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Cirrhotic patients on proton pump inhibitors are at a twofold risk of spontaneous bacterial peritonitis independently of gastrointestinal bleeding: a population-based retrospective study

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Abstract

Background Recent findings suggest that cirrhotic patients on proton pump inhibitors (PPIs) are at a higher risk for developing spontaneous bacterial peritonitis (SBP) than non-PPI users. We aimed to identify whether PPI use is an independent risk factor for the development of SBP among cirrhotic patients in the United States (US).

Methods We enrolled a retrospective cohort using a validated multicenter database. Patients with a SNOMED-CT diagnosis of "cirrhosis" between 1999 and 2022 were identified. All patients below 18 years of age were excluded. We calculated the prevalence of individuals using PPIs in the total US population and in cirrhotic patients from 1999 to date, and the incidence of SBP in the past year. Finally, we constructed a multivariate regression model, controlling for multiple covariates.

Results The final analysis included 377,420 patients. The 20-year-period prevalence of SBP in patients with cirrhosis was 3.54% and the prevalence of patients using PPIs in the US population was 12,000 per 100,000 people (12.00%). The 1-year incidence of SBP in cirrhotic patients using PPIs was 2500 per 100,000 people. After accounting for confounders, the risk of SBP was higher among males, patients with a diagnosis of gastrointestinal bleeding, and those using β-blockers and PPIs.

Conclusions To date, this is the largest cohort used to examine the prevalence of SBP among cirrhotic patients in the US. PPI use and hepatic encephalopathy offered the highest risk for the development of SBP, independently of gastrointestinal bleeding. Focusing on judicious PPI use should be encouraged among cirrhotic patients.

Keywords Cirrhosis, gastrointestinal bleeding, proton pump inhibitor, spontaneous bacterial peritonitis

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Introduction

Cirrhosis is a well-known and prevalent chronic liver condition that has recently attracted interest from scientists seeking to research its economic and physical burden, as well as its mechanistic properties [1]. Liver dysfunction in cirrhosis alters the immune system's humoral and cellular components and promotes bacterial translocations, making cirrhotic patients much more susceptible to infections and subsequently to decompensation [2]. Bacterial infections are not only the most common complications seen among cirrhotic patients, but also the deadliest [3,4]. The most renowned complications seen are spontaneous bacterial peritonitis (SBP), urinary tract infections, pneumonia, and bacteremia [5]. SBP refers to the infection of the peritoneal fluid (or ascites) in the absence of an apparent source of intra-abdominal infection. SBP increases the morbidity and mortality burden associated with the disease. Cirrhotic patients with SBP are more likely to progress to sepsis, acute renal failure, gastrointestinal bleeding (GIB), and hepatic encephalopathy [4,6,7].

Conflict of Interest: None

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The 1-year mortality rate of cirrhotic patients after infections has not changed significantly over the past decades, despite the tremendous advances in diagnosis and treatment [4]. This underlines the need to find additional risk factors and implement better preventative strategies, rather than solely focusing on its treatment. Important known risk factors for SBP include upper GIB (prevented with β-blockers), previous episodes of SBP, a low concentration of ascitic protein (<1.5 g/dL), alcohol consumption, and hepatitis B and C [8,9]. Targeting these factors and looking for others remain key and cost-effective elements in controlling the disease progression.

On the same note, recent studies have suggested that patients with cirrhosis who use proton pump inhibitors (PPIs) are at a higher risk for developing SBP than non-PPI users. However, many of these results are conflicting and lack generalizability [10-20]. It is essential to tackle this subject, as PPI drugs are widely used among patient populations, particularly among cirrhotic patients [14]. In this study, we aimed to identify whether PPI use is an independent risk factor for developing SBP among cirrhotic patients in the United States (US).

Materials and methods

Database

We enrolled a retrospective cohort using a validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the US, containing data accumulated from 1999 to the present date (Explorys Inc., Cleveland, OH, USA). It was developed and has been prospectively maintained by IBM Corporation, Watson Health [21]. Explorys includes electronic health records (EHR) from more than 60 million unique patients, who have a broad regional distribution over the US and represent approximately 15% of the population. Diagnoses, findings, and procedures are arranged into the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) hierarchy [22], while prescription drug orders are mapped into SNOMED and RxNorm [23]. Explorys allows for the generation of multiple cohorts based on the presence or absence of SNOMED-CT diagnoses. Institutional Review Board approval was not required, as the source data are de-identified. To protect patient confidentiality, Explorys rounds population counts to the nearest 10 and treats all counts between 0 and 10 as equivalent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Access to the database is granted to participating healthcare systems. The use of the Explorys platform has been validated in multiple fields, including gastroenterology and endocrinology [24,25].

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Patient selection

A cohort of patients with a SNOMED-CT diagnosis of "cirrhosis" between 1999 and 2022 was identified. A subgroup of patients with a diagnosis of "spontaneous bacterial peritonitis" (SBP) was later selected and used in the analysis. All patients younger than 18 years of age were excluded from the study. The control group was identified as patients who did not have a diagnosis of SBP.

Statistical analysis

We compared patients who developed SBP to those who did not. The overall period prevalence was calculated by dividing the total number of individuals with SBP by the total number of individuals in our cohort. The prevalence of individuals using PPIs in the total US population from 1999 to date was also calculated. We divided the number of new cases of SBP by the number of patients with cirrhosis using PPIs to obtain the incidence of the disease in the past year. Chi-squared tests were used to compare proportions (Table 1). We calculated the risk of developing SBP in patients with cirrhosis using a univariate regression model. To adjust for potential confounding factors, we performed a multivariate regression model, controlling for multiple covariates including use of β-blockers, use of PPIs, male sex, Caucasian ethnicity, age greater than 65, and GIB. A 2-sided P-value <0.05 was considered statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Results

Descriptive epidemiology

A total of 69,969,210 individuals above the age of 18 years were screened in the database and 377,420 were included in the final analysis. The baseline characteristics of our cohort are displayed in Table 1. The 20-year-period prevalence rate of SBP in patients with cirrhosis was 3.54%. Age less than 65 and male sex were more common in cirrhotic patients with SBP compared to those without (62.81% and 62.32% respectively). Multiple comorbidities, including non-alcoholic steatohepatitis (10.54%), chronic hepatitis C infection (27.98%), GIB (46.35%), gastroesophageal reflux disease (44.34%), and hepatic encephalopathy (49.53%) were more common in patients with a diagnosis of SBP. The use of PPIs (77.67%) and β-blockers (62.94%) was also more common in the latter group. Hyperlipidemia was more common in those patients who did not develop SBP. The prevalence of patients using PPIs in the US population from 1999 to date was 12,000 per 100,000 people (12.00%). The 1-year incidence of SBP in cirrhotic patients using PPIs was 2500 per 100,000 people.

Table 1 Baseline characteristics of cirrhotic patients with SBP and control

Characteristics	Total	Cirrhotics with SBP (%)	Cirrhotics without SBP (%)	P-value
		n=12,900	n=364,520	
Age (years)	18-65	8103 (62.81)	177,690 (48.74)	<0.001
	>65	4760 (36.89)	185,600 (50.91)	<0.001
Gender	Male	8040 (62.32)	204,120 (55.99)	<0.001
	Female	4820 (37.36)	159,860 (43.85)	<0.001
Race	Caucasian	9280 (71.93)	258,030 (70.78)	<0.001
	African-American	1560 (12.09)	43,260 (11.86)	<0.001
	Asian	190 (1.47)	6170 (1.69)	<0.001
Comorbidities	Type 2 diabetes mellitus	5230 (40.54)	136,730 (37.50)	<0.001
	Benign hypertension	2170 (16.82)	60,450 (16.58)	<0.001
	Hyperlipidemia	4840 (37.51)	163,140 (44.75)	<0.001
	Obesity	3490 (27.05)	90,820 (24.91)	<0.001
	NASH	1360 (10.54)	23,150 (6.35)	<0.001
	Chronic hepatitis C infection	3610 (27.98)	70,080 (19.22)	<0.001
	Hemochromatosis	870 (6.74)	29,490 (8.09)	<0.001
	Primary biliary cholangitis	210 (1.62)	10,880 (2.98)	<0.001
	Primary biliary cirrhosis	660 (5.11)	21,050 (5.77)	<0.001
	Autoimmune hepatitis	390 (3.02)	7850 (2.15)	<0.001
	GERD	5720 (44.34)	143,950 (39.49)	<0.001
	Hepatic encephalopathy	6390 (49.53)	54,790 (15.03)	<0.001
	GIB	5980 (46.35)	106,510 (29.21)	<0.001
Medication	PPI use	10,020 (77.67)	204,190 (56.01)	<0.001
	β-Blocker use	8120 (62.94)	177,530 (48.70)	<0.001
Substance abuse	Alcohol	5840 (45.27)	81,350 (22.31)	<0.001
	Smoking	3240 (25.11)	76,010 (20.85)	<0.001
	Cannabis	790 (6.12)	13,230 (3.62)	<0.001

GERD, gastroesophageal reflux disease; GIB, gastrointestinal bleeding; NASH, nonalcoholic steatohepatitis; SBP, spontaneous bacterial peritonitis; PPI, proton pump inhibitor

Risk and predictors of SBP in patients with cirrhosis using univariate regression analysis

Cirrhotic patients with SBP were more likely to be male and Caucasian (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.33-1.43, and OR 1.12, 95%CI 1.07-1.16, respectively). PPIs (OR 2.48, 95%CI 2.37-2.58) and β-blockers (OR 1.65, 95%CI 1.59-1.71) were also associated with a greater risk of developing SBP. GIB also indicated a higher risk for SBP (OR 1.99, 95%CI 1.92-2.06) (Table 2).

Risk and predictors of SBP in patients with cirrhosis using multivariate regression analysis

We used a multivariate regression model in order to adjust for age greater than 65 years, male sex, Caucasian ethnicity, and use of PPIs and β-blockers. Cirrhotic patients with SBP had a higher risk of being male (OR 1.30, 95%CI 1.25-1.35), and using β-blockers (OR 1.26, 95%CI 1.21-1.31) or PPIs (OR 2.31, 95%CI 2.21-2.42) (Table 3).

To further investigate the risk of SBP in cirrhotic patients who use PPIs, we controlled for GIB in addition to controlling for the covariates used previously in the multivariate logistic regression model. The risk of SBP was higher in male patients (OR 1.30, 95%CI 1.25-1.34), patients with a diagnosis of GIB (OR 1.70, 95%CI 1.64-1.76), and those using β-blockers (OR 1.22, 95%CI 1.17-1.27) or PPIs (OR 2.13, 95%CI 2.03-2.23) (Fig. 1).

Discussion

The results of this study identified apparent clinical and demographic factors independently associated with the

Table 2 Risk of developing SBP in patients with cirrhosis using the univariate regression analysis model

Factors	SBP	
	OR (95%CI)	P-value
Age >65 years	0.61 (0.59-0.64)	<0.001
Male	1.38 (1.33-1.43)	<0.001
Caucasian	1.12 (1.07-1.16)	<0.001
PPI use	2.48 (2.37-2.58)	<0.001
β-Blocker use	1.65 (1.59-1.71)	<0.001
GIB	1.99 (1.92-2.06)	<0.001

SBP, spontaneous bacterial peritonitis; OR, odds ratio; CI, confidence interval; GIB, gastrointestinal bleeding; PPI, proton pump inhibitor

Table 3 Risk of developing SBP in patients with cirrhosis using multivariate regression analysis model before controlling for gastrointestinal bleeding

Factors	SBP	
	OR (95%CI)	P-value
Age >65 years	0.57 (0.55-0.59)	<0.001
Male	1.30 (1.25-1.35)	<0.001
Caucasian	0.96 (0.92-1.00)	<0.001
PPI use	2.31 (2.21-2.42)	<0.001
β-Blocker use	1.26 (1.21-1.31)	<0.001

SBP, spontaneous bacterial peritonitis; OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor

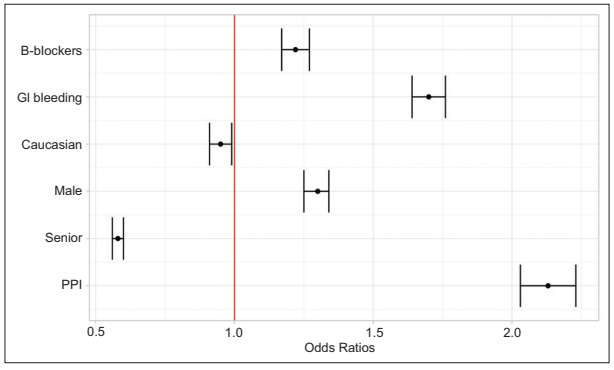

Figure 1 Forest plot for risk of spontaneous bacterial peritonitis in patients with cirrhosis using multivariate regression analysis model after controlling for GI bleeding
GI, gastrointestinal; PPI, proton pump inhibitor

development of SBP in cirrhotic patients. In particular, PPI use was associated with a significantly higher risk of progression to SBP. To our knowledge, this is the largest multicenter cohort ever to examine the association between PPI use and the development of SBP throughout the US and worldwide. The results of this study are generalizable and can be incorporated into future management guidelines for SBP patients.

Infection is a leading cause of mortality among cirrhotic patients, increasing it 4-fold [4,5]. According to a recent study by Arvaniti *et al*, the occurrence of infection, even after its resolution, is indicative of the subsequent prognosis stage and must therefore be taken into consideration when classifying cirrhosis [4]. SBP is the most frequently encountered infection in cirrhotic patients [26] and is always associated with a poor prognosis [27]. In terms of prevalence, the number varies with time and with the population in question. However, the numbers have plateaued within a range hovering around 10-30% for the past 2 decades [26,28,29], with the most recent systematic review pointing to a pooled prevalence of 17.12% [30]. The prevalence in our population-based study fits within this range (18.36%), further validating the generalizability of the results. The first episode of SBP has a survival rate of 40% [31], with a recurrence rate reaching 70% [6], accounting for 4% of emergency department visits in the cirrhotic population [30]. Acute kidney injury has been reported in about 33-50% of patients with SBP [32]. Management strategies of SBP include prophylactic and therapeutic antibiotic use, intravenous albumin infusion [33], and control of the significant risk factors.

Based on the previous literature, old age, female sex, hepatic encephalopathy, coagulopathy, and variceal bleeding are already established risk factors for SBP [34]. These risk factors were accounted for in our univariate multivariate analyses. As previously higlighted in the literature, the use of β-blockers is protective against the devlopment of SBP [35,36]. However, the results obtained from our statistical analysis were not consistent with the literature. Since we did not incoporate liver disease severity in our model, this association was probably due to the fact that patients on β-blockers already had more advanced cirrhosis than those not on the medication and thus were naturally more prone to develop SBP later on.

Documented side-effects of long-term use of PPIs include *Clostridioides difficile* infection, and nosocomial and community-acquired pneumonia [37,38]. Recently, there has been a growing body of evidence regarding the use of PPIs and its association with the development of SBP in cirrhotic patients. Going back to the physiopathology of cirrhosis and SBP, PPIs and liver dysfunction share a similar mechanism regarding immune dysfunction. Previous research has shown that PPI use can inhibit phagocytosis, impair oxidative burst and promote bacterial translocation [12,16,39-41], leading to higher risks of bacterial infections including SBP; however, clinical findings on this topic remain controversial. This not only hampers the possibility of establishing clear recommendations, but also highlights the need for larger, population-based studies to confirm this association. On the one hand, some previous studies found no association between the use of PPIs and the development of SBP [11,17,18,42,43]. However, these studies were conducted on smaller samples, defined exposures and outcomes differently, or did not consider appropriate confounders. On the other hand, an increasing number of publications have identified a positive association [40-42,44], with most of these publications displaying higher levels of evidence [20,38,45]. All these studies reported an approximate 2-fold risk of developing SBP, similar to our results. Mandorfer *et al* showed that variceal bleeding is

much more frequent among PPI users [17]. In our model, to address possible confounding bias, we accounted for GIB when comparing SBP by PPI use, and the results obtained were still significant after this adjustment (OR 1.81, 95% CI=1.72-1.90; P<0.001). Correcting for appropriate confounders strengthens the validity of our results.

Given the fact that PPIs are an over-the-counter medication [46], they are easily prescribed and dispensed, commonly used and very well marketed, especially in the US. Analyses from the database showed that 12.5% of the US population recruited over the last 20 years were on PPIs. Misuse of PPIs is particularly common in cirrhotic patients [38], with 47% taking PPIs without any formal indication [10]. The prevalence of PPI use among SBP patients was 77.86%, in line with previous results [10,17]. However, the calculated 1-year incidence of developing SBP in cirrhotic patients on PPIs was 2.5%. This is an alarmingly high number compared to the incidence of developing SBP among cirrhotic patients. A national study in Taiwan defined the 1-year incidence of SBP to be around 0.1% (124.8/100,000) [12].

In light of our findings and since the safety profile of PPIs still needs to be clearly defined, close surveillance for PPI use should be warranted in clinical practice settings. Current recommendations should lean towards limiting the prescription of PPIs unless medically indicated. This recommendation applies to the general population and to cirrhotic patients in particular, given their higher risk of decompensating to SBP.

This study had several limitations, starting with its retrospective nature. Prospective studies with prolonged patient follow up allow the establishment of a higher level of evidence. In addition, although the database used is longitudinal, our study looked at the use of PPIs as a whole, without assessing their time-sensitive nature (such as the date of initiation and duration of the course), or their cumulative effect. These limitations could affect the outcome measured and should be taken into consideration to help further understand and quantify the association between PPI use and the emergence of SBP, as clearly displayed in the study by Chang *et al* [12]. Another significant limitation is the lack of information in the database about the Child-Pugh and model for end-stage liver disease scores of the patients in the population included. Since the risk of SBP is higher in individuals with severe liver disease, it would be interesting for further prospective studies to stratify the population at risk of developing SBP according to their liver disease severity. Moreover, the database used does not offer any information regarding previous episodes of SBP, and a previous history of the latter is a significant risk factor in the development of a subsequent SBP episode. Despite all these limitations, the strength of this study lies within the database itself. This cohort is the largest to assess the association between PPI use and SBP occurrence in the US and worldwide. Since it is a population-based study, it provides comprehensive coverage of hospital admissions, and thus its results can be generalized to cirrhotic patients overall in the US. Additionally, the large sample size allowed us to better account for all possible confounders and to perform many subgroup analyses.

To date, this is the largest cohort to examine the prevalence of SBP among cirrhotic patients in the US. PPI use and hepatic encephalopathy were associated with the highest risks for developing SBP independently of GIB. The results of this study are in line with previous ones and can prepare the ground for implementing judicious PPI use in future recommendations for cirrhotic patients.

Summary Box

What is already known:

- Decompensation of liver disease is a distinct characteristic of cirrhosis
- Proton pump inhibitors (PPIs) are a widely-used class of medication, as about 50 million people in the United Stated (US) are on PPIs
- Scattered evidence in the literature suggests a potentially higher risk of spontaneous bacterial peritonitis (SBP) in cirrhotic patients on PPIs, compared to those not on PPIs

What the new findings are:

- The use of PPIs in the US is highly prevalent, reaching 12.00% in our cohort
- In the US, the incidence of SBP in patients on PPIs is 2500 per 100,000 individuals
- The use of PPIs is an independent risk factor for the development of SBP in cirrhotic patients

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