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The Impact of Proton Pump Inhibitor Therapy on Outcomes in COVID-19 Patients: A Retrospective, Multicenter Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Proton pump inhibitor (PPI)–coated prodrugs remain inactive until they enter the alkaline atmosphere of the duodenum, where they are absorbed and transmitted to parietal cells. This study aimed to evaluate the impact of PPI medication on patients with coronavirus disease 2019 (COVID-19) and their outcomes.
Methods: This was a retrospective, multicenter study conducted at two regional hospitals in Saudi Arabia. All confirmed COVID-19 patients between March 1 and August 15, 2020, were included in the study. The Mann–Whitney *U* and chi-squared tests were performed to appropriately determine the difference between treatment groups.
Results: Out of 346 patients, 136 (39.3 %) were users of PPIs with standard care, and 210 (60.7%) standard care and the average age was 43.5 years. The mean hospital length of stay in users of PPIs with standard care was 4.25 days. In contrast, the death cases of PPIs with standard care group were 3 cases out of 9 cases.
Conclusion: The impact of PPIs on COVID-19 patients is so far still a debate, and the discovery of novel therapies for COVID-19 is paramount. However, it is important for scientists and treating physicians to thoroughly identify the comorbidities of patients and other treatments before PPI administration.

Keywords: Comorbidity; COVID-19; proton pump inhibitors; Saudi Arabia.

1. INTRODUCTION

Proton pump inhibitors (PPIs) play a significant role in the treatment of acid-related disorders. They are coated prodrugs that remain inactive until they enter the alkaline atmosphere of the duodenum, where they are absorbed and transmitted to parietal cells. They bind and inhibit the H,K-ATPase irreversibly in parietal cells, resulting in a nearly 90% decrease in acid secretion in the cells [1]. The excessive suppression of gastric acid caused by PPI administration increases the alkalinity of the stomach. It decreases the eradication of ingested pathogens with various immunomodulatory and anti-inflammatory effects that contribute to the entry of the virus into the body's immune system [2].

PPIs are widely used in and out of healthcare institution settings because of their high efficacy. They can be prescribed by a treating physician or obtained as over-the-counter drugs. However, several studies have reported side effects associated with PPI use, such as cardiovascular disease, acute kidney injury, chronic kidney disease, dementia, and pneumonia [3,4].

The entry of enveloped viruses into host cells occurs via the fusion of viral envelopes with the cell membrane. The endocytosed virions are activated in the acidic endosome to deliver genomes into the cytosol or via exploitation of the host cell endocytic machinery, culminating in the fusion of the viral and endosomal membranes and viral genome released into the cytosol [5,6]. Severe acute respiratory syndrome coronavirus (SARS-CoV) enters cells via pH- and receptor-dependent endocytosis, and the treatment of cells with SARS spike-bearing pseudoviruses culminates in the translocation of angiotensin-converting enzyme 2 (ACE-2) from the cell surface to endosomes [5]. The endosomal and lysosomal lumen pH is in the range of 6.5–4.5 because of the membrane-traversed ATP-dependent proton pumps [7,8]. PPIs have been shown to be highly effective in inhibiting vacuolar-type ATPase (ATP-dependent proton pumps) in vitro [9]. Since PPIs are activated by acid [10], these drugs could be activated by the acidic environment of endosomes and thereby inhibit the activity of ATP-dependent H+ pumps, ceasing the cleavage of coronavirus disease 2019 (COVID-19) S-protein and fusion of viral envelope with the endosomal membrane. The release of the viral genome into the host cell would then be arrested. Indeed, omeprazole has been reported to escalate the in vitro activity of acyclovir against herpes simplex virus 1 and 2 [11]. Omeprazole (8 μM) has also been shown to enhance the efficacy of aprotinin (2.7-fold) and remdesivir (10-fold) against SARS-CoV-2 [12].

The impact of PPIs on COVID-19 patients is so far still a debate. Recent studies have reported that PPIs increase the risk for enteric infections, which is possibly related to PPI-induced hypochlorhydria [2,3,13]. Also, previous studies

have reported that the use of PPIs likely weakens the immune system and influences susceptibility to infections, leading to increased risks of pneumonia [2,3]. Short-duration PPI administration has been linked with worsening outcomes in COVID-19 patients, contrary to long-term PPI users [2,14].

In the search for COVID-19 treatments, many researcher-physicians focus on the entry mode that allows the virus to infect human cells. ACE-2 provides the entry point of coronavirus to enter human cells and infect a wide range of them [14]. The ACE-2 receptor is expressed in various human organs. The higher expression of ACE-2 allows higher viral entry into cells. As a result, viral loads may trigger pneumonia, possibly causing more severe illness because of overreaction of the body's immune system [2,14].

Most critically ill COVID-19 patients have been reported to have suffered multiple organ failures, including acute lung injury, acute kidney injury, cardiac injury, pneumothorax, and liver dysfunction [14,15]. Also, a high mortality rate due to various organ failures was observed in the participants who took PPIs [3]. Considering that individuals with comorbidities such as cardiovascular disease, chronic kidney disease, pulmonary disease, and diabetes and those immunocompromised are more susceptible to COVID-19, these comorbidities have been observed to pose an increased risk of life-threatening side effects with PPI use [3,4]. It has also been seen that secondary infections are strongly associated with the development of acute respiratory distress syndrome (ARDS), indicating an indirect negative impact of PPI treatment on the development of ARDS [16]. In line with these findings, index mortality has also been found to be higher in patients with PPI treatment.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This was a retrospective, multicenter study conducted at two regional hospitals in Riyadh (King Fahad Medical City and Prince Mohammed bin Abdulaziz Hospital) and one in Medina (Ohud Hospital). A well-designed, structured checklist was used to extract the required information from the medical records of patients. All confirmed COVID-19 patients between March 1 and August 15, 2020, were included in the study. This study was followed by observational studies in epidemiology guidelines for cross-sectional studies [17].

2.2 Population

This study included male and female patients of all ages with laboratory-confirmed COVID-19 infection who were admitted to the targeted hospitals during the study period and received PPI medication added to standard care or standard care alone. All others not meeting these criteria were excluded. The total number of patients initially included was 1495 patients both with and without chronic diseases, such as diabetes, hypertension, and cardiovascular disease. Those with chronic conditions were excluded, and confounders were examined for all the patients to remove the factors that might interfere in data analysis. The confounders were per age, patients without chronic diseases, and patients whose outcomes could not be tracked. After excluding these patients, the final number of patients was 346 (Fig. 1).

2.3 Variable Definitions

The data gathered from the medical records of the patients consisted of demographic information, including age, sex, history of any chronic conditions, signs and symptoms, prescription medications, outcomes, and disease severity status. Severe clinical COVID-19 outcomes were defined as admission to the intensive care unit, administration of invasive ventilation, or death. Our outcome was determined in terms of whether the patient had recovered or died. Disease severity was assessed in accordance with the Saudi Arabian Ministry of Health (MOH) protocols.

While measuring disease severity, the same classification of the COVID-19 protocol by the MOH (mild–moderate, severe, and critical) was followed [18]. A well-designed, structured checklist was used to acquire and extract information from the medical records of the patients.

2.4 Data Collection

The study coordinators included the medical staff from each center. These coordinators were trained to collect data from the medical records of the patients and record these data in a datasheet using a link.

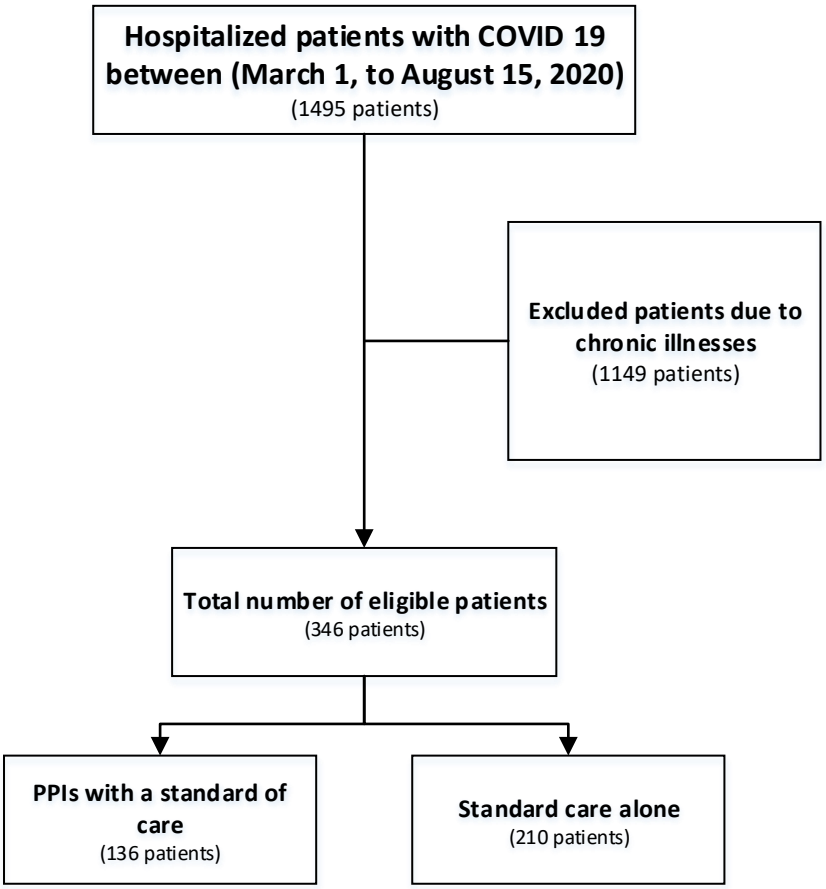

Fig. 1. Scheme of eligible patients

2.5 Data Protection

The principal investigator created a specific data entry system with a link. The link with a password was then shared only with the coinvestigators to provide them with full access to review and enter data, but they were unable to modify any data. Simultaneously, all the study coordinators had access to data entry, with no access to review or modify the data.

2.6 Statistical Analysis

All statistical analyses were performed using SPSS (v.25.0; IBM Corp., Armonk, NY, USA). The demographic and clinical characteristics of the patients were reported as mean ± standard deviation or median (minimum and maximum) for continuous variables and counts (percentage) for categorical variables. The Mann–Whitney *U* and chi-squared tests were performed to appropriately determine the difference between treatment groups.

3. RESULTS

The study population included 1495 patients. Patients with chronic diseases were excluded to neutralize the influencing factors of the effectiveness measurement of PPI medication. Out of 346 patients who tested COVID-19 positive at the selected hospitals and met the inclusion criteria, 273 (78.9%) were males and 73 (21.1%) females. The average age was 43.5 years. There were 278 (80.4%) non-Saudi participants and 68 (19.7%) Saudi participants. The majority of the participants—319 (92.2%)—exhibited symptoms of COVID-19, whereas 27 (7.8%) did not have any symptoms. There were 135 (39.02%) participants with abnormal X-ray results and 211 (61.0%) with normal x-ray results. Disease severity was 243 (70.23%) in the mild–moderate category, 75 (21.7 %) in the severe category, and 28 (8.1%) in the critical category (Table 1).

A total of 136 (39.3%) participants were treated with PPIs in addition to standard care, and 210

(60.7%) were treated with standard care alone. The length of hospital stay in the PPI group was shorter. However, the difference was not significant (p = 0.7; Table 2). In terms of disease severity, the number of people in the PPI group was slightly lower compared to standard care in the severe (p = 0.05) and critical categories (p = 0.685; Table 3).

Collectively, these findings will contribute to the building up knowledge regarding the use of drugs and COVID19 comorbidities.

Table 1. Demographic and clinical characteristics of study participants (N=346)

Age (Mean)		43.5	
		n	%
Gender	Male	273	78.9
	Female	73	21.1
Nationality	Non-Saudi	278	80.35
	Saudi	68	19.65
symptoms	No	27	7.80
	Yes	319	92.20
chest X-Ray	Normal	211	60.98
	Abnormal	135	39.02
Disease severity status	Mild-Moderate	243	70.23
	Severe	75	21.68
	Critical	28	8.09
Symptoms			
Fever		278	33.99
Dry cough		247	30.20
Dyspnea		124	15.16
Vomiting		30	3.67
Fatigue		24	2.93
Abdominal pain		15	1.83
Diarrhea		36	4.40
Chest pain		4	0.49
runny nose		4	0.49
sore throat		18	2.20
Myalgia		9	1.10
Nausea		19	2.32
Dizziness		9	1.10
body ache		1	0.12
Status of a patient			
Recovered		337	97.40
Died		9	2.60

Table 2. Association between PPI medication and Hospital length of stay (N=346)

	PPIs with standard care (n= 136)	Standard care (n= 210)	p-value
	Mean	**Mean**	
Duration	4.25	6.5625	0.7

Table 3. Association between PPI medication and disease severity status

		PPIs with standard care		Standard care		p-value
		n	**%**	**n**	**%**	
Disease severity	Mild-Moderate	89	25.7	154	44.5	0.12
	Severe	37	10.7	38	11.0	0.05
	Critical	10	2.9	18	5.2	0.685
Outcome	Recovered	133	38.4	204	59.0	0.710
	Died	3	0.9	6	1.7	0.710

4. DISCUSSION

This is the first study in Saudi Arabia that clearly describes the impact of PPI use on COVID-19 patients. Other published studies in Saudi Arabia have either generally described the treatment pattern of COVID-19 [19-21], assessed the impact of hydroxychloroquine compared to other treatment patterns on patient clinical outcomes [20], or evaluated the severity of illness in COVID-19 patients [21].

Several observational studies have assessed the impact of PPI use on mortality among COVID-19 patients [2,16,22-24]. The relative risk associated with higher mortality among PPI users was 2.24 (95% confidence interval: 1.13–4.45) [16]. In this study, PPIs have been shown to have some beneficial effects in terms of reducing hospitalization, disease severity, and death compared with standard care; however, the difference was not significant. Therefore, administering PPIs to COVID-19 patients might worsen their condition. However, some studies that analyzed the effect of PPI treatment on the development of pneumonia have shown conflicting results [16,25]. Moreover, some administered PPIs had medically desired COVID-19 outcomes [2,13]. In addition, another study reported that PPIs effectively treated COVID-19 in a case–control study conducted on 179 elderly patients [26]. In contrast, many studies have reported negative outcomes in COVID-19 patients who were administered PPIs. Others have shown it to be an efficacious COVID-19 treatment. This study sought to clarify these conflicting findings and aimed to evaluate the impact of PPI treatment on COVID-19 patients and their outcomes among Saudi patients.

Several studies worldwide have reported a trend of overuse of PPIs [27-31]. A similar pattern has been observed in Saudi Arabia [32,33]. The trend mainly involves prescribing higher doses for an extended duration. Despite the efficacy of PPIs in managing various types of gastric ulcers, their safety profile—especially with long-term use—is an emerging issue that needs full assessment and timely intervention [34,35]. Furthermore, the acquisition cost of PPIs is substantial, and it continues to grow over time [36-38].

The effectiveness of PPI stewardship programs has been established in several studies [39-41]. The role of pharmacists in these programs usually targets patients, physicians, and policymakers. Patient education and counseling are important, as 50% of patients experience suboptimal PPI effectiveness because of postprandial administration [42]. Physicians also need to be aware of the indication, correct doses, and duration of PPIs. This can be achieved by establishing hospital policy and procedures, such as mandatory medication reconciliation upon admission and discharge counseling. This is important to either discuss the discontinuation of PPIs or change to antacids if appropriate. Finally, policymakers should also consider restricting PPI prescriptions to “gastroenterologists only” and establish some regulations on dispensing PPIs in community pharmacies.

Generally, policymakers should invest in a healthcare system infrastructure that can fully capture the long-term impact of PPIs. This would help future researchers to conduct longitudinal studies using representative national data. The value of such a system extends beyond research purposes, as having such a data source would help policymakers assess the impact of PPI optimization intervention on patient outcomes and associated costs.

Given the uncertainty of the results, the use of PPIs in reducing hospitalization and disease severity is not recommended. This is mainly informed by the nonsignificant difference between the groups and the strong evidence around the negative impact of PPIs on patient outcomes (Ramachandran, 2022 #385)[16]. Indeed, other drugs administrated by COVID19 patients can also affect the final outcome. As we reported previously, drugs such as anticoagulants and low molecular weight heparin are taken by 92.6% of patients (Khattab, 2021 #384). Antibiotics and antiviral drugs may also contribute to the final outcome in these patients.

There are, however, some limitations to this study. First, selection bias might have been introduced into the study because of a lack of randomization. Second, the sample size was relatively small. Therefore, statistical analyses could detect the potential impact of PPIs on patient outcomes. In addition, it was not feasible to adjust for confounders at baseline; therefore, the effect on outcomes cannot be directly attributed to PPI use. Finally, prescribing and practice patterns vary considerably across different hospitals and practice settings. This could ultimately impact the generalizability of the results.

5. CONCLUSIONS

The impact of PPIs on COVID-19 patients is so far still a debate. The discovery of novel therapies for COVID-19 is of the utmost importance. Still, it is necessary for scientists and treating physicians to thoroughly identify the comorbidities of patients and other treatments before PPI administration.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was reviewed and approved by the Institutional Review Board of King Fahad Medical City (No.: 20-478). Permission to conduct this study was obtained from the MOH and hospital management.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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