

# Proton Pump Inhibitors Use and Increased Risk of Spontaneous Bacterial Peritonitis in Cirrhotic Patients: A Retrospective Cohort Analysis

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## Abstract

**Background:** Since their introduction in the early 1980s, proton pump inhibitors (PPIs) have been used worldwide for a broad range of indications. Unfortunately, however, PPIs have become overly prescribed by healthcare providers, sometimes in the absence of clear indications. Although PPIs were initially presumed to have an excellent safety profile, emerging studies have shed light on the association between their long-term use and a myriad of side effects, including the possibility of an increased risk of spontaneous bacterial peritonitis (SBP). Data available to date regarding the association between PPI use and SBP development in cirrhotic patients is conflicting. While some observational studies provide no association between PPI use in cirrhotic patients and an increased risk of SBP development, many others support this association. As a result of the conflicting conclusions from case controls, cohorts, and meta-analyses, we aimed to carry out this retrospective cohort analysis of data from cirrhotic patients included in the electronic medical record-based commercial database, EXPLORYS (IMB-WATSON, Cleveland, Ohio). Our aim was to evaluate for a possible association between PPIs use and the risk of SBP development in cirrhotic patients and to compare the prevalence of SBP development between cirrhotic patients who were actively using PPIs and those who were not.

**Methods:** A retrospective cohort analysis with chart review was conducted on patients with cirrhosis who were included in the electronic medical record-based commercial database, EXPLORYS (IMB-WATSON, Cleveland, Ohio). Using this database, records were reviewed between December 2017 and 2020. Included patients were adults aged 30 to 79 years with a Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) diagnosis of liver cirrhosis.

Included patients with a SNOMED-CT diagnosis of liver cirrhosis were divided into two groups: the first group included all cirrhotic patients who did not use PPIs and the second group included all cirrhotic patients who were on PPIs at home.

**Results:** In our analysis, SBP occurred in 1.7% (1,860 patients) of the included cirrhotic patients whether they were actively taking PPIs or not. Among the 40,670 cirrhotic patients who were on PPIs at home, 1,350 (3.3%) patients developed SBP. On multivariate analysis, PPI use was the strongest predictor for SBP in cirrhotic patients (odds ratio (OR) = 4.24; 95% confidence interval (CI): 3.83 - 4.7, P value < 0.0001), with cirrhotic patients taking PPIs being 4.24 more likely to develop SBP than those not on PPIs. In addition, PPI use, history of bleeding varices, age, race, and gender were found to be independent predicting factors for SBP, in descending order of importance.

**Conclusions:** Our retrospective cohort analysis has shown that the use of PPIs in patients with liver cirrhosis is an independent predicting risk factor for SBP development. It solidified the argument that cirrhotic patients receiving this form of therapy seem to have a higher risk of developing SBP. In the setting of the emerging evidence that PPIs might impose health risks in cirrhotic patients, further studies are needed to settle the current debate between supporters and opponents of this proposition. In addition, future studies may help clarify the relationship between the occurrence of SBP in cirrhotic patients and the type, dose, and duration of PPIs used. We recommend that unless it is clearly indicated, PPI therapy should be avoided or administered with caution in patients with cirrhosis.

**Keywords:** Cirrhosis; Proton pump inhibitors; Spontaneous bacterial peritonitis

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## Introduction

Since their introduction into the pharmaceutical market around three decades ago, proton pump inhibitors (PPIs) have been increasingly prescribed for various indications [1]. These include gastroesophageal reflux disease (GERD), eradication of *Helicobacter pylori* infection, Barrett's esophagus, upper gastrointestinal bleeding, and gastroprotection in patients taking

non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin. In addition, PPIs have been used in cirrhotic patients in the absence of specific acid-related disease to prevent bleeding complications of gastroesophageal varices or hypertensive gastropathies [2].

Initially, PPIs were presumed to have an excellent safety profile and were preferred over other antacid drugs. As a result, their use has been widespread in the inpatient and ambulatory settings, often over extended periods and with no clear indications [3, 4]. More recently and following more than 20 years of post-marketing experience, a growing number of emerging data have alluded to the side effects associated with the long-term use of PPIs, particularly in patients with comorbidities. For instance, several studies have raised concerns about an increased risk of falls and fractures in postmenopausal women [5], a reduction in renal and liver function, vitamin B12 deficiency, iron deficiency, and hypomagnesemia. They have also shed light on an increased risk of infection-related events, including hospital-acquired pneumonia [6, 7], *Clostridium difficile* infection, even after a short-term use of 2 days in the intensive care setting [8], and spontaneous bacterial peritonitis (SBP) [9-11].

SBP is a very common and life-threatening bacterial infection of the ascitic fluid in patients with cirrhosis and ascites [12]. It should be suspected in patients with ascites and a temperature greater than 37.8 °C (100 °F), abdominal pain with or without tenderness, altered mental status, or ascitic fluid polymorphonuclear leukocyte (PMN) count more than or equal to 250 cells/mm<sup>3</sup> [13]. The diagnosis of SBP entails a very poor prognosis [14], with an in-hospital mortality rate ranging between 11% and 67% [6].

Although the mechanism through which PPIs might increase the risk of SBP development in cirrhotic patients is still not well established, several aspects about PPI use were suggested to contribute to this increased risk. PPIs facilitate the proliferation of intestinal bacteria by suppressing gastric acid secretion [15]. They might also favor small intestinal bacterial overgrowth (SIBO) and translocation of bacteria through the intestinal epithelial barrier to the lymph nodes by impairing gastrointestinal motility and increasing intestinal permeability, respectively [15-18]. After mesenteric lymph nodes are colonized, subsequent infection of peritoneal fluid becomes possible and is further facilitated by the impairment of the body's defense mechanisms [19, 20].

While some observational studies provide no association between PPI and an increased risk of SBP development in cirrhotic patients [17, 21, 22], many others support this association [9, 15, 23]. In order to address this controversial issue, several meta-analyses have been carried out [24-27], and promising evidence seems to point toward a significant association between PPI use and an increased risk of SBP development in patients with cirrhosis. In light of these conflicting conclusions from case controls [23, 28], cohorts [21, 29, 30], and meta-analyses [31, 32], we carried out this retrospective cohort analysis of data from cirrhotic patients included in the electronic medical record-based commercial database, EXPLORYS (IMB-WATSON, Cleveland, Ohio). Our aim was to evaluate for a possible association between PPIs use and the risk of SBP development in cirrhotic patients and to compare

the prevalence of SBP development between cirrhotic patients who were actively using PPIs and those who were not.

## Materials and Methods

### Study population

A retrospective cohort analysis with chart review was conducted on patients with cirrhosis who were included in the electronic medical record-based commercial database, EXPLORYS (IMB-WATSON, Cleveland, Ohio). EXPLORYS is one of the largest databases available in the United States, containing deidentified data from more than 26 healthcare systems. The data are shared by electronic medical records from the participating institutions, and they are gathered, standardized, and stored in a cloud-based system. Using this database, records were reviewed between December 2017 and 2020. Included patients were adults aged 30 to 79 years with a Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) diagnosis of liver cirrhosis.

### Ethical compliance with human

Instead of relying on International Classification of Diseases (ICD) codes for diagnoses, EXPLORYS uses the SNOMED-CT system. Since this database relies on deidentified data, it is compliant with Health Insurance Portability and Accountability Act.

### Institutional Review Board approval and informed consent

Since our study relied on the EXPLORYS database, it did not require approval from the Northwell Institutional Review Board, and data analysis and anonymous results reporting without informed consent were made possible.

### Data collection and definitions

Data were collected retrospectively from the database using a data collection form. Cirrhotic patients included in the database were identified based on the SNOMED-CT system. The etiologies of liver cirrhosis, Child-Pugh score, and (model for end-stage liver disease sodium) MELD-Na score were neither identified nor recorded.

For each patient, the following basic demographic information were collected: age, gender, and race. In addition, note was made of whether each patient was on PPIs at home, had a history of esophageal or gastric variceal bleeding, or developed SBP. Patients with a history of peptic ulcer disease (PUD) or gastrointestinal malignancy were excluded from our analysis.

Included patients with a SNOMED-CT diagnosis of liver cirrhosis were divided into two cohorts. While the control group included all cirrhotic patients who did not use PPIs, the second group included all cirrhotic patients who were actively

**Table 1.** Baseline Characteristics of Included Patients With Liver Cirrhosis

	Use of PPI (n = 40,670)	No use of PPI (n = 67,080)
SBP	1,350 (3.3%)	510 (0.76%)
Age group in years		
30 - 64	23,130 (57%)	38,630 (58%)
65 - 79	17,540 (43%)	28,450 (42%)
Gender		
Male	21,780 (53%)	36,040 (53%)
Female	18,890 (47%)	31,040 (47%)
Race		
Caucasians	35,680 (88%)	56,020 (84%)
African Americans	4,650 (11%)	10,710 (15.5%)
Others	340 (1%)	350 (0.5%)
History of variceal bleeding	3,650 (9%)	760 (1%)

PPI: proton pump inhibitor; SBP: spontaneous bacterial peritonitis.

taking PPIs at home. The types, doses, and duration of PPIs used were not recorded. The specific indication behind active PPI use was neither identified nor recorded. The prevalence of a SNOMED-CT diagnosis of SBP was calculated and compared between both study groups.

### Outcome measures

The aim of our retrospective cohort analysis was to evaluate for a possible association between PPI use and the risk of SBP development in cirrhotic patients and to compare the prevalence of SBP development between cirrhotic patients who were actively using PPIs and those who were not.

### Statistical analysis

Chi-square analysis was used for categorical variables expressed as numbers (percent), while the independent *t*-test was used for continuous variables (e.g., age) expressed as the mean  $\pm$  standard deviation. Univariate and multivariate logistic regression analysis were performed using Statistical Package for Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY), to adjust for the aforementioned factors. For our analysis, significance was defined as a P value of less than 0.05.

## Results

### Study identification algorithm

Records corresponding to 20,619,520 individuals were identified in the database from December 2017 to 2020. Using the abovementioned SNOMED-CT system, 107,750 patients with

the diagnosis of liver cirrhosis were identified between December 2017 and 2020. The records corresponding to these patients were reviewed from the electronic medical record-based commercial database, EXPLORYS.

### General characteristics and use of PPIs

The 107,750 subjects were divided into two study cohorts depending on whether they used PPIs at home (second group) or not (control group). While 37.7% (40,670) of the included cirrhotic patients actively used PPIs at home, the majority of them (62.3%) did not.

The comparison of demographic and clinical data between the abovementioned two cohorts is presented in Table 1. No significant differences were noted when comparing the distribution of age, gender, and race among both groups of cirrhotic patients, whether on PPIs at home or not. When it comes to age distribution, most cirrhotic patients in both cohorts were younger than 64 years. In fact, 57% (23,130) of cirrhotic patients who were on PPIs at home were between ages 30 and 64 years, and 58% (38,630) of cirrhotic patients who were not on PPIs at home were between ages 30 and 64 years. When it comes to gender, distribution was almost 1:1 among cirrhotic patients in both cohorts. In fact, 53% (21,780) and 47% (18,890) of cirrhotic patients who were on PPIs at home were men and women, respectively. Similarly, 53% (36,040) and 47% (31,040) of cirrhotic patients who were not on PPIs at home were men and women, respectively. In addition, when comparing the race of cirrhotic patients receiving PPIs at home to that of patients not taking PPIs, it is noted that Caucasians constitute the majority of patients in both groups (88% versus 84%, respectively), followed by African Americans (11% versus 15.5%, respectively), followed by other races (1% versus 0.5%, respectively) (Table 1).

### Prevalence and risk factors for SBP development

In our analysis, SBP occurred in 1.7% (1,860) of the included cirrhotic patients, whether they were on PPIs or not. Among the 40,670 cirrhotic patients who were actively taking PPIs at home, 1,350 (3.3%) patients developed SBP. On the other hand, among the 67,080 cirrhotic patients who were not taking PPIs at home, 510 (0.76%) patients developed SBP. In other words, the prevalence of SBP development was higher among the group of cirrhotic patients taking PPIs at home compared to those not taking PPIs (Table 1).

On multivariate analysis, PPI use, history of bleeding varices, age, race, and gender were shown to be independent predicting factors for SBP, with significant P values of < 0.05 (Table 2). Interestingly, PPI use was the strongest predictor for SBP in cirrhotic patients (odds ratio (OR) = 4.24; 95% confidence interval (CI): 3.83 - 4.7, P value < 0.0001), with cirrhotic patients taking PPIs being 4.24 more likely to develop SBP than those not on PPIs. A history of variceal bleeding was the second most important predictor of SBP (OR: 3.28; 95% CI: 2.85 - 3.80), followed by age (OR = 1.62; 95% CI: 1.47

**Table 2.** Multivariate Analysis With Spontaneous Bacterial Peritonitis Being the Outcome

	OR	95% CI		P value
		Lower	Upper	
Bleeding varices	3.283	2.85	3.805	0.0001
Non-Caucasians vs. Caucasians	1.231	1.108	1.369	0.0001
Male vs. female	1.123	1.025	1.23	0.013
Age < 65 vs. > 65	1.624	1.475	1.789	0.0001
PPI use	4.248	3.83	4.702	0.0001

OR: odds ratio; CI: confidence interval; PPI: proton pump inhibitor.

- 1.78, P value < 0.0001), followed by race (OR = 1.23; 95% CI: 1.10 - 1.46, P value < 0.0001) and gender (OR = 1.12; 95% CI: 1.02 - 1.23, P value < 0.013). Interestingly, when it comes to age, cirrhotic patients under the age of 65 years were 1.62 times more likely to develop SBP than those older than 65 years, with a significant P value of < 0.0001. When it comes to race, cirrhotic patients who were non-Caucasians were 1.23 times more likely to develop SBP than those who were Caucasians, with a significant P value of < 0.0001. Moreover, when it comes to gender, male cirrhotic patients were 1.23 times more likely to develop SBP than female patients, with a significant P value of < 0.013.

## Discussion

Since their introduction in the early 1980's, PPIs have been widely used for a broad range of indications. Not only have they been prescribed for the treatment of PUD, GERD, Zollinger-Ellison syndrome, NSAID-associated ulcers, and *Helicobacter pylori* eradication [33, 34], but also they have been used in cirrhotic patients with no specific acid-related disease to prevent bleeding complications of gastroesophageal varices or hypertensive gastropathies [2].

Unfortunately, however, PPIs have become overly prescribed by physicians, sometimes in the absence of clear indications. When this practice becomes habit-related rather than evidence based, it eventually culminates in increasing health costs and compromising patient safety [2]. In fact, although PPIs were initially presumed to have an excellent safety profile, emerging studies have shed light on the association between their long-term use and a myriad of side effects, including the possibility of an increased risk of SBP.

Data available to date regarding the association between PPI use and SBP development in cirrhotic patients is conflicting. On the one hand, several observational studies have provided no association between the PPI use in cirrhotic patients and the increased risk of SBP development. In a case-control study performed by Campbell et al in 2008 [22], 116 cirrhotic patients were included, and no clear association between PPI use and SBP development was shown. Results from a retrospective study by Mandorfer et al [29] that included 607 cirrhotic patients to assess the effect of PPI use on SBP development also failed to reveal a significant association. Similarly, in a large prospective study that included 770 patients with decompensated

cirrrosis from 23 hospitals in Argentina, no association between PPI therapy and an increased risk of SBP was found [21]. In addition, when comparing the incidence of the development of a second SBP episode among 307 cirrhotic patients with a history of SBP in Korea between PPI users and non-PPI users, no significant difference was noted between both groups even after a follow-up of 5 years [35]. Moreover, results from a cohort study that included 258 cirrhotic patients with ascites from southern Brazil did not reveal an increased risk of SBP development in PPI users compared to PPI nonusers [36].

On the other hand, emerging studies with stronger evidence have supported the association between PPI use and the risk of SBP development [9, 15, 23]. These include several meta-analyses. The first one was conducted in 2011, and it reviewed four studies involving 772 patients. Results showed a significant association between PPI use and the development of SBP (OR: 2.77, 95% CI: 1.82 - 4.23) [24]. A second meta-analysis was conducted in 2013 and reviewed eight studies on cirrhotic patients to evaluate for an association between the use of PPIs or histamine-2 receptor antagonists (H2RAs) and the risk of SBP development. Compared to cirrhotic patients taking H2RAs (n = 562; OR: 1.71, 95% CI: 0.97 - 3.01), subjects taking PPIs had a greater risk of SBP development (n = 3,815; OR: 3.15, 95% CI: 2.09 - 4.74) [25]. In 2015, a third meta-analysis reviewed 12 journal articles and five conference abstracts published between 2008 and 2014 involving 8,204 patients. Results revealed a significant association between PPI use in cirrhotic patients and both, an increased risk of SBP (OR: 2.17, 95% CI: 1.46 - 3.23) and an overall increased risk of bacterial infections (OR: 1.98, 95% CI: 1.36 - 2.87) [26]. More recently in 2021, the largest meta-analysis to date was conducted and reviewed 23 observational studies. It included 10,386 cirrhotic patients with or without ascites to evaluate for an association between PPI use and the risk of SBP development. Results showed statistically significant but quantitatively small associations between the development of SBP and PPI use, with the pooled data revealing a 1.8-fold increased risk of SBP development for cirrhotic patients using PPIs. It is important to note, however, that this increased risk of SBP development was limited to cohort studies and that the data from case-control studies demonstrated no causal relationships between PPI use and SBP [27].

Many other investigations in the medical literature further support this association. A recent Taiwanese case-control study that was published in 2015 identified a total of 947 patients

with advanced liver cirrhosis who were on some form of acid suppressive therapy. Results were significant and supported an association between the risk of developing SBP and higher cumulative days of gastric acid suppression ( $P < 0.0001$ ) [37]. Another large Korean study performed by Kwon et al included 1,140 patients and revealed that PPI use within 30 days in cirrhotic patients with ascites increased both, the risk of SBP development, especially in the elderly and in patients with a high MELD score on admission, and mortality rates [38]. In another study in 2016, the use of PPIs has been found to be a risk factor for developing hepatic encephalopathy and SBP in cirrhotic patients with ascites [39].

As a result of these conflicting conclusions from case controls [23, 28], cohorts [21, 29, 30], and meta-analyses [31, 32], we aimed to carry out this retrospective cohort analysis of data from cirrhotic patients included in the electronic medical record-based commercial database, EXPLORYS (IMB-WATSON, Cleveland, Ohio) from December 2017 to 2020. Our analysis has shown that PPI use was the strongest predictor for SBP in cirrhotic patients (OR = 4.24; 95% CI: 3.83 - 4.7,  $P$  value  $< 0.0001$ ), with cirrhotic patients taking PPIs being 4.24 more likely to develop SBP than those not on PPIs.

Although data from randomized clinical trials (RCTs) is lacking, the fact that an association between PPIs and SBP might exist should make healthcare providers taking care of cirrhotic patients more cautious when it comes to prescribing PPIs. In a systematic review and meta-analysis by Xu et al, the rates of PPI use in cirrhotic patients in the absence of clear indications ranged from 19.7% to 86% [26]. In a study by Kalaitzakis et al, the main reason for inadequate PPI use in cirrhotic patients was history of variceal bleeding [40]. Although clinical guidelines recommend PPI administration prior to endoscopic variceal ligation, it is not reasonable to continue PPIs for long-term following variceal ligation [41, 42]. Similarly, there is no sufficient evidence to support PPI use for prophylaxis of peptic complications in patients with portal hypertension or esophageal varices since acid secretion is constitutively reduced during cirrhosis [43]. In this respect, it is the healthcare provider's duty to reassess the indication of existing PPI therapy and to restrict its prescription for indications of proven benefit only.

While the precise mechanism through which acid suppression in cirrhosis increases the risk of SBP development is uncertain, several aspects about PPI use were suggested to contribute to this increased risk.

PPI use in cirrhotic patients has been hypothesized to compromise these patients' "already" degraded immunity. In fact, cirrhosis has been associated with some sort of an immune dysfunction syndrome [44]. This has been reflected by a decrease in T-helper cells and phagocytic potential of both monocytes and neutrophils [45], an increased level of cyclooxygenase-derived eicosanoid prostaglandin E2 [46], and a decreased human leukocyte antigen (HLA)-DR expression on monocytic cells defined as immune paralysis [47]. Preclinical data suggest that PPIs might contribute to some degree of immunosuppression by inhibiting neutrophil function and natural killer cell activity [48] and decreasing the cellular oxidative burst [49]. In an early study, the administration of omeprazole was shown to inhibit *in vitro* human neutrophil phagocytosis and phagolysosome acidification [50]. In another preclinical

study, the exposure of blood samples from 10 healthy subjects to omeprazole resulted in the impairment of reactive oxygen intermediates by human neutrophils, which alludes to the bactericidal activity of the reduced neutrophils [48]. Supporting evidence was obtained from an observational study by Garcia-Martinez et al, whereby results revealed a significant reduction in granulocyte and monocyte cellular oxidative burst in cirrhotic patients exposed to PPIs. As a result, it was speculated that this worsening in cirrhotic patients' immunosuppressed state with PPI use explains the reportedly high rates of bacterial infections in this population [51].

Other theories were also proposed to explain the increased risk of SBP with PPIs. PPIs might facilitate the proliferation of intestinal bacteria by suppressing gastric acid secretion [15]. They might promote SIBO and translocation of bacteria through the intestinal epithelial barrier to the lymph nodes by impairing gastrointestinal motility and increasing intestinal permeability, respectively [15, 17, 18, 24, 25, 37]. After mesenteric lymph nodes are colonized, subsequent infection of peritoneal fluid becomes possible and is further facilitated by the impairment of the body's defense mechanisms [19, 20].

Studies suggest that mechanisms other than the ones listed above could be implicated in SBP development among cirrhotic patients who use PPIs. Interestingly, results from a study comparing SBP rates among cirrhotic patients taking PPIs in the previous 7 days to patients who had been on them for 8 to 90 days revealed that only patients who had taken PPIs in the previous 7 days were at risk of SBP [28]. The fact that SIBO and bacterial translocation rarely develop in a short period implies that additional mechanisms that need to be uncovered may be implicated.

## Conclusions

In conclusion, our retrospective cohort analysis has shown that the use of PPIs in patients with liver cirrhosis is an independent predicting risk factor for SBP development. It solidified the argument that cirrhotic patients receiving this form of therapy seem to have a higher risk of developing SBP. In the setting of the emerging evidence that PPIs might impose health risks in cirrhotic patients, further prospective comparative RCTs may help settle the current debate between supporters and opponents of this proposition and shed more light on all potential adverse effects of PPIs in cirrhotic patients. In addition, future studies are needed to better understand the relationship between the occurrence of SBP in cirrhotic patients and the type, dose, and duration of PPIs used. We recommend that unless it is clearly indicated, PPI therapy should be avoided or administered with caution in patients with cirrhosis only when benefit outweighs the potential harm.

## Study limitations

There are several limitations to our findings. First, our study is observational in nature and, therefore, have intrinsic shortcomings, including differences in populations and possible unidentified confounders. Although our results support the as-

sociation between PPI use and SBP development in cirrhotic patients, it does not take into consideration the severity of the included patients' liver disease at baseline. For instance, the fact that more cirrhotic patients with a history of variceal bleeding (9%) used PPIs than those without a history of variceal bleeding (1%) implies that the former group of patients might have had a more severe form of liver disease at baseline. These patients' supposedly high MELD or Child-Pugh scores could have, in turn, predisposed them into SBP development. In other words, it is the severity of the patients' liver disease rather than their PPI use that might have put them at risk of SBP development. Unfortunately, however, the electronic medical record-based commercial database we used for our study did not provide us with sufficient information needed to assess the severity of the included patients' liver disease and to calculate their MELD and Child-Pugh scores at baseline. Similarly, our study does not take into consideration the effect of the presence of ascites, history of SBP in the past, compliance with PPI, or alcohol intake on the risk of SBP development. In addition, the fact that our study is retrospective implies that our results merely suggest an association between PPI use and SBP development without establishing causality with certainty. Well-designed, multi-center RCTs that would reinforce this association are unlikely to be designed and implemented as the use of acid suppressive therapy is not among the indicated therapies in the management of cirrhotic patients. In addition, the complications of cirrhosis, including the development of gastroesophageal varices or hypertensive gastropathy, are not related to excess of gastric acid secretion and as such are unlikely to be prevented with the use of PPIs. As supported by Savarino et al, there are no current prospective clinical trials randomizing cirrhotic patients with/without ascites to PPI use or non-use, as this could be difficult to justify on clinical, ethical, and economic bases [52]. Moreover, the types, doses, compliance with, and duration of PPI use were not included in our analysis which further makes it difficult to support a causal association.

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## Conflict of Interest

The authors declare that they have no competing interests.

## Author Contributions

LD, MA, and AAY carried out the study design, data entry, and statistical analysis. MK and LD carried out the drafting of the manuscript and its critical revision.

## Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Abbreviations

CI: confidence interval; GERD: gastroesophageal reflux disease; HLA: human leukocyte antigen; H2RA: histamine-2 receptor antagonist; ICD: International Classification of Diseases; MELD-Na: model for end-stage liver disease sodium; NSAID: non-steroidal anti-inflammatory drug; PMN: polymorphonuclear leukocyte; PPIs: proton pump inhibitors; PUD: peptic ulcer disease; RCTs: randomized clinical trials; SBP: spontaneous bacterial peritonitis; SIBO: small intestinal bacterial overgrowth; SNOMED-CT: Systematized Nomenclature of Medicine-Clinical Terms; SPSS: Statistical Package for Social Sciences

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