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Long-term proton pump inhibitor use is a risk factor for mortality in patients hospitalized for COVID-19

Ahmet YOZGAT[1,*], Benan KASAPOĞLU[2], Güray CAN[3], Alpaslan TANOĞLU[4], Yusuf Serdar SAKİN[5], Kadir Serkan YALÇIN[6], Müjgan GÜRLER[7], Mustafa KAPLAN[4], Mehmet Göktürk KABAN[5], Mehmet KIRSOY[8], Umut KARA[9], Murat KEKİLLİ[10]

[1]Department of Gastroenterology, Faculty of Medicine, Ufuk University, Ankara, Turkey
[2]Department of Gastroenterology, Faculty of Medicine, Lokman Hekim University, Ankara, Turkey
[3]Department of Gastroenterology, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey
[4]Department of Gastroenterology, Haydarpaşa Training Hospital, University of Health Sciences, İstanbul, Turkey
[5]Department of Gastroenterology, Gülhane Training and Research Hospital, University of Health Sciences, Ankara, Turkey
[6]Department of Internal Medicine, Faculty of Medicine, Lokman Hekim University, Ankara, Turkey
[7]Department of Internal Medicine, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey
[8]Department of Internal Medicine, Haydarpaşa Training Hospital, University of Health Sciences, İstanbul, Turkey
[9]Department of Anesthesiology and Reanimation, Gülhane Training And Research Hospital, University of Health Sciences, Ankara, Turkey
[10]Department of Gastroenterology, Faculty of Medicine, Gazi University, Ankara, Turkey

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Background and aim: The aim of this study is to evaluate whether the long-term (≥4 weeks) use of proton pump inhibitors (PPIs) is a risk factor for intubation requirement and mortality in patients hospitalized for COVID-19.

Materials and methods: In this multicentric retrospective study, a total of 382 adult patients (≥18 years of age) with confirmed COVID-19 who were hospitalized for treatment were enrolled. The patients were divided into two groups according to the periods during which they used PPIs: the first group included patients who were not on PPI treatment, and the second group included those who have used PPIs for more than 4 weeks.

Results: The study participants were grouped according to their PPI usage history over the last 6 months. In total, 291 patients did not use any type of PPI over the last 6 months, and 91 patients used PPIs for more than 4 weeks. Older age (HR: 1.047, 95% CI: 1.026–1.068), current smoking (HR: 2.590, 95% CI: 1.334–5.025), and PPI therapy for more than 4 weeks (HR: 1.83, 95% CI: 1.06–2.41) were found to be independent risk factors for mortality.

Conclusion: The results obtained in this study show that using PPIs for more than 4 weeks is associated with negative outcomes for patients with COVID-19. Patients receiving PPI therapy should be evaluated more carefully if they are hospitalized for COVID-19 treatment.

Key words: Covid-19, proton pump inhibitors, mortality

1. Introduction

In December 2019, a pneumonia-causing disease was discovered in Wuhan, China, which was later identified as COVID-19 by the World Health Organization (WHO) [1]. COVID-19 spread rapidly throughout the world and was identified as a pandemic by the WHO in March 2020 [2]. The etiological agent of this disease was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of its phylogenetic similarity with SARS virus. This disease exhibits a wide spectrum of manifestations, ranging from asymptomatic disease to pneumonia, severe respiratory failure, and even death, and it is generally more severe in the elderly and individuals with comorbid diseases [3]. COVID-19 primarily affects the respiratory system and causes severe pneumonia, with the possibility of ground-glass opacities in the lung and cardiac damage occurring [4].

Proton pump inhibitors (PPIs) fully inhibit the H^+-K^+-ATPase pump in parietal cells for a long time and also inhibit basal and stimulated gastric acid secretion for

* Correspondence: a_yozgat@yahoo.com

up to 16–18 h [5]. Generally, PPIs are superior to other antisecretory drugs in the presence of gastroesophageal reflux disease, peptic ulcer, and dyspepsia [6]. Since the risk of developing tolerance against the effects of PPIs is low and they remain effective for a long time, they have been increasingly used in the treatment of acid-related diseases and have become the first treatment option [7]. It should, however, be noted that the long-term use of PPIs may cause some problems, such as vitamin and mineral absorption disorders, decreased effectiveness of antiplatelet drugs, increased risk of osteoporotic fractures, and acute and chronic renal failure [8,9]. It has also been found that using PPIs causes changes in the intestinal microbiota and may, therefore, increase the rate of infections due to enteric pathogens, such as infection with *Clostridium difficile* [10]. Moreover, it has been shown that the reduced gastric acidity (hypochlorhydria) resulting from long-term PPI use may cause an increased risk of community-acquired pneumonia due to bacterial colonization and aspirations in the stomach [11]. Therefore, the aim of this study is to evaluate whether the long-term (≥4 weeks) use of PPIs has an effect on the mortality and morbidity of patients who are hospitalized for COVID-19.

2. Materials and methods

In this multicentric retrospective study, 382 adult patients (≥18 years of age) with confirmed COVID-19 who were hospitalized for treatment were enrolled. This study was approved by the Local Ethics Committee of Lokman Hekim University, Ankara, Turkey.

Diagnosis of COVID-19 was confirmed using nasopharyngeal swab real-time reverse transcriptase PCR according to the WHO guidelines[1]. Patients were treated in line with the recommendations of the Turkish Health Ministry COVID-19 adult patient treatment guidelines[2]. Demographic features, complete medical history, and the laboratory findings of the study participants at admission were obtained from the medical records. Patients under any other type of antisecretory medication (H2 receptor antagonists) were not included in the study. Patients with missing data (n = 21), patients with any known malignancies (n = 5), patients under immunosuppressive therapy (n = 4), and patients under 18 years of age (n = 2) were also excluded from the study. In total, 411 patients were evaluated for the study, 29 of whom were excluded according to the exclusion criteria, ultimately leading to the inclusion of 382 patients.

Some data in the literature have supported the notion that using PPIs increases the risk of pneumonia during the first month of therapy. Therefore, we determined the cutoff for the use of PPIs as 4 weeks [12]. Patients were divided into two groups according to the periods during which they used PPIs: the first group included those who were not on PPI treatment, and the second group included those who have used PPIs for more than 4 weeks. Patients taking any type of PPIs from time to time were not included in the study.

Age, sex, the presence of comorbid diseases, medications used, duration of drug use, smoking habits, treatments received after the diagnosis of the disease, whether these patients were admitted to the intensive care unit or not, and whether they were intubated were recorded with their outcomes. Those whose treatment or hospitalization periods were still ongoing during the data collection were not included in the study.

2.1. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics v. 22.0 (IBM Corp., Armonk, NY, USA). Independent student's t-test and one-way analysis of variance (ANOVA) were used for continuous variables, and the results are presented as the mean ± standard deviation. The chi-square test was used for categorical variables in independent groups, and the results are presented as numbers and percentages. Normal distribution for continuous variables was evaluated with the Kolmogorov–Smirnov test. The Mann–Whitney U test was used to perform a comparative analysis between the two independent groups. Cox regression analysis was used to evaluate the risk factors related to intubation and mortality. A p-value of 0.05 was regarded as statistically significant.

3. Results

A total of 382 patients were included in this study and divided into two groups according to their PPI usage history over the last 6 months: 291 patients reported that they did not use any type of PPI over the last 6 months, and 91 patients reported using PPIs for more than 4 weeks (lansoprazole, n = 12; esomeprazole, n = 10; pantoprazole, n = 58; and rabeprazole, n = 11).

Table 1 summarizes the demographic characteristics of the study participants as well as their patterns of use of PPIs. Those who reported using PPIs for more than 4 weeks were found to be significantly older (p = 0.001). Regarding the presence of comorbid chronic diseases (e.g., hypertension, diabetes, asthma, or chronic obstructive pulmonary disease), hypertension, and diabetes were found to be significantly more common in the PPI-using group (Table 1). No significant difference was found

[1] Organization WH. Assessment tool for laboratories implementing COVID-19 virus testing: interim guidance . Website. https://apps.who.int/iris/handle/10665/331714 [acessed on].

[2] Bakanligi TCS. COVID-19 (SARS-CoV-2 ENFEKSİYONU) ERİŞKİN HASTA TEDAVİSİ. Website https://covid19.saglik.gov.tr/TR-66926/eriskin-hasta-tedavisi.html [acessed on].

Table 1. Demographic characteristics according to PPI therapy.

Parameters	PPI Therapy		p
	No current PPI use (G1) n=291	**>4 weeks PPI use (G2) n=91**	
Age, years Median (IQR)	49 (32-66)	70 (59-77)	**<0.001***
Sex, n (%) Female	111 (38.1)	32 (35.2)	0.6**
Male	180 (61.9)	59 (64.8)	
Current smoking status, n (%) No	219 (75.3)	50 (54.9)	**<0.001****
Yes	72 (24.7)	41 (45.1)	
Comorbidities, n (%) No	160 (55)	12 (13.2)	**<0.001****
Yes	131 (45)	79 (86.8)	
Hypertension, n (%) No	187 (67.8)	36 (39.6)	**<0.001****
Yes	89 (32.2)	55 (60.4)	
ACE inh or ARB Therapy, n (%) No	211 (78.7)	45 (50.6)	**<0.001****
Yes	57 (21.3)	44 (49.4)	
Diabetes mellitus, n (%) No	226 (82.8)	64 (71.9)	**0.026****
Yes	47 (17.2)	25 (28.1)	
Antidiabetic Therapy, n (%) No	238 (88.1)	64 (72.7)	**0.001****
Yes	32 (11.9)	24 (27.3)	
Place of treatment, n (%) Pandemic service	245 (84.2)	54 (59.3)	**<0.001****
Intensive care unit	46 (15.8)	37 (40.7)	
Intubation, n (%) No (IQR)	254 (87.3)	52 (57.1)	**<0.001****
Yes	37 (12.7)	39 (42.9)	
Exitus, n (%) No	254 (87.3)	57 (62.6)	**<0.001****
Yes	37 (12.7)	34 (37.4)	
Duration of stay in hospital, day Median (IQR)	14 (8-14)	13 (7-18)	0.298*
Duration of stay in ICU, day Median (IQR)	8 (4-13)	8 (5-20)	0.259*

*Mann–Whitney U test; **Chi-Square test; PPI: proton pump inhibitor; ACE inh: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ICU: intensive care unit.

between groups regarding the distribution of medications used for the treatment of COVID-19 ($p > 0.05$).

Table 2 summarizes the results of the Cox regression analysis for intubation and mortality. According to the Cox regression analysis, current smoking, the use of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and PPI therapy for more than 4 weeks were found to be independent risk

Table 2. The evaluation of risk factors related to intubation and mortality with regression analyses (n = 382).

	Risk factors related to intubation				Risk factors related to mortality			
	Univariate logistic regression (LR) analysis		Multivariate LR model		Univariate COX regression (CR) analysis		Multivariate CR model	
	Crude OR (95%CI)	P	Adjusted OR (95% CI)	P	Crude HR (95% CI)	P	Adjusted HR (95% CI)	P
Sex (ref: male)	1.114 (0.665–1.865)	0.682	3.022 (1.183–7.719)	0.021	1.418 (0.882–2.281)	0.150	1.533 (0.802)	0.196
Age	1.056 (1.039–1.074)	<0.001	1.039 (1.014–1.065)	0.002	1.043 (1.028–1.059)	<0.001	1.047 (1.026–1.068)	<0.001
Current smoking* (ref: no)	4.723 (2.784–8.011)	<0.001	9.364 (3.769–23.267)	<0.001	2.011 (1.231–3.284)	0.005	2.590 (1.334–5.025)	0.005
Hypertension (ref: no)	6.633 (3.681–11.953)	<0.001	0.497 (0.156–1.584)	0.237	3.187 (1.859–5.464)	<0.001	0.937 (0.400–2.192)	0.880
Diabetes mellitus (ref: no)	2.696 (1.492–4.873)	0.001	0.785 (0.351–1.756)	0.556	2.107 (1.250–3.551)	0.005	1.271 (0.719–2.246)	0.409
ACE inh or ARB use (ref: no use)	8.992 (4.963–16.293)	<0.001	5.363 (1.870–15.382)	0.002	2.566 (1.529–4.305)	<0.001	0.937 (0.433–2.028)	0.870
PPI therapy, ≥4 weeks PPI use (ref: no use)	5.149 (3.001–8.833)	<0.001	4.532 (2.233–9.200)	<0.001	1.944 (1.188–3.182)	0.008	1.83 (1.065–2.419)	0.031

PPI: proton pump inhibitor; ACE inh: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; OR: odds ratio; HR: hazard ratio; CI: confidence interval.

factors for intubation. In addition, older age (HR: 1.047, 95% CI: 1.026–1.068), current smoking (HR: 2.590, 95% CI: 1.334–5.025), and PPI therapy for more than 4 weeks (HR: 1.83, 95% CI: 1.06–2.41) were found to be independent risk factors for mortality.

4. Discussion

The results obtained in this study show that using PPIs for more than 4 weeks is an independent risk factor for both intubation and mortality. For patients with COVID-19, which is currently affecting millions of people worldwide and is causing high rates of mortality, it is critical to determine the risk factors that may lead to intubation requirement and mortality.

In general, PPIs are one of the most frequently prescribed drugs worldwide. Long-term PPI use has been related to some adverse events associated with vitamin absorption and alterations in intestinal microbiota [13]. These effects are associated with hypochlorhydria, which disturbs the body's defenses against ingested viruses and bacteria [14].

Data regarding the effects of long-term PPI use on the outcomes of patients diagnosed with COVID-19 have rapidly increased. For example, recently, Almanaro et al. found a dose–response relationship between COVID-19 positivity and PPI use, and they found that patients who take PPIs twice a day are at an increased risk for testing positive for COVID-19 on PCR [15]. In general, the normal pH level is 3 or less in a healthy stomach. While this acidic environment impairs the infectivity of SARS-CoV-1, the virus responsible for severe acute respiratory syndrome, the higher pH resulting from the use of PPIs does not inactivate the virus [16].

SARS-CoV-2 can enter the body via the gastrointestinal (GI) system through the angiotensin-converting enzyme 2 receptor, which is widely expressed in the GI system [17,18]. This helps the virus spread easily outside the GI system and cause inflammation in other systems [19]. The gut microbiota plays an essential role in the regulation of metabolic, defensive, and immunological processes in the human body. Any change in the microbial balance, namely, dysbiosis, can directly affect the immunological response [20–22]. PPIs cause hypoacidity, which results in negative effects on the stomach functions and defense mechanisms of the body, leading to decreased gastric mucus viscosity, delayed gastric emptying, and increased bacterial translocation and bacterial load [23]. Impairment of neutrophil functions induced by PPI use can impair the body's ability to recover from an infection and may contribute to harmful outcomes for an infection [24]. In this respect, our results reporting the negative effects of PPI use for more than 4 weeks on intubation requirement and mortality rates of patients with COVID-19 may be associated with the altered immunity and intestinal microbiota of the patients using PPIs.

Several recently published studies have shown that using PPIs is associated with poor outcomes for patients with COVID-19. In a national cohort study by Lee et al., the authors found that using PPIs is associated with mortality (adjusted OR: 1.79, 95% CI: 1.3–3.1) and poor clinical outcomes. However, since these data have been taken from electronic health records, they may not match the actual usage data [25]. In another study, Ramachandran et al. showed that, in 295 patients hospitalized for COVID-19, prehospitalization PPI exposure is an independent risk factor for mortality (OR: 2.33, 95% CI: 1.18–4.59) [26]. It has also been shown that H2 receptor blockers do not increase but rather decrease the risk of mortality for patients with COVID-19 [15,27]. In a pooled meta-analysis, Hariyanto et al. [28] also showed that using PPIs is associated with a significant increase in the risk of severe COVID-19. However, in all of these reports, data on the duration or type of PPIs used were not available or standardized. In contrast to these findings, in an opinion paper evaluating the data of many studies, the potential benefits of using PPIs in the treatment of COVID-19 were evaluated, and it was stated that PPIs may be effective in the treatment of COVID-19 [29].

This study has several limitations, the most important of which are the small number of patients included and its retrospective design. All the data were obtained from hospital records and patient databases. We did not evaluate the presence of pneumonia in our patients, which is considered another limitation of this study. Therefore, we were unable to suggest a direct association between PPI use and pneumonia. Although our two groups were not balanced in terms of age, smoking habits, and the presence of comorbidities, this did not affect the results thanks to the significant findings obtained in the regression analysis. Because of the highly common use of these medications, larger prospective, randomized, controlled studies are warranted to determine the direct effects of long-term PPI use on the outcomes of patients with COVID-19.

In conclusion, we found that using PPIs for more than 4 weeks is associated with negative outcomes for patients with COVID-19. Therefore, patients under PPI therapy should be evaluated more carefully if they are hospitalized for COVID-19.

Disclaimers/Conflict of interest

Authors declare that they have no conflict of interest. There is no funding.

Author contributions

A.Y: conceptualization, formal analysis, investigation, Writing; B.K: conceptualization, formal analysis,

investigation, writing; G.C: data curation, software, validation, writing ; A.T: data curation, formal analysis, writing; Y.S.S: data curation, formal analysis, writing; K.S.Y: data curation, investigation, software, validation; M.G: data curation, investigation, software, validation; M.K: data curation, formal analysis, writing; M.G.K: data curation, investigation, software; M.K: data curation, formal analysis, writing , U.K: data curation, formal analysis, writing; M.K: conceptualization, formal analysis, Investigation, writing.

Ethical approval/Informed consent

Lokman Hekim University Local Ethics Committee approved the study with the number of 2021-023. Informed consent was not obtained from the patients because the study was retrospective.

References

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. Journal of Medical Virology 2020; 92 (4): 401-402. doi: 10.1002/jmv.25678
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Bio-medica: Atenei Parmensis 2020; 91 (1): 157-160. doi: 10.23750/abm.v91i1.9397
3. Zhu N, Zhang D, Wang W, Li X, Yang B et al. A novel coronavirus from patients with pneumonia in China, 2019. The New England Journal of Medicine 2020; 382 (8): 727-733. doi: 10.1056/NEJMoa2001017
4. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity 2020; 109: 102433. doi: 10.1016/j.jaut.2020.102433
5. Savarino V, Mela GS, Zentilin P, Bisso G, Pivari M et al Comparison of 24-h control of gastric acidity by three different dosages of pantoprazole in patients with duodenal ulcer. Alimentary Pharmacology & Therapeutics 1998; 12 (12): 1241-1247. doi: 10.1046/j.1365-2036.1998.00416.x
6. Kahrilas PJ, Shaheen NJ, Vaezi MF, Hiltz SW, Black E et al. American Gastroenterological Association Medical position statement on the management of gastroesophageal reflux disease. Gastroenterology 2008; 135 (4): 1383-1391, 1391 e1-5. doi: 10.1053/j.gastro.2008.08.045
7. Savarino V, Marabotto E, Zentilin P, Furnari M, Bodini G et al. Proton pump inhibitors: use and misuse in the clinical setting. Expert Review of Cinical Pharmacology 2018; 11 (11): 1123-1134. doi: 10.1080/17512433.2018.1531703
8. Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. American Heart Journal 2009; 157 (1): 148. doi: 10.1016/j.ahj.2008.09.017
9. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. JAMA Internal Medicine 2016; 176 (2): 172-174. doi: 10.1001/jamainternmed.2015.7927
10. Imhann F, Vich Vila A, Bonder MJ, Lopez Manosalva AG, Koonen DPY et al. The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. Gut Microbes 2017; 8 (4): 351-358. doi: 10.1080/19490976.2017.1284732
11. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM et al. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ: Canadian Medical Association journal = Journal De l'Association Medicale Canadienne 2011; 183 (3): 310-319. doi: 10.1503/cmaj.092129
12. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB et al. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One 2015; 10 (6): e0128004. doi: 10.1371/journal.pone.0128004
13. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Alimentary Pharmacology & Therapeutics 2011; 34 (11-12): 1269-1281. doi: 10.1111/j.1365-2036.2011.04874.x
14. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology 2017; 153 (1): 35-48. doi: 10.1053/j.gastro.2017.04.047
15. Almario CV, Chey WD, Spiegel BMR. Increased risk of COVID-19 among users of proton pump inhibitors. The American Journal of Gastroenterology 2020; 115 (10): 1707-1715. doi: 10.14309/ajg.0000000000000798
16. Darnell ME, Subbarao K, Feinstone SM, Taylor DR. Inactivation of the coronavirus that induces severe acute respiratory syndrome, SARS-CoV. Journal of Virological Methods 2004; 121 (1): 85-91. doi: 10.1016/j.jviromet.2004.06.006
17. Chen L, Lou J, Bai Y, Wang M. COVID-19 disease with positive fecal and negative pharyngeal and sputum viral tests. The American Journal of Gastroenterology 2020; 115 (5): 790. doi: 10.14309/ajg.0000000000000610
18. Wu Y, Guo C, Tang L, Hong Z, Zhou J et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. The Lancet Gastroenterology & Hepatology 2020; 5 (5): 434-435. doi: 10.1016/S2468-1253(20)30083-2
19. Lamers MM, Beumer J, Van der Vaart J, Knoops K, Puschhof J et al. SARS-CoV-2 productively infects human gut enterocytes. Science 2020; 369 (6499): 50-54. doi: 10.1126/science.abc1669
20. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M et al. Role of the normal gut microbiota.World Journal of Gastroenterology 2015; 21 (29): 8787-803. doi: 10.3748/wjg.v21.i29.8787

21. Belizario JE, Faintuch J, Garay-Malpartida M. Gut microbiome dysbiosis and immunometabolism: new frontiers for treatment of metabolic diseases. Mediators of Inflammation 2018; 2018: 2037838. doi: 10.1155/2018/2037838

22. Wandall JH. Effects of omeprazole on neutrophil chemotaxis, super oxide production, degranulation, and translocation of cytochrome b-245. Gut 1992; 33 (5): 617-621. doi: 10.1136/gut.33.5.617

23. Huang JQ, Hunt RH. Pharmacological and pharmacodynamic essentials of H(2)-receptor antagonists and proton pump inhibitors for the practising physician. Best Practice & Research Clinical Gastroenterology 2001; 15 (3): 355-70. doi: 10.1053/bega.2001.0184

24. Zedtwitz-Liebenstein K, Wenisch C, Patruta S, Parschalk B, Daxbock F et al. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. Critical Care Medicine 2002; 30 (5): 1118-1122. doi: 10.1097/00003246-200205000-00026

25. Lee SW, Ha EK, Yeniova AO, Moon SY, Kim SY et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. Gut 2021; 70 (1): 76-84. doi: 10.1136/gutjnl-2020-322248

26. Ramachandran P, Perisetti A, Gajendran M, Jean-Louis F, Bansal P et al. Pre-hospitalization proton pump inhibitor use and clinical outcomes in COVID-19. European Journal of Gastroenterology & Hepatology 2020. doi: 0.1097/MEG.0000000000002013

27. Wu C, Liu Y, Yang Y, Zhang P, Zhong W et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharmaceutica Sinica B 2020; 10 (5): 766-788. doi: 10.1016/j.apsb.2020.02.008

28. Hariyanto TI, Prasetya IB, Kurniawan A. Proton pump inhibitor use is associated with increased risk of severity and mortality from coronavirus disease 2019 (COVID-19) infection. Digestive and Liver Disease: Official Journal of The Italian Society of Gastroenterology and The Italian Association for The Study of the Liver 2020; 52 (12): 1410-1412. doi: 10.1016/j.dld.2020.10.001

29. Ray A, Sharma S, Sadasivam B. The potential therapeutic role of proton pump inhibitors in COVID-19: hypotheses based on existing evidences. Drug Research (Stuttgart) 2020; 70 (10): 484-488. doi: 10.1055/a-1236-3041