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ИНГИБИТОРЫ ПРОТОННОЙ ПОМПЫ В ПЕРИОД ПАНДЕМИИ COVID-19

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Proton Pump Inhibitors in the COVID-19 Pandemic

Резюме

Безопасность применения ингибиторов протонной помпы (ИПП) при коронавирусной инфекции (COVID-19) является недостаточно изученной. ИПП являются мощными супрессорами желудочной секреции и входят в десятку наиболее широко используемых препаратов в мире. Предполагается, что препараты влияют на восприимчивость к вирусу, тяжесть течения и исходы у пациентов с диагнозом COVID-19. Это беспокойство основано на механизме действия ИПП — подавлении кислотности желудочного сока, который считается первой линией защиты от инфекций. В совокупности результаты большинства исследований и метаанализов подтверждают возможность того, что использование ИПП может способствовать развитию более тяжелой формы COVID-19. Однако учесть все потенциальные факторы риска тяжести COVID-19 в реальной клинической практике представляется затруднительным, поэтому следует с большой осторожностью относиться к выводам о причинно-следственных связях применения ИПП. Дополнительная интересная точка зрения на использование ИПП во время пандемии заключается в том, что их прием может привести к снижению всасывания некоторых витаминов. С другой стороны, в литературе появилось несколько исследований в отношении защитных терапевтических эффектов ИПП. Все больше доказательств иммуномодулирующей и антифиброзной роли ИПП, что может быть использовано в лечении COVID-19. Кроме того, способность препаратов подщелачивать содержимое эндосом и лизосом служит препятствием для проникновения вируса в клетки. В представленном обзоре проанализированы возможные эффекты приема ИПП у пациентов с COVID-19.-

Ключевые слова: *ингибиторы протонной помпы, COVID-19, SARS-CoV-2, пневмония, смертность, тяжесть течения, факторы риска, лечение, витамины*

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Abstract

The safety of proton pump inhibitors (PPIs) use in coronavirus infection (COVID-19) is not well understood. PPIs are potent suppressors of gastric secretion and become one of the ten most widely used drugs in the world. They are expected to influence virus susceptibility, severity, and

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outcomes in patients diagnosed with COVID-19. This concern is based on their mechanism of action — suppression of gastric acidity, which is considered the first line of defense against infections. Taken together, the results of most studies and meta-analyses support that PPIs use has been associated with increased risk of COVID-19 and severe outcomes. However, taking into account all potential risk factors for disease severity seems impossible in the real world in the context of COVID-19, so conclusions about causal relationships between PPI use and COVID-19 should be treated with great caution. An additional interesting point about the use of PPIs in the pandemic is that it reduced absorption of certain vitamins. On the other hand, several studies have appeared in the literature regarding the protective therapeutic effects of PPIs. There is growing evidence of an immunomodulatory and antifibrotic role of PPIs that could be used in the treatment of COVID-19. In addition, their ability to alkalize the contents of endosomes and lysosomes serves as an obstacle to the penetration of the virus into host cells. This review analyzes the possible effects of PPIs in patients with COVID-19.

Key words: *proton pump inhibitors, COVID-19, SARS-CoV-2, pneumonia, mortality, severe outcomes, risk factors, treatment, vitamins*

Conflict of interests

The authors declare no conflict of interests

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ACE — angiotensin-converting enzyme, ATPase — adenosine triphosphatase, BMI — body mass index, CI — confidence interval, GERD — gastroesophageal reflux disease, GIT — gastrointestinal tract, HR — hazard ratio, NSAIDs — nonsteroidal anti-inflammatory drugs, OR — odds ratio, PPI — proton pump inhibitors, RCT — randomized controlled trial

Introduction

The coronavirus disease (COVID-19) pandemic, which was first reported in December 2019 [1], was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 infection had led to more than 5.9 million deaths from COVID-19 by early 2022 worldwide, as well as a global health crisis [2]. Although common post-COVID complications caused by this virus include damage to the respiratory system, SARS-CoV-2 was found to affect almost all organs, including the gastrointestinal tract (GIT) [3]. Tian Y. et al. (2020) [4] described gastrointestinal symptoms in patients infected with SARS-CoV-2, with a frequency of 3 % to 79 %.

There are several confirmed risk factors for severe COVID-19: elderly age, smoking, obesity, diabetes mellitus, malignant neoplasms, HIV infection, chronic diseases of the lungs, kidneys, or cardiovascular system [1]. There were also concerns over the use of different medications in cases of COVID-19. Evidence emerged that angiotensin-converting enzyme (ACE) inhibitors have a possible modulating effect on disease severity [5]. However, no further evidence was obtained of a positive or negative association with the use of ACE inhibitors in cases of COVID-19 [6–8].

Currently, there is uncertainty regarding the safety of using proton pump inhibitors (PPIs) in patients with SARS-CoV-2, as available data demonstrate both protective and adverse effects. PPIs are expected to have an effect on viral susceptibility, disease severity, and outcomes in patients with COVID-19. This concern is due to the mechanism of action of these agents, i.e., suppression of gastric acid secretion [9]. SARS-CoV-2 is similar to two other previously identified coronaviruses, namely severe acute (SARS-CoV) and Middle East (MERS-CoV) respiratory syndromes [10]. SARS-CoV was reportedly inactivated under acidic conditions (pH 1.0–3.0), while higher gastric pH, which can be achieved with the help of PPIs, does not inactivate this virus [11]. This seems crucial since SARS-CoV-2 can enter the body not only through the respiratory but also through the digestive system [3]. The virus uses the ACE2 receptor, which is extensively expressed in the gastrointestinal tract, for rapid entry and replication in enterocytes [12]. In addition, since the gut is the largest immune organ and can host colonies of rapidly replicating SARS-CoV-2, there is concern that the virus could spread outside the gastrointestinal tract, specifically in the respiratory tract via the gut-lung axis [3, 13]. Therefore, gastric fluid is considered the first line of defense, so the risk of viral infection increases with hypoacidity [14].

This review analyzes the safety of using PPIs during the COVID-19 pandemic. Studies on the link between the use of PPIs and coronavirus infection were searched between January 2020 and March 2022 in three electronic databases, including MEDLINE/PubMed, the Cochrane Library, and Google Scholar.

PPIs as a risk factor for severe COVID-19

PPIs are potent suppressors of gastric secretion and are among the ten most widely used agents in the world. The U.S. Food and Drug Administration (FDA) has approved these drugs for the long-term management of

a range of gastrointestinal conditions, including peptic ulcer, Barrett's esophagus, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, as well as for the prevention of gastrointestinal bleedings during the administration of non-steroidal anti-inflammatory drugs (NSAIDs) [9]. However, in less than 30 years, PPI use has turned into an epidemic — prescription with no clear indications in up to 70 % of cases. According to studies, PPIs are prescribed for 2/3 of hospitalized patients with no corresponding indications [15]. It is generally accepted that PPIs are relatively well tolerated, with most patients reporting adverse reactions such as headache, rash, dizziness, and gastrointestinal symptoms including nausea, abdominal pain, flatulence, constipation, and diarrhea. Physicians are generally not concerned about the serious side effects of PPIs at approved dosages for a short treatment period of about two weeks. However, prolonged and often unjustified use significantly increases the number of adverse events [16, 17]. Although a large randomized controlled trial (RCT) by Moayyedi P. et al. (2019) that included 17,598 patients did not confirm most of the supposed side effects, it was found that daily use of PPIs for three years increased the possibility of intestinal infection by 33 % (odds ratio (OR) = 1.33; 95 % confidence interval (CI) 1.01–1.75) [18]. This effect was probably related to hypochlorhydria and developed due to the long-term use of PPIs, which reduced microbial diversity in the gut, contributing to the colonization of certain pathogenic gut bacteria [19]. However, the authors found no increased risk for the most dangerous associations reported previously, such as cardiovascular diseases (OR = 1.04; CI 0.93–1.15), kidney diseases (OR = 1.17; CI 0.94–1.45), dementia (OR=1.20; CI 0.81–1.78), pneumonia (OR = 1.02; CI 0.87–1.19), fractures (OR = 0.96; CI 0.79–1.17), malignant neoplasms (OR = 1.04; CI 0.77–1.40) [18, 20]. However, not all researchers agreed with the correctness of the method and the duration of this work, considering that the evidence for the long-term safe use of PPIs was insufficient [21, 22].

In July 2020, Almario C.V. et al. [23] conducted an online survey among the American population (n = 53,130) and identified 6.4 % of participants who tested positive for COVID-19. Regression analysis revealed that individuals who took PPIs once a day (OR = 2.15; 95 % CI 1.90–2.44) or twice a day (OR = 3.67; 95 % CI 2.93–4.60) were significantly more likely to test positive for COVID-19 than those who did not take PPIs (Table 1). However, this study had a number of significant shortcomings: the PPI-treated group was younger than the overall population; the number of participants tested for COVID-19 was not reported for either the cohort or separate groups; it is not clear if the control group participants were tested for COVID-19 and the results were negative, or if there were both tested and untested participants [24]. Tarlow B. et al. (2020) [25] also pointed out the disadvantages of the unusual distribution of demographic data in the study conducted by Almario C.V.

In contrast, Lee S.W. et al. (2021) [1] published the results of a nationwide cohort study and reported that short-term ongoing use of PPIs may be a risk factor for severe COVID-19, but not for infection. Similarly, Zhou J. et al. (2021) [26] reported a link between PPIs and severe COVID-19 outcomes, including intensive care unit hospitalization, intubation, or death. A retrospective observational study of 152 hospitalized patients with confirmed COVID-19 performed by Luxenburger H. et al. (2021) [27] revealed an increased risk of secondary infections (statistical significance $p = 0.032$) and acute respiratory distress syndrome when taking PPIs after considering other predisposing comorbidities. Moreover, GERD became an important independent prognostic factor ($p = 0.034$), which indicates the important role of microaspiration in the pathogenesis of secondary infection in this category of patients.

A meta-analysis conducted by Kim H.B. et al. (2021) demonstrated a significant association between PPIs and severe COVID-19 outcomes (including the development of acute respiratory distress syndrome), albeit with a high degree of heterogeneity (hazard ratio (HR) = 1.53; 95 % CI 1.20–1.95, I^2 =74.6 %) [28]. In regard to the subgroup analysis of patients taking PPIs, an increase in severe COVID-19 outcomes was observed in individuals younger than 60, in the Asian population, and during hospitalization. However, a separate analysis with adjustment for body mass index (BMI) or smoking status revealed no significant association. All studies included in the meta-analysis were observational. Several important factors associated with the use of PPIs in cases of COVID-19 were not considered in several studies. This includes, for example, using concomitant medications such as ACE inhibitors, angiotensin II receptor blockers, or statins. While other studies with adjustment for these factors demonstrated no significant association between PPIs and COVID-19 severity (HR = 1.24, 95 % CI: 0.76–2.00, I^2 =68.7 %).

According to Israelsen S.B. et al. (2021) (n = 83,224) [29], current use of PPIs was associated with an increased risk of SARS-CoV-2 infection and was not associated with an increased risk of severe disease outcomes, including intensive care unit hospitalization or death, as reported in previous meta-analyses [30–33]. In addition, a multicenter study in North America and a nationwide study in the United Kingdom, which were not included in any meta-analysis, also revealed no association between PPIs and severe COVID-19 outcomes [34, 35].

In a meta-analysis conducted by Italian researchers led by Zippi M. (2021) [9], no difference in severity or mortality due to COVID-19 was found between patients taking and not taking PPIs.

Another point of view on PPIs during the COVID-19 pandemic is that their administration may lead to the decreased absorption of some vitamins [36].

Table 1. Large studies and meta-analyses examining the association between PPI use and COVID-19

№	Author	Study design	Number of patients	Risk of COVID-19	Severe outcomes and mortality risk of COVID-19
1.	Almario C.V. et al. [23]	Online survey	53 130 (14 855 PPI use once daily)	OR=2,15 (95 % CI 1,90-2,44)	no data
2.	Lee S.W. et al. [1]	Nationwide cohort study	132 216 (14 163 PPI users)	*OR=0,90 (95 % CI 0,78-1,01)	OR=1,90 (95 % CI 1,46-2,77)
3.	Zhou J. et al. [26]	Territory-wide study	4 445 (524 PPI users)	*OR=1,18 (95 % CI 1,13-1,23)	HR=2,73 (95 % CI 2,05-3,64)
4.	Kim H.B. et al. [28]	Meta-analysis	18 109 (no data about PPI users)	*OR=1,26 (95 % CI 0,89-1,79)	OP=1,53 (95 % ДИ 1,20-1,95)/ HR=1,53 (95 % CI 1,20-1,95)
5.	Israelsen S.B. et al. [29]	Nationwide study and meta-analysis	83 224 (4 473 PPI users)	OR=1,08 (95 % CI 1,03-1,13)	*OR=1,0 (95 % CI 0,75-1,32)
6.	Kow C.S. et al. [30]	Meta-analysis	37 372 (14 452 PPI users)	no data	OR=1,46 (95 % CI 1,34-1,60)
7.	Li G.F. et al. [31]	Meta-analysis	318 261 (87 074 PPI users)	*OR=1,33 (95 % CI 0,86-2,07)	OR=1,67 (95 % CI 1,19-2,33)
8.	Kamal F. et al. [32]	Meta-analysis	21 285 (no data about PPI users)	no data	OR=1,79 (95 % CI 1,25-2,57) — severe outcomes OR=2,12 (95 % CI 1,29-3,51) — mortality
9.	Toubasi A.A. et al. [33]	Meta-analysis	195 230 (no data about PPI users)	*OR=1,19 (95 % CI 0,62-2,28)	OR=1,67 (95 % CI 1,41-1,97)
10.	Zippi M. et al. [9]	Meta-analysis	42 086 (no data about PPI users)	no data	*OR=1,65 (95 % CI 0,62-4,35, p=0,314) — severe outcomes *OR=1,77 (95 % CI 0,62-5,03, p=0,286) — mortality

Notes: *study results are not statistically significant; CI — confidence interval, PPI — proton pump inhibitors; HR — hazard ratio; OR — odds ratio

PPIs reduce the bioavailability of vitamin C, which leads to its decreased concentration [37]. This observation is important in the context of COVID-19, considering the data obtained by Feyaerts A.F. et al. (2020) [38] that low doses (0.5–2 g/day) of vitamin C can be used for prevention, and high doses lower the level of inflammatory mediators (interleukin-6 and endothelin-1) in the development of a severe disease. The benefits of vitamin C in high doses for the management of COVID-19 were also shown by Hoang B.X. et al. (2020) [39]. Regarding the role of magnesium and vitamin D in the pathogenesis of coronavirus infection, hypomagnesemia should be considered one of the side effects of PPIs. Magnesium is absorbed in the intestines with the help of two proteins located on the apical membrane of enterocytes — TRPM6 (Transient Receptor Potential Cation Channel Subfamily M Member 6) and TRMP7 (Transient Receptor Potential Cation Channel Subfamily M Member 7) [40–42]. PPIs reduce the activity of TRPM6, which leads to decreased magnesium absorption and hypomagnesemia [43]. Fat-soluble vitamin D requires magnesium to turn into its active form (1,25[OH]2D) [44]. Moreover, more and more studies are demonstrating the link between low vitamin D levels and increased susceptibility to SARS-CoV-2 infection, as well as the severity of the clinical course of this disease [45, 46].

It should be noted that study results can be interpreted in different ways. For example, the information obtained on the decreased anti-inflammatory activity of neutrophils when taking PPIs is regarded by some authors as a factor of aggression, considering the decrease in protection against infectious agents [28]. Other researchers suggest that this phenomenon is a protective factor, since the ability of PPIs to inhibit the production of pro-inflammatory cytokines indicates their ability to suppress the cytokine storm associated with COVID-19 and prevent the development of acute respiratory distress syndrome [30].

Taken together, most of the above studies support the possibility that using PPIs may be a risk factor for a more severe course of COVID-19. However, study results should be interpreted with caution, as some studies provide limited information on the type, dose of studied drug, duration of its administration, concomitant therapy, and indications for PPIs [47]. Most studies are retrospective observational cohorts or case-control studies that are prone to bias even after the necessary adjustments. For example, there is a significant risk of protopathic bias, as in the case of the increased risk of developing pneumonia with PPIs [48]. Protopathic bias, or reverse causality, is a source of bias when exposure conditions change in response to a demonstration of potential consequences. Smoking, NSAIDs, and obesity increase the risk of gastroesophageal reflux and the severity of GERD. GERD patients taking PPIs are at increased risk of developing pneumonia, so an increase in severe COVID-19 outcomes may be due to obesity, smoking, or NSAIDs rather than to the use of PPIs.

It is noteworthy that all studies reporting the effect of PPIs on the severity of COVID-19 differed significantly in their design. First, the study populations were heterogeneous, including different ethnicities and ages (from young to elderly with several comorbidities), as well as hospitalized and non-hospitalized patients. Second, several studies had obvious shortcomings in design. For example, many scientists [49–52] have highlighted the questionable reliability of the sampling method in the online survey of the American population [23]. Based on this work, the American College of Gastroenterology has issued an information letter for gastroenterologists and patients. However, Tarlow B. et al. (2020) [25], having studied the relationship between the use of PPIs and COVID-19 using STARR Stanford Research Repository databases, found no confirmation of the results obtained by Almario C.V. [23]; they concluded that before making changes in practical instructions, a more thorough study of the issue and independent verification of data in reliable medical databases that are not based on surveys is required.

In most studies, the observed associations were relatively weak and were in the zone of "potential bias" (OR < 3, according to observational studies, indicates a weak relationship between two events, which is multifactorial but not causal in such cases). Many factors are known to have an effect on COVID-19 outcomes, including the male sex, age, geographic region, and comorbidities [53], so results should be interpreted in relation to a specific population. For example, Gao M. et al. (2021) [54] reported that patients with BMI >23 kg/m^2 have a linear increase in the risk of severe COVID-19, leading to death. Perez-Araluce R. et al. (2021) [55] found that adherence to a Mediterranean diet was associated with a lower risk of COVID-19. Therefore, BMI and the effect of a diet on risk and disease severity should not be ignored, as has been observed in some studies.

The strongest link between PPIs and severe COVID-19 outcomes was found in Asia. The first possible mechanism is that the use of PPIs may suppress gastric acid secretion to a greater extent in Asians due to lower parietal cell mass. Secondly, the frequency of cytochrome P450 2C19 genetic polymorphism is higher in Asians compared to the representatives of other regions, which facilitates the slowing down of PPI metabolism, and, therefore, inhibition of gastric acidity may be stronger [56]. Finally, the prevalence of *Helicobacter pylori* infection in Asia is higher than in Europe or North America [57]. Therefore, PPIs may inhibit gastric acid secretion more strongly. The study by Mena G.E. et al. (2021) [58], which was published in Science (Journal of the American Association for the Advancement of Science), demonstrated that socioeconomic status has an effect on COVID-19-related mortality; this fact was also not considered in most of the studies mentioned.

According to Burchill E. et al. (2021) [59], COVID-19 has a direct or indirect effect on the gut microbiota, suggesting a difference in immune response to the pathogen. Wearing masks, hygiene practices, and social distancing also affect COVID-19 outcomes. Consideration of all potential risk factors, such as BMI, diet, geographic area, socioeconomic status, gut microbiota status, degree of reducing social interaction, and other yet unidentified causes, seems impossible in real clinical practice; therefore, conclusions about causal relationships between the use of PPIs and COVID-19 should be taken with caution.

PPIs do not worsen the course of COVID-19

Several studies based on experimental data were performed that have confirmed the benefits of using PPIs in COVID-19 [24]. Tastemur S. et al. (2020) [60] suggested that PPIs may play a role in the prevention and management of COVID-19 due to their anti-inflammatory, immunomodulatory, and antifibrotic properties.

Ray A. et al. (2020) [61], based on available research papers, proposed using PPIs for therapeutic purposes in the management of COVID-19 (Fig. 1). An *in vitro* study demonstrated that these drugs can inhibit the production of pro-inflammatory cytokines such as interleukin-6, interleukin-8 and tumor necrosis factor-α [62]. In addition, there is evidence that supports the protective role of omeprazole and lansoprazole in reducing oxidative stress in gastric epithelial and endothelial cells. Lansoprazole has been shown to reduce the number of monocytes expressing ICAM-1 (Inter-Cellular Adhesion Molecule 1) in peripheral blood. According to the *in vivo* study, omeprazole reduced the production of cytokines by duodenal epithelial cells [61].

PPIs can also regulate fibrogenesis, exhibiting antifibrotic properties by inhibiting molecules such as fibronectin, collagen, and matrix metalloproteinase enzymes [63]. Many studies associate the use of PPIs with clinical improvement in patients with idiopathic pulmonary fibrosis. These results are important as they involve the use of antifibrotic agents in the management of COVID-19 [61].

Vacuolar adenosine triphosphatase (V-ATPase), which is located on the plasma membrane and on the surface of acidic organelles such as lysosomes and endosomes, is one of the key factors controlling vesicular pH [64]. Endosomal acidification mediated by V-ATPase is an essential step for the entry of viruses, including coronaviruses. The use of PPIs leads to the acidification of the cytosol and alkalinization of endolysosomes [65]. *In vitro* screening of 60 FDA-approved drugs revealed the antiviral activity of omeprazole, which justifies its use in COVID-19 [66]. It was proved that taking omeprazole, along with vonoprazan, is associated with increased pH within the endosomes and the Golgi apparatus. This is thought to occur either by blocking V-ATPase pumps or by acting as a pH buffer.

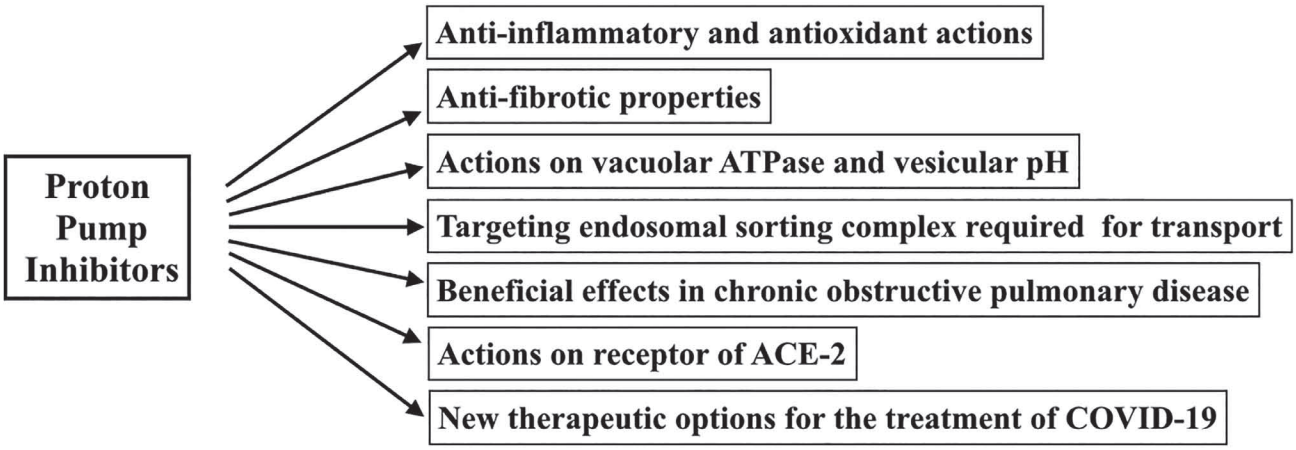

Figure 1. *Potential beneficial effects of proton pump inhibitors. (adapt. from Ray A., et al. [61])*
Notes: ACE-2 — angiotensin-converting enzyme 2, ATPase — adenosine triphosphatases

Such changes in pH will interfere with the processing of the spike protein (S1) by endosomal proteases and limit the spread of SARS-CoV-2 infection [61].

As mentioned earlier, SARS-CoV-2 uses ACE2 as a receptor to enter the human body [12], while the activity of ACE2 depends on pH level. A pH in the range of 7–7.5 is considered optimal for its functioning [67]. It is known that PPIs tend to alkalize the intraluminal environment by inhibiting V-ATPase. Since a significant decrease in the activity of ACE2 receptors occurs at pH above 7.5, using PPIs that increase pH level may prevent the penetration of SARS-CoV-2 into cells [61].

In addition to the direct antiviral activity, PPIs can also be used together with other therapeutic agents. In an *in silico* study, omeprazole increased the efficacy of aprotinin — a serine protease inhibitor, and remdesivir by 2.7 and 10 times, respectively [68]. Therefore, the combination of aprotinin and remdesivir with omeprazole may be a potential candidate for the management of COVID-19. The combination of PPIs with NSAIDs with antiviral properties, such as indomethacin, was also proposed as a new therapeutic option for COVID-19 [69].

Therefore, the antiviral mechanism of PPIs needs further exploration in clinical studies in order to confirm whether PPIs can be used in the management of COVID-19.

Conclusion

Currently, there is uncertainty regarding the safety of using PPIs during the COVID-19 pandemic, as available data demonstrate both protective and adverse effects. Taken together, most of the above studies and meta-analyses support the possibility that the use of PPIs may be a risk factor for a more severe course of COVID-19. However, these results should be interpreted with caution and with consideration of different study designs, limited information on concomitant treatment, and other risk factors for disease severity, indications for the use of PPIs, and the risk of protopathic bias. There is evidence that PPIs may play a positive role in the prevention and management of COVID-19 due to their antiviral, immunomodulatory, and antifibrotic properties. To provide more convincing evidence, further randomized controlled trials and prospective studies are required, considering that the effects of PPIs are likely to influence clinical decision-making in COVID-19 cases.

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Yarovaya N.F.: formulation of conclusions, work with literature

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