**).

Comparisons between socio-demographic characteristics and COVID-19 test results were evaluated in case and control groups. Multivariable analysis was performed using chi-square test for differences between data sets. There was no significant difference between case (positive) and control (negative) groups in terms of gender ($p = 0.088$), age ($p = 0.712$), marital status ($p = 0.353$), education level ($p = 0.066$), income ($p = 0.071$), and PPIs use ($p = 0.392$) (**Table 2**).

Table 1: The socio-demographic characteristics of individuals participated in this study

| | | Is your test result for SARS-CoV-2 infection negative or positive? | | | |
|-----------------------|---------------------|--|--------------|------------|--------------|
| | | Positive | | Negative | |
| | | N | % | N | % |
| Gender | Female | 82 | 56.2 | 67 | 67.0 |
| | Male | 64 | 43.8 | 33 | 33.0 |
| Age categories | 18-29 | 44 | 30.1 | 31 | 31.0 |
| | 30-39 | 25 | 17.1 | 24 | 24.0 |
| | 40-49 | 25 | 17.1 | 16 | 16.0 |
| | 50-59 | 21 | 14.4 | 9 | 9.0 |
| | 60-69 | 17 | 11.6 | 11 | 11.0 |
| | 70+ | 14 | 9.6 | 9 | 9.0 |
| Marital status | single | 46 | 31.5 | 25 | 25.0 |
| | married | 85 | 58.2 | 69 | 69.0 |
| | widow | 15 | 10.3 | 6 | 6.0 |
| Education | Illiterate | 64 | 44.4 | 56 | 56.0 |
| | High school | 10 | 6.9 | 7 | 7.0 |
| | Diploma | 31 | 21.5 | 9 | 9.0 |
| | Academic | 39 | 27.1 | 28 | 28.0 |
| Occupation | Unemployed | 51 | 34.9 | 35 | 35.0 |
| | Employed | 51 | 34.9 | 24 | 24.0 |
| | Work at home | 37 | 25.3 | 39 | 39.0 |
| | Retired | 7 | 4.8 | 2 | 2.0 |
| Income | Sufficient expenses | 69 | 47.3 | 37 | 37.0 |
| | Does not sufficient | 77 | 52.7 | 63 | 63.0 |
| Total | | 146 | 100.0 | 100 | 100.0 |

Table 2. Comparison of different socio-demographic between negative and positive COVID-19– Herat- Afghanistan 2022

| | Positive | | Negative | | Statistics | |
|--------------------------|------------|-------------|------------|-------------|----------------|-------|
| | N | % | n | % | X ² | p* |
| Socio-demographic | | | | | | |
| Gender | | | | | | |
| Female | 82 | 55.0 | 67 | 45.0 | 2.918 | 0.088 |
| Male | 64 | 66.0 | 33 | 34.0 | | |
| Age Group | | | | | | |
| 18-29 | 44 | 58.7 | 31 | 41.3 | 2.923 | 0.712 |
| 30-39 | 25 | 51.0 | 24 | 49.0 | | |
| 40-49 | 25 | 61.0 | 16 | 39.0 | | |
| 50-59 | 21 | 70.0 | 9 | 30.0 | | |
| 60-69 | 17 | 60.7 | 11 | 39.3 | | |
| 70 and above | 14 | 60.9 | 9 | 39.1 | | |
| Marital Status | | | | | | |
| Single | 46 | 64.8 | 25 | 35.2 | 3.265 | 0.353 |
| Married | 84 | 55.3 | 68 | 44.7 | | |
| Widow | 16 | 71.4 | 7 | 28.6 | | |
| Education Level | | | | | | |
| Illiterate | 64 | 53.3 | 56 | 46.7 | 7.271 | 0.064 |
| High School | 10 | 58.8 | 7 | 41.2 | | |
| Diploma | 31 | 77.5 | 9 | 22.5 | | |
| University | 39 | 58.2 | 28 | 41.8 | | |
| Occupation | | | | | | |
| Unemployed | 51 | 59.3 | 35 | 40.7 | 7.176 | 0.066 |
| Employed | 51 | 68.0 | 24 | 32.0 | | |
| Houswife | 37 | 48.7 | 39 | 51.3 | | |
| Retired | 7 | 77.8 | 2 | 22.2 | | |
| Income | | | | | | |
| Sufficient expenses | 69 | 65.1 | 37 | 34.9 | 2.548 | 0.071 |
| Dose not sufficient | 77 | 55.0 | 63 | 45.0 | | |
| PPI | | | | | | |
| Used | 107 | 61.1 | 68 | 38.9 | 0.804 | 0.392 |
| Not Used | 39 | 54.9 | 32 | 45.1 | | |
| Total | 146 | 59.3 | 100 | 40.7 | | |

The overall rate of SARS-CoV-2 in our case control study was 64 (43.8%) male and 82 (33.0%) female in case group and 33 (33.0%) male and 67 (67.0%) female in control group. Among these patients, 107 (73.3%) COVID-19 positive and 68 (68.0%) COVID-19 negative individuals had a history of current and past PPIs use but 39 (26.7%) COVID-19 positive and 32 (32.0%) COVID-19 negative individuals who have never used PPIs were included 1.29 (0.74 – 2.25).

In this study, there was no significant difference between women with positive events (OR 1.58; 95% CI, 0.93-2.69) compared to men, illiterates (OR 1.63; 95%, CI, 0.98 - 2.72) compared to literates, marrieds (OR 1.38; 95% CI, 0.78 - 2.44) compared to unmarrieds, low incomes (OR 1.52; 95% CI, 0.91 - 2.56) compared to high -income and those who do not use PPIs (OR 1.52; 95% CI, 0.91 2.56) compared to those

who use PPIs.

Odds ratios (ORs) and 95% confidence intervals (CIs) by potential risk factors for COVID-19 are presented in (Table 3).

In multivariable analysis across the full sample, PPI use was independently associated with increased odds with 95 % confidence interval for positive COVID-19 test and clinical outcomes. Comparing individuals not using PPIs with those taking PPIs once or twice daily had significantly increased odds ratio for reporting a positive COVID-19 test. In addition we found the following results: for respiratory and digestive disorders (OR 2.47; 95% CI, 0.71-8.63) and (OR 2.16; 95% CI, 0.97-4.84) were not found to be significant. On the other hand, systemic problems (OR 2.32; 95% CI, 1.01 - 5.31), taste and smell disorders (OR 2.23; 95% CI, 1.05 - 4.72), (OR 2.62;

95% CI, 1.23 - 5.45), requirement of oxygen therapy (ORs 4.38; 95% CI, 2.01-9.51), ICU admission (OR 7.56; 95% CI, 2.93 - 19.6) and requirement of mechanical ventilation (OR

5.99; 95% CI, 2.52 - 14.30) has been received significant (Table 4).

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) by potential risk factors for COVID-19, Herat province Afghanistan 2022

| Characteristics | COVID-19 | | OR (95% CI) |
|-----------------------|-------------------|-------------------|--------------------|
| | Positive N (%) | Negative N (%) | |
| Sex | | | |
| Male | 64 (43.8) | 33 (33.0) | <u>Reference</u> |
| Female | 82 (56.2) | 67 (67.0) | 1.58 (0.93 – 2.69) |
| Literacy | | | |
| Literate | 82 (56.2) | 44 (44.0) | <u>Reference</u> |
| Illiterate | 64 (43.8) | 56 (56.0) | 1.63 (0.98 – 2.72) |
| Marital Status | | | |
| Not married | 46 (31.5) | 25 (25.0) | <u>Reference</u> |
| Married | 100 (68.5) | 75 (75.0) | 1.38 (0.78 – 2.44) |
| Age Group | | | |
| 70 and above | 14 (9.6) | 9 (9.0) | <u>Reference</u> |
| 18-29 | 44 (30.1) | 31 (31.0) | 1.09 (0.42 – 2.84) |
| 30-39 | 25 (17.1) | 24 (24.0) | 1.49 (0.55 – 4.09) |
| 40-49 | 25 (17.1) | 16 (16.0) | 0.99 (0.35 – 2.83) |
| 50-59 | 21 (14.4) | 9 (9.0) | 0.67 (0.21 – 2.09) |
| 60-69 | 17 (11.6) | 11 (11.0) | 1.00 (0.33 – 3.11) |
| Income | | | |
| Sufficient expenses | 69 (47.3) | 37 (37.0) | <u>Reference</u> |
| Dose not sufficient | 77 (52.7) | 63 (63.0) | 1.52 (0.91 – 2.56) |
| PPI Use | | | |
| Used | 107(73.3) | 68 (68.0) | <u>Reference</u> |
| Nonused | 39 (26.7) | 32 (32.0) | 1.29 (0.74 – 2.25) |

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) by potential risk factors for PPI used in positive COVID-19 cases, Herat province Afghanistan 2022

| | PPI Use | | OR (95% CI) |
|------------------------------------|-------------------|------------------------|----------------------------|
| | PPI Used N (%) | PPI Not used* N (%) | |
| Respiratory Complaints | | | |
| Yes | 101 (74.8) | 34 (25.2) | 2.47 (0.71 – 8.63) |
| No | 6 (54.5) | 5 (45.5) | |
| Digestive Complaints | | | |
| Yes | 85 (77.3) | 25 (22.7) | 2.16 (0.97 – 4.84) |
| No | 22 (61.1) | 14 (38.9) | |
| Systemic Complaints | | | |
| Yes | 88 (77.2) | 26 (22.8) | 2.32 (1.01 – 5.31) |
| No | 19 (59.4) | 13 (40.6) | |
| Taste Disturbance | | | |
| Yes | 75 (78.9) | 20 (21.1) | 2.23 (1.05 – 4.72) |
| No | 32 (62.7) | 19 (37.3) | |
| Sense of Smell | | | |
| Yes | 74 (80.4) | 18 (19.6) | 2.62 (1.23 – 5.45) |
| No | 33 (61.1) | 21 (38.9) | |
| Need Oxygen therapy | | | |
| Yes | 76 (84.4) | 14 (15.6) | 4.38 (2.01 – 9.51) |
| No | 31 (55.4) | 25 (44.6) | |
| Admitted to ICU | | | |
| Yes | 62 (91.2) | 6 (8.8) | 7.56 (2.93 – 19.61) |
| No | 45 (57.7) | 33 (42.3) | |
| Need Mechanical Ventilation | | | |
| Yes | 65 (89.0) | 8 (11.0) | 5.99 (2.52 – 14.30) |
| No | 42 (57.5) | 31 (42.5) | |

DISCUSSION

The research results on the effect of PPIs on COVID-19 are remarkably controversial. To find out the role of these drugs on COVID-19 patients, we investigated whether PPI usage increased susceptibility to SARS-CoV-2 infection among 246 patients who were tested for SARS-CoV-2 RNA. Moreover, we tried to find out whether there is association between the use of PPI and the clinical outcomes of COVID-19 among 146 COVID-19 positive patients. Regarding the impact of socio-demographic variables it was found that, 56.2% of the cases were female and 43.8% were male while 67.0% of the controls were female and 33.0% were male. The most participants were aged between 18 to 29 years. This is probably because lack of personal and social hygiene that increases social closeness also distribution of corona mutation that have more transmission power. The mean age of participants in this study was 41.6 ± 16.9 years, which is quite smaller than 48.0 ± 19.7 years results of cohort study conducted in Korea (Lee et al., 2021). Regarding gender, we found that there was a higher occurrence of COVID-19 in women than men 56.2% vs 43.8% cases respectively. It was found much smaller than results of cohort study 64.7% vs 34.5% conducted in Korea (Almario et al., 2020). In our study the possible explanation for why women were more likely to develop COVID-19 than men could be that, women in Afghanistan are vulnerable part of society also they were more available during the time of study. This is in accordance with COVID-19 study by Almario et al. although a lot of research shows that men seem to have higher rates for COVID-19 related hospitalizations vs women. Studies show that socio-demographic factors like gender, age, marital status, education level and income have a substantial impact on the adhering to COVID-19. In our study there was no statistically significant difference between case (positive) and control (negative) groups in terms of gender ($p = 0,088$), age ($p = 0.712$), marital status ($p = 0.353$), education level ($p = 0.066$), income ($p = 0.071$), also the incidence of COVID-19 among PPI-users and PPIs non-users was insignificant ($P < 0.392$). In our study the percentage of PPIs use among COVID-19 positive patients was 61.1% while it was much smaller 71.9% than in Tarlow et al. study (Tarlow et al., 2020).

According to our results, we found that PPIs usage, including current and past use, did increase susceptibility to SARS-CoV-2 infection; with no significantly increase odds ratio

(OR 1.29; 95% CI, 0.74-2.25); however, current PPI usage was associated with a statistically worse outcomes of COVID-19. Unlike to our data, in a study conducted by Almario et al. in 2020 individuals with a history of GI symptoms found that using PPIs up to once daily (OR 2.15; 95% CI, 1.90–2.44) or twice daily (OR 3.67; 95% CI, 2.93–4.60) had significantly increased odds for reporting a positive COVID-19 test compared with those not taking PPIs (Almario et al., 2020). The association between PPIs intake and positive report of COVID-19 test was dose-dependent; risk was higher in individuals who were taking PPIs two times per day compared with patients that were using lower doses of the PPIs (Almario et al., 2020). An observational case-control study conducted by Israelsen et al. in Denmark showed that current PPI use was associated with increased risk of infection; (ORs 1.08; 95% CI, 1.03–1.13) (Israelsen et al., 2021). Among SARS-CoV-2 cases, PPI use was associated with increased risk of hospital admission (ORs 1.13; 95% CI, 1.03-1.24), but not with other severe outcomes (Israelsen et al., 2021). Moreover an updated of this study demonstrated no significant relationship between PPIs use and susceptibility to COVID-19 and risk of infection or mortality (ORs 1.00; 95% CI, 0.75 –1.32) and (RRs 1.33; 95% CI, 0.71–2.48) (Pranata et al., 2021). The mechanism by which this class of drugs makes the person susceptible for the SARS-CoV-2 infection may be due to decreased secretion of the gastric acid as a consequence excessive growth of the virus in upper GI system and micro aspiration that eventuate to pneumonia (Luxenburger et al., 2021). Based on Arendse et al. and Sharif-Askari et al. studies ACE-2 receptor is not only expressed in the GI system but also expressed in the testis, brain, intestines (Arendse et al., 2019) kidney and liver tissue (Sharif-Askari et al., 2020). Indeed, it may be another mechanism for causing SARS CoV-2 infection through ACE-2 receptor (Sharif-Askari et al., 2020). However some studies suggested that, by inhibiting viral serine protease enzyme the PPIs may demonstrate antiviral effect (Ray et al., 2020) also they can inhibit the production of pro-inflammatory cytokines such as IL-6, IL-8 and TNF- α that shows their anti-inflammatory and anti-oxidative actions (Sasaki et al., 2011). Many other research have been done to show using these drugs may be a risk factor for COVID-19 (Charpiat et al., 2020; Lee et al., 2021; Park et al., 2022; Pranata et al., 2021; Ramachandran et al., 2022; Yozgat et al., 2021; Zippi et al., 2021).

In this study we observed, there was no significant difference between women with positive events (OR 1.58; 95% CI, 0.93-2.69) compared to men, illiterates (OR 1.63; 95% CI, 0.98 - 2.72) compared to literates, marrieds (OR 1.38; 95% CI, 0.78 - 2.44) compared to unmarrieds, low incomes (OR 1.52; 95% CI, 0.91 - 2.56) compared to high -income and those who do not use PPIs (OR 1.52; 95% CI, 0.91 - 2.56) compared to those who use PPIs. This reflects the result of a meta-analysis done by Toubasi et al. that shows the risk of developing COVID-19 among current PPI-users increased but did not reach significant levels (ORs 1.19; 95% CI, 0.62-2.28) (Toubasi et al., 2021). In contrast, study done by Almario et al indicates that patients taking PPIs had significantly increased odds for reporting a positive COVID-19 test compared to those not taking PPIs (Almario et al., 2020). Additionally, our result is inconsistent with previously reports that show use of PPI does not increase susceptibility of COVID-19 infection (ORs 1.00; 95% CI, 0.75 - 1.32), (ORs 0.90; 95% CI, 0.78-1.01) and (ORs 1.49; 95% CI, 0.66-3.36) respectively (Israelsen et al., 2021; Lee et al., 2021; Park et al., 2022; Fei Xiao et al., 2020). We examined the association between PPIs use and GI COVID-19 symptoms. In our study, the PPI-users did not show significantly higher GI symptoms (nausea, vomiting, dyspepsia and diarrhea) compared to PPIs non-users but dysgeusia (OR 2.23; 95% CI, 1.05 - 4.72) and anosmia (OR 2.62; 95% CI, 1.23 - 5.45) among PPI-users was strongly higher than PPIs non-users. This is due to the GI symptoms are prevalent in those with COVID-19. Similarly, Ramachandran et al. reported that the patients using PPIs did not have higher GI symptoms compared to controls (Ramachandran et al., 2022). Furthermore, some studies reported digestive symptoms such as dysgeusia and anosmia (Aziz et al., 2020; Bénézit et al., 2020), nausea, loss of appetite, and diarrhea are common in COVID-19 patients (Aziz et al., 2020; Pan et al., 2020; Perisetti et al., 2020). Luxenburger et al. indicated that treatment with PPI before hospitalization may be a factor for development of acute respiratory distress syndrome (ARDS) and secondary infection (Luxenburger et al., 2021). Besides, cohort study by Lee et al. have reported the higher risk of severe clinical outcomes (requirement of oxygen therapy, intensive care unit admission, administration of invasive ventilation or death) with ORs 1.63; 95% CI, 1.03-2.53 in patients taking PPIs (Lee et al., 2021). Compared to Lee et al. study our results also show statistically significant relationship between the PPIs

use and worse outcomes of COVID-19 infection (requirement of oxygen therapy (ORs 4.38; 95% CI, 2.01-9.51), ICU admission (OR 7.56; 95% CI, 2.93 - 19.6) and requirement of mechanical ventilation (OR 5.99; 95% CI, 2.52 - 14.30). Similarly the result of retrospective cohort study conducted by Ramachandran et al in USA indicated the higher risk of mechanical ventilation requirement in PPI-users than non-users with ORs 2.5; 95% CI, 1.1-5.4 (Ramachandran et al., 2022).

SARS-CoV-2 most likely infects respiratory epithelial cells (Wang et al., 2019) which enter via ACE2 receptor of alveolar epithelial cells causing SARS-CoV-2 (Arendse et al., 2019; Wang et al., 2019). This implies that not only the respiratory tract but also the GI tract may be point of viral entry in the human body (Effenberger et al., 2020; Wang et al., 2019). Consequently, by decreasing the intraluminal environment pH PPIs reduce the activity of ACE2 enzyme (Liu et al., 2010). The higher expression of ACE2 allows higher viral entry to cells, resulting more severe disease due to cytokine storm (Hoffmann et al., 2020). As the GI tract expresses higher levels of ACE-2, individuals who use PPIs may be more vulnerable to the effect of high viral loads. Even in respiratory tract diseases, individuals with more virus colonisation in the stomach due to increased gastric alkalinity caused by PPI administration may be more susceptible to severe courses of COVID-19 (Hoffmann et al., 2020). In a study of Middle East Respiratory Syndrome coronavirus (MERS-CoV), lethal outcomes were observed in mice treated with PPIs after enteric infection for MERS-CoV by intragastric inoculation (Zhou et al., 2020). This supports our finding of association between severe coronaviral systemic and respiratory symptoms (OR 2.32; 95% CI, 1.01 - 5.31) and (OR 2.47; 95% CI, 0.71-8.63) respectively, with the use of PPIs. In contrast, a randomized control trial showed that PPIs (lansoprazole) use could be associated with reduction of frequency of common cold and chronic obstructive pulmonary disease (COPD) exacerbation, as a result they may reduce chances of viral Infections (Sasaki et al., 2009).

Limitations and strengths

Small number of patients included and unbalanced of cases and controls are the limitations of this study. The main strength of this study is that it addresses a clinically significant issue about the effect of PPIs use and COVID-19.

Conclusion

We found a significant increased risk of COVID-19 negative outcomes in PPIs users. Therefore, patients infected with SARS-Cov-2 should be evaluated more carefully if they are using PPIs. Further studies with larger sample size are needed to assess the exact role of PPIs use on COVID-19.

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