Afghanistan Research Journal
ISSN (Online): 0000-0000
Volume 1, Issue 1, pp. 38-46, December 2021

Risk of SARS-Cov-2 Infection Among Proton Pump Inhibitors Users: A Systematic Review

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Abstract

Public health is affected seriously by COVID-19. Its mortality rate varies within different nations and identification of its risk factors is in progress. Here, we systematically reviewed articles that have evaluated the association between proton pump inhibitors (PPIs) intake and SARS-CoV-2 infection.

PubMed, Google Scholar, Scopus, and Cochrane databases from their inception till 2nd December 2020 were systematically searched to obtain any possible article for inclusion.

Results of this research reveal that After screening and removing unrelated or duplicate articles by the title and abstract by two independent reviewers, 6 articles were included. Results revealed a direct and dose-dependent relationship among PPIs intake and possibility of infection with SARS-CoV-2, the severity of the clinical manifestations of the COVID-19, and expression of SARS-CoV-2 receptors in the kidney and liver tissues.

In Conclusion, PPIs increase the risk of the infection with SARS-CoV-2 and cause severe clinical outcomes in the COVID-19 patient. They should be used when a clear indication is present at the lowest effective dose.

Keywords: Clinical outcome, COVID-19, Proton pump inhibitors, Risk factor, SARS-CoV-2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the known cause of coronavirus disease 2019 (COVID-19) that affected negatively the health, economy, and education of the society (Imielski, 2020; Wu et al., 2020; Zhu et al., 2020). COVID-19 has shown obvious different mortality rate amid different populations and specification of its risk factors are in progress (Choi et al., 2020; Guan et al., 2020). Angiotensin-converting enzyme 2 (ACE2) has been qualified to have diverse physiologic roles in the human body; counter the action of the ACE, helps in the carriage of amino acid, and as a receptor for entry of several kinds of coronaviruses, including SARS-CoV-2 (Gheblawi et al., 2020). Activation of both SARS coronavirus of 2003 and newly identified SARS-CoV-2 is through transmembrane protease, serine 2 (TMPRSS2) (Huggins, 2020). It is stated that ACE2 is used by SARS-CoV-2 for entrance and the TMPRSS2 for S protein priming (Rahman et al., 2020).

Numerous risk factors have been confirmed for COVID-19, including chronic lung disease and smoking, old age, cardiovascular disease (CVD), chronic kidney disease (CKD), high blood pressure (Guan et al., 2020; Li et al., 2020), obesity and diabetes mellitus (Lighter et al., 2020), chronic HIV infection (Blanco et al., 2020) and malignancy (Dai et al., 2020). Fear regarding the role of medication as a risk factor for COVID-19 is growing. Amid medications, PPIs, due to their good efficacy, acceptable tolerance, and scarce side effects, are globally used as over the counter and prescribed drugs and, their usage show a rising pattern. (Reinberg, 2015). Gastroesophageal reflux disease (GERD), the abolition of Helicobacter pylori infection, gastrointestinal bleeding, various forms of peptic ulcer, and Zollinger-Ellison Syndrome are clear indications for PPIs (Savarino et al., 2018). Besides using correctly

and on the advice of a physician, they are used without a good indication by some patients (van Herwaarden et al., 2016).

Previous studies have shown an increased risk of pneumonia and enteric bacterial infections in patients taking PPIs for the long term (Fohl & Regal, 2011; Lin et al., 2019; Reimer & Bytzer, 2012). This background has given rise to the hypothesis that long-term PPIs usage could be a risk factor COVID-19. For testing this hypothesis, a number of studies have been done recently. In this review, we performed a systematic review to evaluate the association between long-term PPIs usage and the risk of SARS-CoV-2 infection.

Material and methods

The method for this systematic review was directed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

Search strategy

This systematic review was performed in order to evaluate whether long-term PPI taking might be harmful considering the risk of SARS-CoV-2 infection. In this regard, we aimed to review studies which have evaluated associations of the use of PPIs with the infection rates of COVID-19 among patients who experienced SARS-CoV-2 testing. PubMed, Google Scholar, Scopus, and Cochrane databases were searched from database inception till 2nd December 2020. We did not apply any restrictions on the date of the articles. The following search terms based on "AND" "OR" operators were used in mentioned databases: ("Proton Pump Inhibitors" OR "Pantoprazole" OR "Omeprazole" OR "Dexlansoprazole" AND "COVID-19" OR "Coronavirus" OR "SARS"). References within each article were evaluated for inclusion in the systematic review.

Inclusion criteria based on PICOS criteria

We included all human studies with randomized and placebo or controlled design addressing the association between PPI taking and acquiring the COVID-19 and its severe outcomes. No restrictions for language, country and route of administration were applied.

Exclusion criteria

Secondary studies, editorials, commentaries, case reports, articles lacking a placebo or control group, and studies without the full-text accessibility were not reviewed.

Selection among the studies

All the mentioned databases were reviewed based on the title, abstract and full text independently by the two authors (SS and MG). In the cases that the authors were not being able to assess the studies, a third author (KD) made the final decision. The selection method is shown in Figure 1.

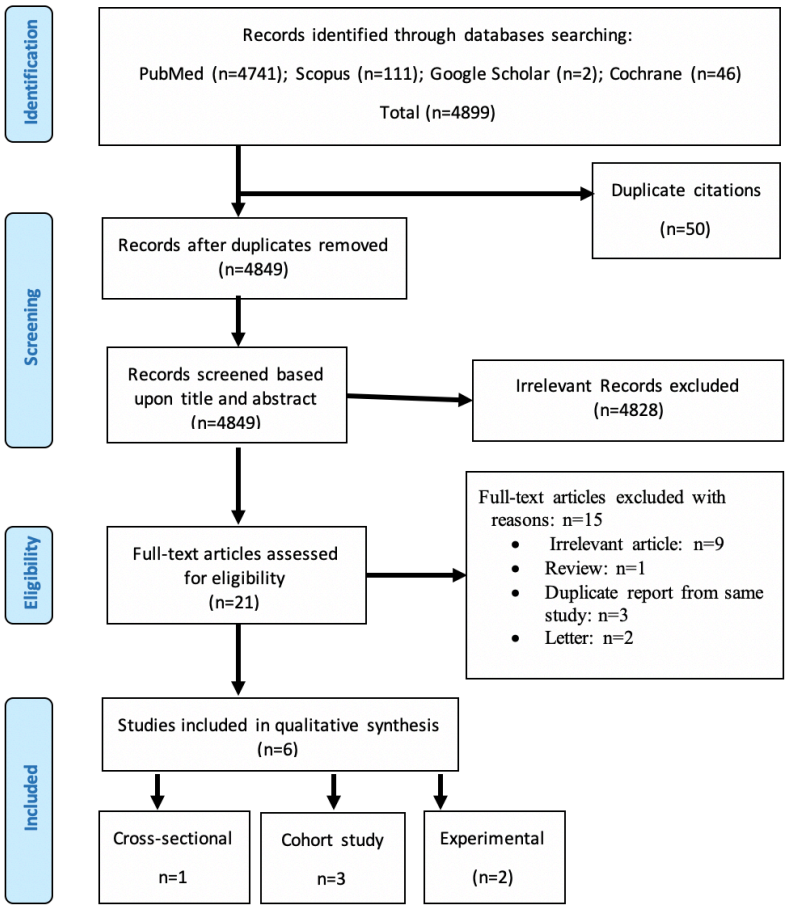

Figure 1. Literature search and filtering of studies according to the PRISMA flow diagrams.

Habbu's checklist (Habbu & Krishnappa, 2015) was applied for qualitative assessment of the studies. 19 items are included in this checklist. If all criteria were present, the maximum mark of 19 was achieved. Studies with scores lower than 12 were excluded from the study. Therefore, the minimum and maximum scores were 12 and 19, respectively. Table 1 shows the characters used for the qualitative assessment.

Table 1. Quality assessment criteria

Number	Quality assessment criteria
1	randomized
2	Randomization kind clear
3	Blinding of the participants
4	Presence of the placebo
5	Statement of the study plan
6	Calculation of the sample size
7	Insertion and rejection principles
8	Statistical examination
9	Objective of the study is clear and definite
10	Features of dropouts
11	Number of participants for every group
12	Intervention and control similarity

13	Particulars of intervention
14	Outcome measures defined
15	Outcome measures objectively measured
16	Means and SD of baseline and final test
17	Definite monitoring
18	knowledgeable permission is taken
19	Moral permission received

Data extraction

The authors extracted the following data from each included study using a standardized data extraction process: authors, publication date, place of study, study type, study design, and outcome measures.

Results

According to the specified search criteria, 4899 articles were obtained; including 111 articles from Scopus, 4741 articles from PubMed, 46 articles from Cochrane, and 2 articles from Google Scholar. After deleting duplicate articles, 4849 articles remained. Subsequently, screening was done on the remaining articles according to the form prepared considering the Population, Intervention, Comparison, Outcome, Study design (PICOS) as a framework. 4828 irrelevant records were excluded and 20 eligible articles remained. Further screening resulted in excluding more 15 articles due to irrelevancy, being review, duplicity or letter to editor. Finally, 6 eligible articles included in our systematic review (Table 2).

Table2 . Characteristics of included studies

Author, year	Country	Type	Study	population	Sex	Result
Christopher V, 2020	USA	Human	Cohort	53130	M/F	Participants using PPIs had considerably increased possibilities for COVID-19 exam positivity.
Seung Won Lee, 2020	Korea	Human	cohort	132316	M/F	Severe clinical outcomes of the COVID-19 were found among 90% of participants who use PPIs currently
Jesus Miguel Garcia-Menaya, 2020	Spain	Human	Cross-sectional	113	M/F	A direct relationship was found between past use of PPIs and admittance to ICU and mortality rate
Narjes Saheb Sharif-Askari, 2020	Emirates	*In vitro*	Cell line	-	-	Omeprazole increased the expression level of TMPRSS2 in the liver
Narjes Saheb Sharif-Askari, 2020	Emirates	*In vitro*	Cell line	-	-	Omeprazole increased ACE2 expression in the kidney tissues
Preethi Ramachandran, 2020	USA	Human	Cohort	295	M/F	Death-rate was higher and clinical outcomes were more severe among patients who were on PPIs treatment before hospitalization

Table 2. PPIs, Proton Pump Inhibitors; ICU, Intensive Care Unit; TMPRSS2, Transmembrane Protease, Serine 2; ACE2, Angiotensin-Converting Enzyme 2.

Relationship between the use of PPIs and COVID-19 test positivity

Christopher V. Almario *et al.* did a cross-sectional study in 2020 to determine whether use of PPIs intensifies the chances for acquiring coronavirus disease 2019 (COVID-19) among Americans. Their analysis revealed that chances of reporting a positive COVID-19 test was significantly higher in persons taking PPIs one or two time per day compared with those that were not using PPIs. Amazingly, this risk was not high among persons that were using blockers of H2 receptors such as famotidine (Almario et al., 2020). The relationship 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). Seung Won Lee *et al.* launched a cohort study in 2020 to evaluate the likely associations of the present intake of PPIs with the results of the test amid patients who have experienced SARS-CoV-2 testing. Their study results showed the history of past or present taking of PPIs was not linked with the positive result of the test (Lee et al., 2020).

Clinical outcomes of COVID-19 among users of PPIs

Preethi *et al.* hypothesized that the decreased gastric acid secretion due to PPIs use may have role in the susceptibility of the individuals to SARS-CoV-2 infection and subsequently can cause severe clinical outcomes. For testing their hypothesis, they launched a study on COVID-19 patient that were hospitalized. Their study results revealed that death-rate were higher and clinical outcomes were more severe in patients who were on PPIs treatment at home, before hospitalization (Ramachandran et al., 2020). As mentioned, Lee *et al.* conducted a cohort study in 2020 to assess the possible association between PPIs current use and the chance of a positive SARS-CoV-2 test among those who done the test. They found that persons currently taking PPIs were 79% more likely to have severe clinical consequences than those who were not taking PPIs. Additionally, those who had been taking the drug for a month were 90% more likely to have severe clinical consequences than those who were not taking PPIs (Lee et al., 2020). Another cohort study was conducted by Jesus Miguel García-Menaya *et al.* in Spain in 2020 to assess the progression of COVID-19 disease in patients with a history of asthma and patients with no history of asthma. 113 successive patients with COVID-19 were assessed. In the drug history of the patients, they found that one of the prognosticators of Intensive Care Unit (ICU) admission is the previous use of PPIs (García-Menaya et al., 2020). Initially they imagined that the association of ICU admission with PPIs use could be related to age, but their multivariate analyses revealed that the association is statistically important unrelatedly of the age (García-Menaya et al., 2020).

Effect of PPIs use on the appearance of SARS-CoV-2 entrance receptors in kidney and liver tissue

Narjes Saheb Sharif-Askari and colleagues conducted two separate studies to evaluate effects of some medication on the appearance of SARS-CoV-2 entrance receptor in kidney and liver. Their results of their studies showed that few number of medication are present that enhance appearance of SARS-CoV-2 entrance receptor, angiotensin-converting enzyme (ACE) 2, in the kidney (Saheb Sharif-Askari, Saheb Sharif-Askari, Alabed, et al., 2020), and TMPRSS2 in the liver (Saheb Sharif-Askari, Saheb Sharif-Askari, Mdkhana, et al., 2020). One of those drugs was omeprazole, the most famous proton pump inhibitor (Saheb Sharif-Askari, Saheb Sharif-Askari, Alabed, et al., 2020; Saheb Sharif-Askari, Saheb Sharif-Askari, Mdkhana, et al., 2020). As a consequence of the increased appearance of TMPRSS2, priming of ACE2 and the viral membrane protein responsible for cell entry will be up regulated, which in turn surge infectivity degree (Saheb Sharif-Askari, Saheb Sharif-Askari, Mdkhana, et al., 2020).

Discussion

Two separate studies have evaluated association of PPIs use with COVID-19 test results. Although study of Seung Won Lee and colleagues didn't show any relationship between PPIs use and results of COVID-19 test, Christopher V. Almario *et al.* found a dose-

related association between PPIs intake and testing positive for COVID-19. It is noteworthy that the previous studies have also shown positive relationship between PPIs use and augmented possibility of norovirus infection (Prag et al., 2017). The associations between PPIs use and amplified possibility of other respiratory and gastrointestinal infections-inducing viruses such as rotavirus, influenza virus, norovirus, and MERS-CoV have been proven (Charpiat et al., 2020).

Three studies that evaluated the relationship between intake of PPIs with the severity of the clinical outcomes of COVID-19, have found a direct link between PPIs use and higher death-rate and sever outcomes of the disease (García-Menaya et al., 2020; Lee et al., 2020). These findings indicate that beside increased risk of infection with SARS-CoV-2 among PPIs user, they are at high risk for the development of the sever form of the disease too.

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 and as a consequence excessive growth of the virus in upper GI system and micro aspiration that eventuate to pneumonia (Luxenburger et al., 2020). Findings of Narjes Saheb Sharif-Askari and teammates in two separate *in vitro* researches revealed another aspect of the underlying mechanism for the increased risk of SARS-CoV-2 infection with PPIs use. They detected high degree of the expression of SARS-cov-2 entry receptors in kidney and liver tissue concomitant with PPIs use (Saheb Sharif-Askari, Saheb Sharif-Askari, Alabed, et al., 2020; Saheb Sharif-Askari, Saheb Sharif-Askari, Mdkhana, et al., 2020).

Findings of the current study highlight worthy clinical point that PPIs indication should be limited and they must be used at the lowest effective dose when clear indication is present.

Apparently, this is the first review article about the association of PPIs use with COVID-19. In addition, we clarified the mechanism that are involved in the making PPIs as a risk factor for the development of COVID-19 and its sever clinical outcomes.

Omeprazole is the only assessed PPI in all studies that are reviewed here. Effects of other PPIs, such as esomeprazole, lansoprazole and so on were not studied. Availability of few numbers of articles for reviewing is the next limitation that we were faced.

Conclusion

PPIs, very effective and widely used acid secretion lowering drugs, through increased expression of SARS-cov-2 entry receptors in the tissues and making the environment of upper GI system susceptible for their colonization, increase the risk of the infection with SARS-cov-2 and severe clinical outcomes in the COVID-19 patient. They should be used when clear indication is present at the lowest effective dose.

Acknowledgment

We declare that there is no funding for this study by any agency.

Authorship

SS, MGh and KD were responsible for study design and literature search. MGh did screening of the articles. SS and MGh wrote the manuscript. SS, MGh, and KD revised the manuscript and final approval is done by KD.

Conflict of interest

The authors have no conflict of interests to declare.

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