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Use of proton pump inhibitors is associated with a higher risk of pneumonia in cirrhotic patients: a systematic review and meta-analysis

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Abstract

Background Proton pump inhibitors (PPIs) are commonly prescribed for cirrhotic patients. However, the use of PPIs in these patients may increase the risk of bacterial infection. The current study aimed to investigate the risk of developing pneumonia among cirrhotic patients exposed to PPIs.

Methods A literature search was independently conducted by 2 investigators using the MEDLINE and EMBASE databases up to September 2019. To be eligible, a study had to be an observational (cohort, case-control or cross-sectional) study that included one group of cirrhotic patients with PPI use and another group of cirrhotic patients without PPI use. Effect estimates of the association between PPI use and pneumonia had to be reported. Point estimates and standard errors from each eligible study were combined together using the generic inverse variance method of DerSimonian and Laird.

Results Of 1947 articles identified from the 2 databases, 3 cohort and 5 cross-sectional studies with 40,295 participants met the eligibility criteria and were included in the meta-analysis. The pooled analysis found that cirrhotic patients with a history of PPI use had a significantly higher risk of developing pneumonia than those without PPI use, with a pooled risk ratio of 1.36 (95% confidence interval 1.00-1.85; I^2 47%).

Conclusion A significantly increased risk of pneumonia among cirrhotic patients exposed to PPIs was demonstrated in this study.

Keywords Pneumonia, proton pump inhibitors, cirrhosis, epidemiology, meta-analysis

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Introduction

Cirrhosis accounts for approximately 1 million deaths annually [1]. Common complications of liver cirrhosis include variceal bleeding, ascites, hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis (SBP) [2]. In addition, cirrhosis is associated with an increased risk and poorer prognosis of several other types of bacterial infection, such as bacteremia, enterocolitis, skin and soft tissue infection, urinary tract infection, meningitis, and infective endocarditis [3]. Cirrhosis-associated immune dysfunction is thought to be the key player in this increased risk [4].

Proton pump inhibitors (PPI) are commonly prescribed for cirrhotic patients, although studies have shown that over half of PPI use was without valid indications [5], which may lead to an unnecessary increased incidence of several complications, such as hepatic encephalopathy, *Clostridium difficile* infection and SBP [6]. The possible explanation for the increased likelihood of developing SBP among PPI users is that acid suppression facilitates bacterial overgrowth and translocation [7-9]. The use of PPI may also lead to an increased risk of other types of organ-specific bacterial infection. In fact, studies have suggested an increased risk of bacterial pneumonia among cirrhotic patients who use PPIs, although the results are inconsistent [10-17]. The current study aimed to further investigate this risk by identifying all available studies and summarizing their results together.

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Conflict of Interest: None

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Materials and methods

Information sources and search strategy

A systematic literature review based on the EMBASE and MEDLINE databases was performed independently by 2 investigators (WW and NC) from inception to September 2019 to identify all published studies that examined the risk or association between pneumonia and PPI use in cirrhotic patients. The search strategy, which included the terms "proton pump inhibitors" and "cirrhosis", is available as Supplementary Table 1. In addition, we manually reviewed the references of the eligible studies to identify any additional potential articles. This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Table 2).

Selection criteria

To be eligible, a study had to be an observational study (cohort, case-control or cross-sectional study) that included one group of cirrhotic patients with PPI use and another group of cirrhotic patients without PPI use.

- Eligible cohort studies started with recruitment of cirrhotic patients who used and did not use PPIs and followed them for incident pneumonia. Relative risk (RR), incidence rate ratio (IRR), hazard risk ratio (HR) or standardized incidence ratio (SIR) with associated 95% confidence interval (CI) comparing the incidence of pneumonia between cirrhotic patients with and without PPI use had to be provided.
- Eligible case-control studies started with recruitment of cases of cirrhotic patients with pneumonia and controls who were cirrhotic patients without pneumonia and explored their history of PPI use. Odds ratio (OR) with associated 95%CI comparing the prevalence of PPI use between cases versus controls had to be reported.
- Eligible cross-sectional studies recruited cirrhotic patients and explored the history of PPI use and pneumonia at the same time. OR with associated 95%CI of this association had to be reported. No language limitation was applied during the systematic review.

Data extraction

We used a standardized data collection form to extract the following information: last name of the first author, country where the study was conducted, study design, year of publication, number of participants, recruitment of participants, how the diagnosis of pneumonia and ascertainment of PPI use were justified, follow-up period and duration (for cohort studies), baseline characteristics of participants, confounders adjusted in multivariate analysis and adjusted effect estimates with corresponding 95%CI. We appraised the quality of the included cohort and case-control studies using the Newcastle-Ottawa quality assessment scale [18]. The modified version of this scale was used for cross-sectional studies.

Statistical analysis

We utilized Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom) to analyze all data. Point estimates and standard errors from each study were pooled together using the generic inverse variance method of DerSimonian and Laird, which assigns the weight of the study in reverse to its variance [19]. A random-effect model, rather than a fixed-effect model, was used, as the assumption of the fixed-effect model that every study should give rise to the same result is not justified under almost all circumstances, especially in a meta-analysis of observational studies. Statistical heterogeneity was assessed by Cochran's Q test, complimented by the I^2 statistic. This I^2 statistic quantifies the proportion of total variation across studies due to heterogeneity rather than chance. A value of I^2 of 0-25% represents insignificant heterogeneity, 26-50% represents low heterogeneity, 51-75% represents moderate heterogeneity, and 76% or higher represents high heterogeneity [20]. The presence of publication bias was assessed by visualization of a funnel plot along with Egger's regression test. Egger's regression test was conducted using Comprehensive Meta-analysis 3.0 software (Englewood, New Jersey, United States).

Results

A total of 1947 articles (276 from MEDLINE and 1671 from EMBASE) were identified, from which 237 duplicated articles were removed, leaving 1710 articles for title and abstract review. At this stage of review, 1675 articles were excluded because they were clearly ineligible based on study design and type of article. Therefore, 35 full-length articles were thoroughly reviewed, and 27 articles were further excluded as they did not report the outcome of interest. Finally, 3 cohort and 5 cross-sectional studies with a total of 40,295 participants met the eligibility criteria and were included in the meta-analysis [10-17]. Two of the 3 included cohort studies were published as conference abstracts [10,14]. No eligible case-control study was identified. Fig. 1 summarizes the literature review and study selection process. Tables 1 and 2 describe the characteristics and Newcastle-Ottawa assessment scales of the included cross-sectional and cohort studies, respectively.

Risk of pneumonia among cirrhotic patients exposed to PPI

Cirrhotic patients with a history of PPI use had a significantly higher risk of developing pneumonia than those without PPI use, with a pooled RR of 1.36 (95%CI 1.00-1.85). The statistical heterogeneity was low, with an I^2 of 47%.

Subgroup analysis by study design showed an increased risk in both cohort and cross-sectional study subgroups, although the number of included studies was not large enough to demonstrate statistical significance (pooled RR 1.26, 95%CI 0.80-1.99, I^2 57%, for cohort studies; pooled RR 1.49, 95%CI

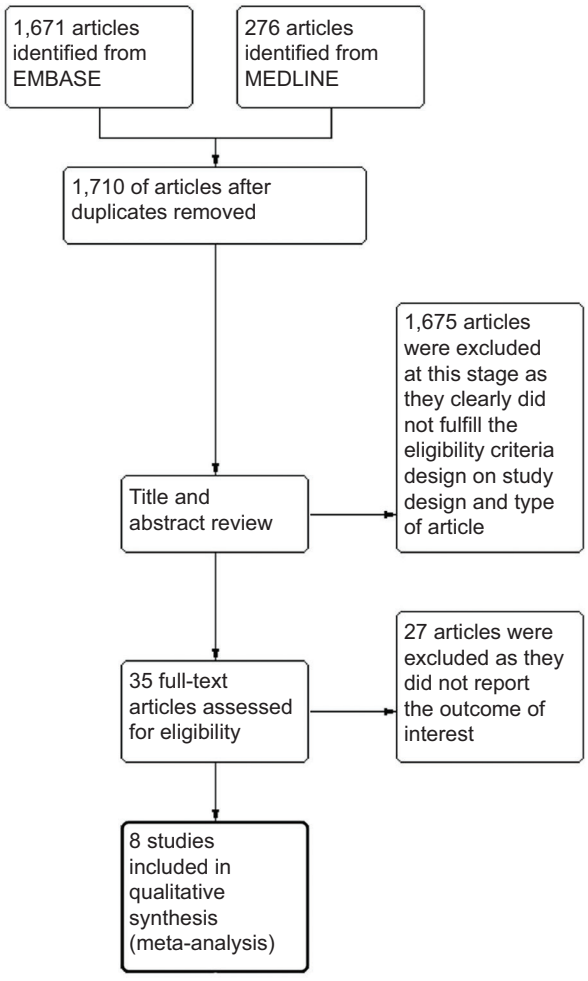

Figure 1 Literature review and study selection process

0.98-2.26, I^2 22%, for cross-sectional studies). Fig. 2 shows the forest plot of this meta-analysis.

Evaluation for publication bias

The funnel plot of this meta-analysis (Fig. 3) was fairly asymmetric. In addition, publication bias was detected by Egger's regression test with a P-value of 0.003.

Discussion

The current study is the first systematic review and meta-analysis to comprehensively identify all observational studies that evaluated the risk of pneumonia associated with PPI use among patients with cirrhosis. The pooled analysis from over 40,000 patients found an approximately 1.4-fold higher risk of pneumonia among cirrhotic patients with exposure to PPI. An increased risk of pneumonia among PPI-users has also been observed in the general population, as demonstrated by a recent meta-analysis [21]. In fact, the magnitude of the increased risk in the general population studies, 1.49-fold, is comparable to this study. The mechanisms accounting for the increased risk of pneumonia have not been clearly elucidated, but there are several possible explanations.

The first possible mechanism is that PPI use decreases gastric acidity, thus facilitating the proliferation of *Streptococcus* spp. and *Lactobacillus* spp. in the stomach [22]. Aspiration of colonized gastric fluid may have a higher tendency to cause pneumonia than aspiration of relatively sterile gastric fluid [23]. In fact, a study by Viasus *et al* identified an increased proportion of *Streptococcus pneumoniae* as a causative

Table 1 Main characteristics of the cross-sectional studies included in this meta-analysis

Characteristics	Merli *et al* [16]	Terg *et al* [17]	Elzouki *et al* [12]
Country	Italy	Argentina	Qatar
Study design	Cross-sectional study	Cross-sectional study	Cross-sectional study
Year of publication	2015	2015	2018
Number of participants	167 (127 PPI users and 40 non-users)	521 (226 PPI users and 295 non-users)	333 (171 PPI users and 162 non-users)
Recruitment of participants	Participants were consecutive cirrhotic patients admitted to the Sapienza University of Rome, Italy from October 2008 to January 2013 Patients with HIV infection, high-dose corticosteroid treatment, immunosuppressive therapy, hepatocellular carcinoma or systemic antibiotic therapy in the last 4 weeks were excluded	Participants were consecutive cirrhotic patients admitted to one of 23 hospitals in Argentina from March 2011 to April 2012 Patients with active gastroduodenal bleeding, antibiotic treatment in the previous 2 weeks, including quinolone or rifaximin prophylaxis, HIV infection and immunosuppressive therapy were excluded	Participants were consecutive cirrhotic patients admitted to Hamad General Hospital from 2007 to 2012 Patients with active gastroduodenal bleeding, disseminated malignancies, antibiotic treatment in the previous 2 weeks, immunosuppressive therapy prior to hospitalization were excluded
Ascertainment of PPI use	History of PPI use was ascertained from direct interview by the investigators	History of PPI use was ascertained from direct interview by the investigators	History of PPI use was ascertained from medical record review

(Contd...)

Table 1 *(Continued)*

Characteristics	Merli *et al* [16]	Terg *et al* [17]	Elzouki *et al* [12]
Definition of PPI users and non-users	PPI users were patients who had used PPI daily for at least 4 weeks prior to admission Those who did not meet the criteria were considered non-users	PPI users were patients with any PPI use in the 3 months prior to hospitalization	PPI users were patients with any PPI use in the 3 months prior to hospitalization
Diagnosis of pneumonia	Diagnosis of pneumonia was made based on standard criteria. Pneumonia was actively sought out throughout the hospital stay	Diagnosis of pneumonia was made based on standard criteria	New pulmonary infiltration in the presence of a) at least 1 respiratory symptom (cough, sputum production, dyspnea, pleuritic chest pain) with b) at least 1 finding on auscultation (rales or crepitation) or signs of infection
MELD score	PPI users: 12.5 Non-users: 13.1	PPI users: 19.2 Non-users: 19.0	PPI users: N/A Non-users: N/A
Child-Pugh score	PPI users: 7.7 Non-users: 8.2	PPI users: 11.2 Non-users: 10.5	PPI users Child–Pugh A: 37.4% Child–Pugh B: 38% Child–Pugh C: 24.6% Non-users Child–Pugh A: 43.8% Child–Pugh B: 34.6% Child–Pugh C: 21.6%
Percentage of male	PPI users: 29.4 Non-users: 69.5	PPI users: 63.6% Non-users: 75.3%	PPI users: 73.7% Non-users: 82.7%
Comorbidities	PPI users Diabetes mellitus: 32.7% Renal failure: 11.5% Non-users Diabetes mellitus: 27.5% Renal failure: 5.3%	PPI users Active alcohol consumption: 53.7% Non-users Active alcohol consumption: 51.1%	PPI users Smoker: 32.2% Diabetes mellitus: 55% Hypertension: 38.6% Chronic kidney disease: 5.3% Non-users Smoker: 29.6% Diabetes mellitus: 36.4% Hypertension: 21.6% Chronic kidney disease: 1.9%
Confounder adjusted in multivariate analysis	None	None	None
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 0 Outcome: 3	Selection: 5 Comparability: 0 Outcome: 3	Selection: 4 Comparability: 0 Outcome: 3

Characteristics	Joao *et al* [14]	Fasullo *et al* [13]
Country	Portugal	United States
Study design	Cross-sectional study	Cross-sectional study
Year of publication	2019	2019
Number of participants	396 (183 PPI users and 213 non-users)	103 (75 PPI users and 28 non-users)
Recruitment of participants	Participants were consecutive cirrhotic patients admitted to the study hospital from January 2015 to June 2018	Participants were consecutive cirrhotic patients admitted with hepatic encephalopathy to the University of Massachusetts Memorial Medical Center from January 2013 to December 2016 Patients with pregnancy and HIV were excluded
MELD score	MELD-Na score PPI users: 18 Non-users: 17	PPI users: 19.7 Non-users: 20.3

(Contd...)

Table 1 *(Continued)*

Child-Pugh score	PPI users Child–Pugh B: 54.6% Non-users Child–Pugh B: 45.5%	N/A
Average age of participants (years)	PPI users: 69.0 Non-users: 66.0	PPI users: 59.6 Non-users: 55.3
Percentage of male	PPI users: 69.4 Non-users: 75.6	PPI users: 63.5% Non-users: 47.2%
Comorbidities	N/A	N/A
Ascertainment of PPI use	History of PPI use was ascertained from medical record review	History of PPI use was ascertained from medical record review
Definition of PPI users and non-users	N/A	PPI users were patients on PPI for a minimum of 30 days prior to hospitalization
Diagnosis of pneumonia	N/A	History of pneumonia was ascertained from medical record review by the attending clinician
Confounder adjusted in multivariate analysis	N/A	N/A
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 0 Outcome: 3

HIV, human immunodeficiency virus; MELD, model for end-stage liver disease; N/A, not available; PPI, proton pump inhibitors

Table 2 Main characteristics of the cohort studies included in the meta-analysis

Characteristics	Bang *et al* [10]	Lazaro-Pacheco *et al* [15]	Dam *et al* [11]
Country	Denmark	Mexico	Canada, Denmark, France, Germany, Italy and Spain
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort
Year of publication	2017	2018	2019
Total number of participants	PPI users: 18,732 Non-users: 18,732	PPI users: 69 Non-users: 44	PPI users at inclusion: 524 Non-users at inclusion: 674
Recruitment of participants	Cirrhotic patients who were PPI users and non-users were identified from the Danish Registry from 1995 to 2014 PPI users and non-users were matched in a 1:1 ratio using propensity score	Cirrhotic patients who were PPI users and non-users were identified from the database of the Liver Clinic in a tertiary health-care center in Mexico Patients with diagnosis of hepatocellular carcinoma, concomitant comorbidities such as diabetes, chronic renal disease, with active alcohol intake during follow-up period and human immunodeficiency virus infection were excluded	Cirrhotic patients who were PPI users and non-users were identified from the databases of the 3 satavaptan randomized-controlled trials conducted in 2006-2008. These trials included only patients with ascites Patients with a functioning trans-jugular intrahepatic portosystemic shunt, hepatocellular carcinoma, variceal bleeding or spontaneous bacterial peritonitis in the 10 days before randomization were excluded
Ascertainment of PPI use	History of PPI use was ascertained from pharmacy database of the registry	History of PPI use was ascertained from medical records of the clinic	History of PPI use was ascertained from the databases of the trials The history was prospectively recorded by investigators of the trials in every visit

(Contd...)

Table 2 *(Continued)*

Definition of PPI user and non-user	PPI users were defined as patients with at least 2 prescriptions for PPI in the database PPI non-users were defined as patients who had no prescription for PPI in the database	PPI users were defined as patients who had history of taking PPI, at least for 1 year, for the last year, and at least 3 times per week, and in a minimum dose of 20 mg/day PPI non-users were defined as patients who had no history of taking PPI	A patient contributed follow-up time to the "PPI user" group when he/she was using PPI and to the "PPI nonuser group" when he/she was not
Diagnosis of pneumonia	Presence of ICD-10 codes for bacterial pneumonia (J15, J17 and J18) in the registry	Diagnosis of bacterial pneumonia was ascertained from medical records of clinic plus confirmation by bacterial culture	Diagnosis of bacterial pneumonia was ascertained from the databases of the trails The diagnosis was made by attending clinicians and was prospectively recorded by investigators of the trials in every visit
Follow up	N/A	Medical records were reviewed for 3 years after index date (PPI users: date start taking PPI; Non users: date of diagnosis of cirrhosis)	Patients were followed up every 4 weeks until completion of study (52 weeks), premature satavaptan treatment cessation or death.
Follow-up duration (years)	N/A	3.0	1.0
MELD score	N/A	N/A	PPI users: 15 Non-users: 14
Child-Pugh score	N/A	PPI users Child–Pugh A: 59.4% Child–Pugh B: 37.7% Child–Pugh C: 31.9% Non-users Child–Pugh A: 56.8% Child–Pugh B: 31.8% Child–Pugh C: 11.4%	N/A
Average age of participants (years	Overall: 55.0	PPI users: 62.6 Non-users: 61.7	PPI users at inclusion: 58.0 Non-users at inclusion: 57.0
Percentage of male	Overall: 70.0%	PPI users: 40.9% Non-users: 43.5%	PPI users at inclusion: 69.7% Non-users at inclusion: 69.6%
Variables adjusted in multivariate analysis	None	None	Age, sex, cirrhosis etiology and cirrhosis severity
Newcastle-Ottawa score	Selection: 4 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3

ICD; International classification of diseases; MELD, model for end-stage liver disease; N/A, not available; PPI, proton pump inhibitors

organism of community-acquired pneumonia in patients with cirrhosis compared with the general population [24].

The second possible mechanism is related to intestinal bacterial overgrowth and translocation. PPIs, as acid suppressors, are known to induce intestinal dysbiosis and subsequent development of small intestinal bacterial overgrowth [25-27]. The complication of small intestinal bacterial overgrowth is more problematic among patients with cirrhosis than in healthy individuals, as they tend to have some degree of immunodeficiency through several mechanisms, including loss of Kupffer in the hepatic reticuloendothelial system, imbalance of cytokines causing immune cell dysfunction, and decreased hepatic synthesis of complements and acute phase reactants [4,11,28,29]. In addition, a significant portion of patients with cirrhosis develop portal hypertension with portal-system shunting that would bypass the normal process of hepatic bacterial clearance [4]. All of these factors may predispose cirrhotic patients to a higher likelihood of intestinal bacterial translocation and bacteremia that would ultimately lead to organ-specific infection, including pneumonia.

The current study has some limitations that should be acknowledged. First, publication bias was present in this systematic review and meta-analysis, as evidenced by the asymmetric funnel plot and positive Egger's regression test. Second, more than half of the studies included were cross-

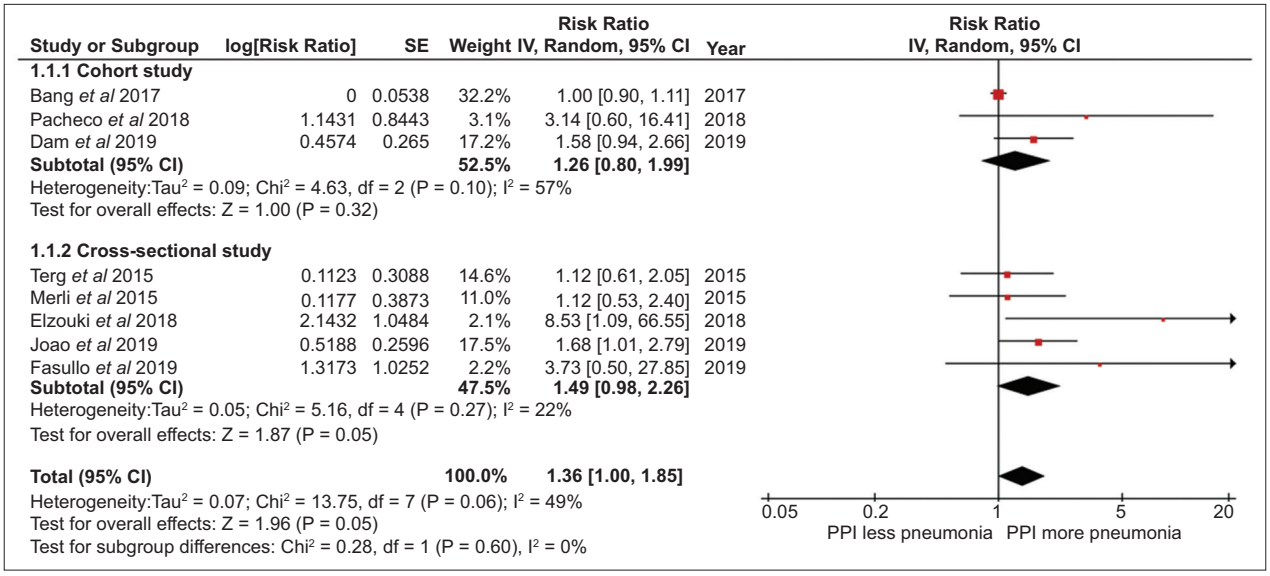

Figure 2 Forest plot of this meta-analysis

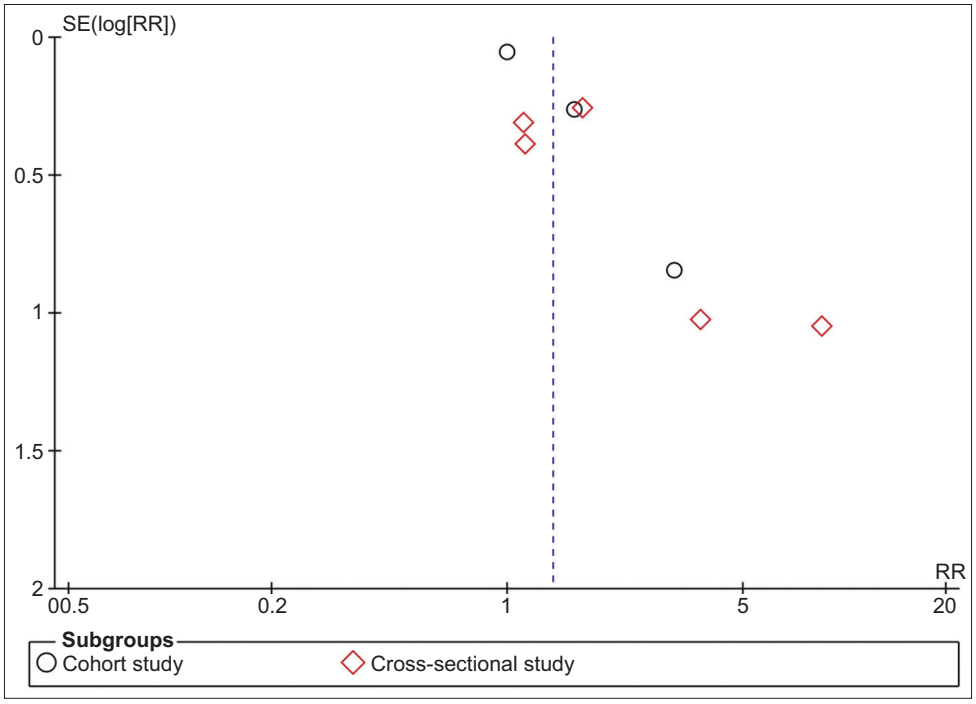

Figure 3 Funnel plot of this meta-analysis

sectional in nature. Therefore, the causality of the observed association cannot be reliably established. Third, the majority of studies included in this meta-analysis did not adjust their results for potential confounders. Therefore, the observed association could be a result of a confounding effect rather than a true association. Fourth, none of the included studies specifically aimed to investigate the relationship between PPI use and the occurrence of pneumonia. Their primary objective was to investigate the relationship between PPI use and the occurrence of either SBP or overall infection. Therefore, the number of patients with pneumonia was relatively small. Finally, the dosing of PPIs varied considerably across the included studies, especially among cross-sectional studies.

In conclusion, the present systematic review and meta-analysis demonstrated a significantly increased risk of pneumonia among cirrhotic patients with PPI use, although some limitations that may jeopardize the validity of the results were noted.

Summary Box

What is already known:

- Proton pump inhibitors (PPIs) are commonly prescribed for cirrhotic patients
- However, over half of PPI regimens are prescribed without valid indications
- This increases the risk of several complications, such as hepatic encephalopathy, *Clostridium difficile* infection and spontaneous bacterial peritonitis

What the new findings are:

- The pooled analysis found that cirrhotic patients with a history of PPI use had a significantly higher risk of developing pneumonia than those without PPI use
- Based on the pooled analysis of 8 eligible studies, the risk was increased by 1.36 times
- Possible mechanisms included decreased gastric acidity and intestinal bacterial overgrowth

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Supplementary Tables

Supplementary Table 1 Search strategy

EMBASE
1. 'proton pump inhibitor'/exp OR 'proton pump inhibitor'
2. 'proton pump antagonist'
3. 'lansoprazole'/exp OR 'lansoprazole'
4. 'dexlansoprazole'/exp OR 'dexlansoprazole'
5. 'omeprazole'/exp OR 'omeprazole'
6. 'esomeprazole'/exp OR 'esomeprazole'
7. 'pantoprazole'/exp OR 'pantoprazole'
8. 'rabeprazole'/exp OR 'rabeprazole'
9. 'dexrabeprazole'/exp OR dexrabeprazole
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. 'liver cirrhosis'/exp OR 'liver cirrhosis'
12. 'cirrhosis'/exp OR cirrhosis
13. cirrhotic
14. 'chronic liver disease'/exp OR 'chronic liver disease'
15. 'chronic hepatitis'/exp OR 'chronic hepatitis'
16. #11 OR #12 OR #13 OR #14 OR #15
17. #10 AND #16
MEDLINE
1. proton pump inhibitors.mp. or exp Proton Pump Inhibitors/
2. proton pump antagonist.mp.
3. lansoprazole.mp. or exp Lansoprazole/
4. dexlansoprazole.mp. or exp Dexlansoprazole/
5. omeprazole.mp. or exp Omeprazole/
6. esomeprazole.mp. or exp Esomeprazole/
7. pantoprazole.mp. or exp Pantoprazole/
8. rabeprazole.mp. or exp Rabeprazole/
9. dexrabeprazole.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. cirrhosis.mp.
12. exp Liver Cirrhosis/ or cirrhotic.mp.
13. chronic liver disease.mp.
14. chronic hepatitis.mp. or exp Hepatitis, Chronic/
15. 11 or 12 or 13 or 14
16. 10 and 15

Supplementary Table 2 PRISMA 2009 Checklist

Section/topic		Cheacklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4 and Supplementary Table 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 and Supplementary Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Table 1and 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Figure 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Study characteristics	48	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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