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Original Article

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Is the Use of Proton Pump Inhibitors a Predisposing Factor for Pyogenic Liver Abscesses?

Ahmed Elfiky[a, c], Mira Alsheikh[b], Jeff Hosry[a], Anum Aqsa[a], Ahmad Abou Yassine[a], Liliane Deeb[b]

Abstract

Background: Proton pump inhibitors (PPIs) increase gastric pH by reducing acid production. The resulting alkaline milieu in the stomach increases the risk of bacterial translocation. This study aimed to investigate if there is a correlation between PPI use and developing pyogenic liver abscesses.

Methods: In this retrospective case-control analysis, we studied adult patients diagnosed with cryptogenic liver abscess at Northwell hospitals between 2015 and 2019. Adult patients with the diagnosis of liver abscess were included. We excluded patients with history of liver abscess prior to admission, biliary disease, hepatobiliary malignancy, or intra-abdominal infections. A group of randomly selected patients without liver abscess from the same hospitals' database were enrolled as the control group. A multivariate logistic regression analysis was performed to adjust for potential confounding factors.

Results: We identified 277 patients diagnosed with first episode of pyogenic liver abscess. Cases were compared to 554 controls. *Klebsiella pneumonia* was the most common pathogen. PPI use was associated with an increased risk of developing a first episode of pyogenic liver abscess in univariate (odds ratio (OR): 2.36, 95% confidence interval (CI): 1.70 - 3.27), and multivariate analysis (adjusted OR: 2.27, 95% CI: 1.55 - 3.32).

Conclusion: This study is the first US population-based analysis to demonstrate that PPI use is associated with increased risk of developing pyogenic liver abscesses. Further prospective studies are needed to shed more light on this association and better evaluate the impact of dose and duration of PPI exposure.

Keywords: Proton pump inhibitors; Liver abscess; Infection

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[a]Department of Internal Medicine, Staten Island University Hospital-Northwell Health, Staten Island, NY, USA
[b]Department of Gastroenterology, Staten Island University Hospital-Northwell Health, Staten Island, NY, USA
[c]Corresponding Author: Ahmed Elfiky, Department of Internal Medicine, Staten Island University Hospital-Northwell Health, Staten Island, NY, USA. Email: aelfiky1@northwell.edu

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Introduction

In 1988, proton pump inhibitors (PPIs), a new class of drugs that control acid secretion in the stomach, were approved for medical use [1]. This discovery changed the way we treat acid-related diseases especially peptic ulcer disease and gastroesophageal reflux disease (GERD). PPIs inhibit H-K-ATPase in parietal cells resulting in impairment of gastric acid secretion. Its effectiveness and tolerability have resulted in widespread use.

PPI use has expanded over the last years given the fact that the general population has an easy access to this medicine as an over-the-counter drug that does not require physician's prescription. PPI use alters gut microbiologic flora which raises concerns over increased risk of infectious processes [2]. PPI use has been linked to increased intestinal colonization with *Klebsiella pneumoniae* and vancomycin-resistant *Enterococcus* spp. [3]. Over the years, multiple studies have suggested that the long-term use of PPI is in fact associated with increased risk for developing variant infections, e.g., community-acquired pneumonia [4], spontaneous bacterial peritonitis [5], and *Clostridium difficile* infection [6-8]. On another note, PPI use has been also linked to developing asthma [9], dementia [10], pancreatic cancer [11], and colorectal cancer [12].

Furthermore, PPI use has been investigated as a possible factor linked to increased risk for developing of cryptogenic liver abscess in patients of Asian descents [13]. Liver abscess has become an endemic disease in East Asia especially in Taiwan where *Klebsiella pneumoniae* was the leading pathogen identified [14]. By decreasing gastric acid secretion, it is hypothesized that PPI use leads to an increased prevalence and survival of various intestinal bacteria, especially the virulent strains of *Klebsiella pneumoniae*.

Our study aimed to investigate possible association between PPI use and risk of developing pyogenic liver abscesses in a United States (US)-based population at Northwell hospitals in New York City (NYC).

Materials and Methods

Study design

This was a retrospective case-control study including adult

patients diagnosed with cryptogenic liver abscess at all the Northwell hospitals in NYC between 2015 and 2019. The study was approved by IRB, and was conducted in compliance with all the applicable institutional ethical guidelines for the care, welfare and use of animals.

Inclusion criteria

Adult patients (age > 18 years old) admitted to the hospital with first episode of pyogenic liver abscess between 2015 and 2019 were identified using the International Classification of Diseases (ICD) code. Cases were matched with patients without liver abscess admitted to Northwell system hospitals in the same time period, based on gender and race, at a 1:2 ratio. We used case to control ratio of 1:2 to consider for underlying confounding factors that may have been missed in our univariate analysis.

Exclusion criteria

We excluded any subjects with prior history of liver abscess at the time of hospital admission, biliary disease, hepatobiliary malignancy, or any other intra-abdominal infections.

Exposure

Exposure was defined as use of any PPI that is available in the USA prior to hospital admission with pyogenic liver abscess. PPIs available in the USA included esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole and dexlansoprazole. In addition, we collected the dosages, frequency and indications of PPI treatment. We used the medication reconciliation list in the electronic medical records for the reference hospital admission to identify the exposure. Subjects who did not use PPI were defined as nonusers of PPI.

Statistical analysis

Categorical data were presented as frequencies and percentages while continuous data were presented as medians and interquartile ranges (IQRs). Relations between nominal categorical variables and study group (cases versus controls) were analyzed with Fisher's exact test and Chi-square test for homogeneity. We used Wilcoxon-Mann-Whitney test to compare continuous variables. A multivariate logistic regression analysis was conducted to determine the variables independently associated with an increased risk for development of pyogenic abscess.

All statistical tests were two-sided. P-values < 0.05 were considered significant. All statistical analyses were performed using SAS software (Statistical Analysis Systems Inc., Cary, NC, USA). We estimated that a total sample size of 300 cases will be required to provide 80% power to detect a risk of exposure to PPI treatment that was 10% higher in the cases than in the control group at an alpha level of 0.05. The rate of exposure to PPI treatment in the control group is assumed to be 21%.

Table 1. Demographics of Patients With Pyogenic Liver Abscesses

Variables	Cases (N = 277)
Age, median (interquartile range), years	63 (52 - 73)
Gender, n (%)	
Male	148 (53%)
Female	129 (47%)
Race, n (%)	
White	184 (66%)
African American	36 (13%)
Asian	45 (16%)
Hispanic	8 (3%)
Others	4 (1%)
BMI, n (%)	
Under weight	1 (0%)
Normal weight	99 (36%)
Over weight	97 (35%)
Obesity class 1	55 (20%)
Obesity class 2	20 (7%)
Obesity class 3	5 (2%)
Smoking, n (%)	51 (18%)
Alcohol use, n (%)	64 (23%)
IV drug use, n (%)	3 (1%)
Diabetes mellitus, n (%)	89 (32%)
Chronic kidney disease, n (%)	25 (9%)
Malignancy, n (%)	43 (16%)
Liver cirrhosis, n (%)	14 (5%)
Cerebrovascular accident, n (%)	8 (3%)
Inflammatory bowel disease, n (%)	11 (4%)
Proton pump inhibitor, n (%)	97 (35%)
Pantoprazole	59 (21%)
Esomeprazole	6 (2%)
Lansoprazole	4 (1%)
Omeprazole	28 (10%)
No proton pump inhibitor, n (%)	180 (65%)

BMI: body mass index; IV: intravenous.

Results

Our study included 277 patients with pyogenic liver abscesses and 554 control participants. Table 1 shows the baseline characteristics and demographics of the cases. Cases and controls had comparable median age (63 years (52 - 73) vs. 63 (51 -

Table 2. Comparison of Cases and Controls

	Cases (N = 277)	Controls (N = 554)	P
Age, median (IQR), years	63 (52 - 73)	63 (51 - 74)	0.733
Gender, male	148 (53%)	296 (53%)	Matched
BMI > 30	80 (29%)	154 (28%)	0.743
Race, white	184 (66%)	368 (66%)	Matched
Smoking	51 (20%)	133 (24%)	0.179
Alcohol	64 (26%)	115 (21%)	0.088
IV drug use	3 (1%)	8 (1%)	0.999
DM	89 (32%)	185 (33%)	0.715
CKD	25 (9%)	70 (13%)	0.123
Immunosuppression	7 (3%)	3 (1%)	0.019
Malignancy	43 (16%)	77 (14%)	0.414
Liver cirrhosis	14 (5%)	14 (3%)	0.057
CVA	8 (3%)	22 (4%)	0.430
CHF	18 (7%)	45 (8%)	0.404
IBD	11 (4%)	13 (3%)	0.251
PPI use	97 (35%)	103 (19%)	0.0001
Sepsis	167 (60%)	19 (3%)	0.0001
Bacteremia	85 (31%)	8 (1%)	0.0001
Mortality	7 (3%)	14 (3%)	0.999
ICU admission	34 (12%)	33 (6%)	0.002

IQR: interquartile range; BMI: body mass index; IV: intravenous; DM: diabetes mellitus; CKD: chronic kidney disease; CVA: cerebrovascular accident; CHF: congestive heart failure; IBD: inflammatory bowel disease; PPI: proton pump inhibitor; ICU: intensive care unit.

74)) and underlying comorbidities.

Table 2 shows that 35% of cases had PPI exposure at the time of the diagnosis of pyogenic liver abscess compared to 18.9% of controls (P = 0.0001). Pantoprazole was the most commonly used PPI in both cases (60.1%) and controls (43.8%). The remaining of cases used omeprazole (28.8%), esomeprazole (6.2%), and lansoprazole (4.1%). The majority of patients with cryptogenic liver abscess used PPI once a day (86.8%). The most common daily dose was 40 mg (70.5%), followed by 20 mg (16.5%), and 80 mg (13.0%). GERD was the most common indication for PPI use among the cases (60.8%).

Among the cases, 77.2% were diagnosed with single liver abscess, while 22.7% were diagnosed with multiple liver abscesses. Sixty percent of cases were diagnosed with sepsis/septic shock on admission and 30% had bacteremia. The most common test used for diagnosis of liver abscess was computed tomography (CT) scan of abdomen (86.6%). Eighty percent of the patients required surgical intervention, and 12.2% patient required intensive care admission. Seven patients died during the same hospital admission. Causative organism was isolated in 162 cases. *Klebsiella pneumonia* was the most common pathogen (27.7%), followed by *Escherichia coli* (*E. coli*) (13%), and polymicrobial (11%).

PPI use was associated with increased risk of development of liver abscess in the univariable analysis with odds ratio (OR) of 2.36 (95% confidence interval (CI): 1.70 - 3.27) and multivariate logistic regression analysis (OR 2.27 (95% CI: 1.55 - 3.32)), after adjusting for potential cofounder (Table 3).

Discussion

To the best of our knowledge, the present study is the first US-based study to demonstrate that PPI use is associated with an increased risk of developing pyogenic liver abscesses. We demonstrated that the use of PPIs was associated with a 2.27-fold increased risk of pyogenic liver abscess.

Liver abscess is more endemic in East Asia especially in Taiwan with an annual incidence of 17.6 cases per 100,000 [14]. In the USA, the estimated incidence based on a nationwide inpatient sample database approximates 3.6 cases per 100,000 population per year [15]. Predisposing factors of pyogenic liver abscess include diabetes mellitus, liver transplantation, and hepatobiliary disease [16]. PPIs are believed to alter the immune response and to decrease gastric acidity which is a major defense mechanism against bacterial pathogens accessing the intestinal lumen. Furthermore, PPIs decrease activity of natural killer cells and have been associated with decreased production of oxygen free radicals which are known for their bactericidal effects [17, 18]. Those factors may result in intestinal bacterial resistance and overgrowth

Table 3. Uni- and Multivariate Logistic Regression Model

	Univariate		Multivariate		P
	Crude OR	95% CI	Adjusted OR	95% CI	
PPI	2.36	1.70 - 3.27	2.27	1.55 - 3.32	< 0.001
Age	1.004	0.99 - 1.01			
Gender	1	0.74 - 1.33			
Race	1.01	0.87 - 1.17			
Smoking	0.78	0.54 - 1.12			
Alcohol	1.35	0.95 - 1.92	1.46	0.98 - 2.17	0.058
IV drug abuse	0.91	0.24 - 3.49			
DM	0.94	0.69 - 1.28			
CKD	0.69	0.42 - 1.10			
Malignancy	1.18	0.78 - 1.77			
Liver cirrhosis	2.05	0.96 - 4.37	1.82	0.77 - 4.31	1.168
CVA	0.71	0.31 - 1.63			
IBD	1.59	0.71 - 3.56			
Immunosuppression	4.76	1.22 - 18.55	6.63	1.5 - 28.37	0.011
Bacteremia	30.21	12.36 - 63.53	28.58	13.39 - 60.96	< 0.001

OR: odds ratio; CI: confidence interval; PPI: proton pump inhibitor; IV: intravenous; DM: diabetes mellitus; CKD: chronic kidney disease; CVA: cerebrovascular accident; IBD: inflammatory bowel disease.

in the absence of acid and adequate immune defense. This increases the risk of bacterial seeding into the enterohepatic circulation via the portal venous system and eventually results in pyogenic liver abscesses. Of note, this is the same mechanism implicated in the increased risk of developing spontaneous bacterial peritonitis in liver cirrhosis patients receiving PPI therapy [5].

The use of PPIs has been linked to increased risk for pyogenic liver abscesses especially in patients of Asian descent. In a population-based study performed in Taiwan, Lin et al demonstrated an increased risk of pyogenic liver abscess associated with the use of PPI in a dose-dependent manner [19]. In their study the authors concluded a higher risk for developing liver abscess was tied to daily PPI doses of 30 mg or more compared to lower doses. This complies with our study where majority of our cases used 40 mg daily of PPI.

Furthermore, the authors of the study concluded no difference in the risk between late users and early users (between 31 and 90 days before the date of admission with pyogenic liver abscess vs. > 90 days before the admission with this condition). While in another population-based case-control study in Taiwan that included 958 adult cases of liver abscesses, Wang et al concluded that PPI use within 90 days can increase the risk of cryptogenic liver abscess [13]. The duration of exposure to PPI needed to increase the risk of developing liver abscess varies and definite cutoff is not yet determined.

Furthermore, Bettinger et al presented a retrospective study that included 181 patients and concluded that in patients with pyogenic liver abscess, concurrent treatment with PPI at the time of admission and during the hospital stay is associated with higher 90-day mortality after adjusting for confounding factors [20]. It is noteworthy that in our study the mortality was noticed to be low (2.5%) which can be explained by the advancement of diagnostic modalities and interventional procedures which helped to mitigate unfavorable outcomes.

Pastagia et al conducted a study based at a community hospital in Queens, NCY, where 56 cases of liver abscess were identified, and 60% of patients were of Asian descent [21]. This complies with prior studies demonstrating increased risk among patients of Asian descents. Prevalence of virulent strains of *Klebsiella pneumonia* such as capsular type K1 and K2 in the intestinal tract is the proposed pathogenesis of pyogenic liver abscesses in Asian population [22]. However, it is important to state that patients of Asian descent accounted for only 16% of our patient population.

The most common isolated pathogen was *Klebsiella pneumonia* which goes with the studies performed in Asia [14]. However, we cannot prove if PPI use is associated with increased risk for certain pathogens causing liver abscess compared to other pathogens, e.g., *E. coli*.

It is noteworthy that alcohol use and liver cirrhosis are not associated with statistical increased risk of developing liver abscess in our study; however, studies have shown that alcohol intake and substantial liver fibrosis secondary to underlying liver disease have been associated with alteration of gut microbiome and bacterial biotransformation [23]. Further studies are needed to highlight the association between these changes and risk for developing pyogenic liver abscess.

In our study, use of PPI was associated with 2.36 times increased risk for developing a liver abscess. Indeed, even after excluding comorbidities, current use of PPIs remained a risk factor for pyogenic liver abscesses.

Our study has some limitations. First, due to its retrospective nature, we could not identify the duration of the exposure

to PPI prior to the diagnosis of pyogenic liver abscess. We identified the PPI use if the patient was taking PPI on daily basis at the time of the hospital admission with the diagnosis of liver abscess. Second limitation is that the case-control design of the study cannot establish causality between PPI and development of liver abscess but rather an association. Third limitation of the study is that both cases and control populations were selected from hospitalized patients which may introduce selection bias.

The strengths of the study include accurate diagnosis of pyogenic liver abscess with different imaging and interventional modalities and multiple comorbidities based on ICD-9 coding system. As well, it is a multicenter study with a relatively large sample size where appropriate statistical analysis was performed.

In conclusion, our study demonstrates that PPI use is associated with an increased risk of developing pyogenic liver abscesses amongst our patients. Further prospective studies are needed to shed more light on this association and study the impact of dosage and duration of PPI exposure on this observed finding. Meanwhile, heightened awareness of this possible adverse effect is warranted when prescribing PPIs. Abiding by practice guidelines regarding indications for their use and limiting the duration of treatment based on symptomatology as well as discussing possible adverse events with patients is the most prudent and recommended strategy for PPI use nowadays.

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Financial Disclosure

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Conflict of Interest

No competing interests.

Informed Consent

Not applicable as it is a retrospective chart review..

Author Contributions

Ahmed Elfiky and Jeff Hosry: literature review and writing manuscript; Mira Alsheikh, Anum Aqsa, and Ahmed Abu Yassine: literature review and data collection; Liliane Deeb: proofreading manuscript, final approval for submission.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

PPI: proton pump inhibitor; GERD: gastroesophageal reflux disease; ICD: International Classification of Diseases; IQR: interquartile range; SAS: Statistical Analysis Systems; BMI: body mass index; *E. coli*: *Escherichia coli*; NYC: New York City; US: United States

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