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Original Article

The use of PPI is associated with spontaneous bacterial peritonitis in cirrhotic patients of different ethnic groups: a meta-analysis

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Abstract: Background: Spontaneous bacterial peritonitis (SBP) is one of the most serious complications of cirrhotic patients. A few studies have shown that use of proton pump inhibitors (PPI) may increase the risk of occurrence of SBP in cirrhotic patients. However, controversial results have been obtained in the last decades. Therefore, the purpose of our analysis was to investigate the relationship between the risk of development of Spontaneous bacterial peritonitis (SBP) and the administration of proton pump inhibitors (PPI) in cirrhotic patients. Methods: Observational studies, about the relationship between PPI therapy and SBP in cirrhotic patients, were searched in PubMed, Medline, Embase, Web of Knowledge and other databases, and retrieval time ended in Jun 2015. Data from the identified studies were evaluated by odds ratios (ORs) and 95% confidence interval (CI) using traditional meta-analytic techniques. Results: Eleven studies (n = 4567 patients) met the inclusion criteria. The results showed that the risk of development of SBP significantly increased (OR = 2.04, 95% CI 1.56-2.69, $P < 0.00001$) in cirrhotic patients with PPI. The fixed effect model was used because of low heterogeneity, $P < 0.1$ and $I^2 = 44\%$. Subgroup analysis was performed in different study regions. The risk of developing SBP in cirrhotic patients with PPI treatment was significantly increased (OR = 2.22, 95% CI 1.72-2.87, $P < 0.0001$; OR = 1.70, 95% CI 0.70-4.13, $P = 0.24$; OR = 1.99, 95% CI 1.19-3.32, $P = 0.009$) in Asian, European, and American patients. Moderate heterogeneity existed in Euro-American patients. Conclusion: There was a significant correlation between the development of SBP and the use of PPI in cirrhotic patients. Therefore, clinicians should be aware of the indications of PPI, and use PPI cautiously in these patients. Further research need to clarify the correlation between the type, dose and course of treatment of PPI and the development of SBP in cirrhotic patients.

Keywords: Proton pump inhibitors, spontaneous bacterial peritonitis, meta-analysis, cirrhotic patients

Introduction

Cirrhosis is a chronic liver disease characterized with chronic liver damage, chronic liver tissue fibrosis, pseudolobule, and regenerative nodule. The main performances are hepatic functional lesion and portal hypertension. It may occur in patients with advanced gastrointestinal bleeding, hepatic encephalopathy, liver cancer and other serious complications. In order to prevent and treat the complications, such as gastrointestinal symptoms and bleeding, clinicians generally use antacids for therapy.

Among the complications occurred in cirrhotic patients, spontaneous bacterial peritonitis is one of the most serious complications with high morbidity and mortality, but it is reversible [1]. The incidence of SBP caused by bacterial infections in cirrhotic patients is 10-30%. Although the pathogenesis of SBP is not clear, studies have shown overgrowth and colonization of gastrointestinal bacterial in cirrhotic patients induced by intestinal activity reduction, intestinal permeability enhancement and application of acid inhibitor drugs [2-4]. The portal hypertension or intestinal edema in patients is liable to result in the invasion of bacteria into mesenteric lymph node and the overgrowth of bacteria beyond the lymph nodes defense into blood system. In addition, insufficient immunologically active molecules including immunoglobulins and complements in the peritoneal leakage fluid lead to the penetration of bacteria in abdominal cavity from the gut

breed and induce the occurrence of spontaneous bacterial peritonitis. The incidence rate of bacterial overgrowth and intestinal dysfunction in SBP patients group was higher than that in non-SBP patients group [5].

Proton pump inhibitor (PPI) is the most widely used antacids and its plays inhibition of gastric acid secretion by blocking parietal cells H^+/K^+-ATP enzyme. It is widely used in peptic ulcer, gastroesophageal reflux or non-ulcer dyspepsia patients [6]. However, more and more evidences about PPI have implied a relationship between the application of PPI and the potential risk of adverse reactions such as hip fracture, damaged about the peristalsis of the stomach, interference the function of neutrophils, intestinal infections, community-acquired pneumonia and SBP [7]. Gastric acid can purify stomach and proximal small intestine, and play an important role in resisting the intestinal pathogens. However, the changes of gastric pH induced by antacids may damage the gastric protective barrier; alter the normal flora of the gastrointestinal pathogens and aggregate pathogenic bacteria, which increases the risk of infection such as pneumonia and diarrhea caused by *Clostridium difficile* and salmonella [8, 9].

A few studies have shown the risk of the SBP occurrence after PPI therapy in cirrhotic patients and the relationship has been assessed in a small sample [3, 4, 10-12]. However, controversial results have been obtained in the last decades. While Goel *et al.* reported that PPIs were found to increase the incidence of SBP in cirrhotic patients significantly [10], Terg R*et al.* and Campbell *et al.* reported that the use of PPI did not affect the incidence of SBP [11, 13]. A few studies assessed the relationship between the risk development of SBP and PPI therapy by meta-analysis, but these studies did not touch on different ethnic groups, nor included the results of the recent two years [14, 15]. Therefore, we further analyzed the relationship between the risk of development of SBP and PPI treatment in cirrhotic patients as well as the differences among different ethnic patients by meta-analysis based on the latest literatures in this study.

Methods

The method of the meta-analysis used in this study was the same as those in observational studies in epidemiology [16].

Data sources and searches

Two researchers independently and systematically retrieved documents using the following inclusion criteria: (1) observational studies, including case-control studies and cohort studies evaluated/associated with the risks of SBP in patients treated with antacids; (2) adult patients over 18 years; (3) patients with peritonitis (defined as ≥ 250 polymorphonuclear leukocytes in the ascitic fluid); (4) Studies based on hospital. Exclusion criteria: (1) the original document did not set the control group; (2) Data (the type of treatment and patients taking the drugs) for treatment with PPIs were not available or cannot be extracted; (3) The data used was not based on actual patients.

The following databases were searched: Medline (1966 to Jun 2015), PubMed (-Jun 2015), Embase (1990 to Jun 2015), Web of Knowledge (-Jun 2015), and all published documents about PPIs associated with peritonitis in English were collected. Search terms included proton pump inhibitors, cirrhosis, spontaneous bacterial peritonitis, acid suppression therapy, omeprazole, pantoprazole, lansoprazole, esomeprazole and rabeprazole.

Study selection

The observational studies included in this meta-analysis article should comply with the following criteria: (1) researches or reports about the relationship between exposure of PPI and the risk of SBP; (2) Observational studies about case-control studies or cohort studies were selected; (3) PPI therapy group was test group or placebo group; (4) SBP diagnosis was clear; (5) Literature provided data integrity, the total number of patients samples and sampling PPI, OR values, etc. were recorded clearly; (6) The factors included in the studies were not affected by publications; (7) When several literatures had the same or overlapping data, we selected the literature with the largest amount of data or the latest published literature.

Literatures met with the inclusion criteria should be evaluated by two independent researchers. Any dispute needs to be discussed and decided by the third investigator.

Data extraction and quality assessment

Two investigators independently extracted data from the literature included in the study, includ-

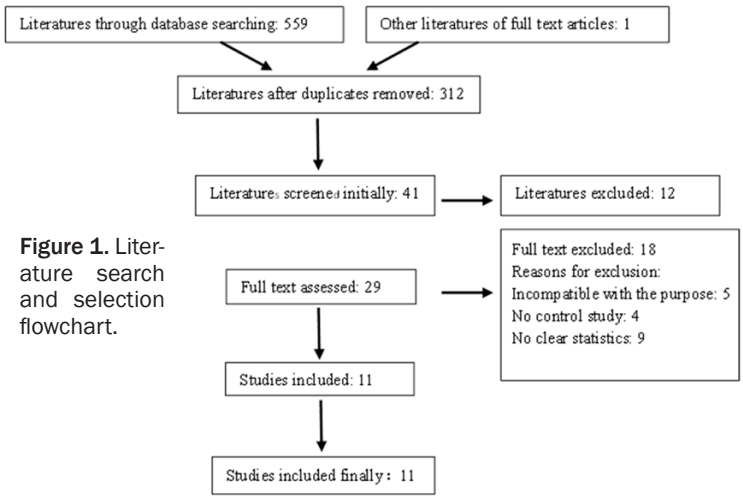

Figure 1. Literature search and selection flowchart.

ing study design, study population, the basic characteristics of the patients, SBP diagnostic methods, quality evaluation criteria and the main results of the obtain the contents. Any objections or deviations need consult with the third party. When data was incomplete, the supplement was attempted by phone or e-mail to contact with authors.

Quality assessment

Two researchers evaluated the quality of included studies according to Newcastle-Ottawa scale (NOS) quality score sheet independently. NOS quality score sheet used two different criteria according to case-control studies or cohort studies. This scoring system consisted of three mainly quality parameters: research object selection, comparability between groups, and the results or exposure factors measurement.

NOS evaluation criteria of case-control studies included 4 items: (1) research object selection: cases to determine whether appropriate, representation of the cases, the choice of control, the determination of control, a total of four items and each item's score was 1; (2) comparability between groups: when the most important confounding factors were controlled, the score was 1; when any other confounding factors were controlled, the score was 1; (3) Exposure measurement included 3 items: the determination of exposure factors, the determination of exposure factors of case group and control group, invalid response. Each item's score was 1.

NOS evaluation criteria of cohort studies: (1) research object selection: the exposed group representatives, non-exposed group representatives, exposure determining factor, and certainly no research outcomes to be observed starting fashion. There were four items in total, and each item was 1 score. (2) Comparability between groups: when the most important confounding factors were controlled, the score was 1; when any other confounding factors were controlled, the score was 1. (3) Outcome measurement included 3 items: to evaluate the outcome indictors, the follow-up time long enough, to expose group and the unexposed group completeness of follow-up. Each item's score was 1.

The study with score 7 points or more was high-quality research, 5-7 point as medium quality, 5 points or less as low quality. Any error was processed by the joint assessment of the original documents.

The funnel plot was drawn to assess the publication bias by two independent investigators, who discussed, and resolved when encountering inconsistent results.

Data synthesis and analysis

Statistical analysis was performed for selected literatures according to the recommended guidelines of epidemiological meta-analysis method [16]. RevMan5.3 software was used during statistical analysis. The heterogeneity was judged by the following criteria: $P > 0.1$ indicated no significant heterogeneity between studies; $P \leq 0.1$ indicated the presence of heterogeneity between studies. $I^2 \leq 25\%$ was believed no heterogeneity, $25\% < I^2 \leq 50\%$ was thought that there was low heterogeneity, $50\% < I^2 \leq 75\%$ was thought that there was moderate heterogeneity, $I^2 > 75\%$ was thought that there was high heterogeneity [17]. Random effects model was suitable for all meta-analysis used. When $I^2 \leq 25\%$ in heterogeneity was detected, the fixed effects model was used; When $I^2 > 25\%$, random effects model was

Table 1. General characteristics of included studies

Study reference (year)	Study location	Sample size (n)	Age (year)/Mean (SD)	Male/n (%)	Study design
Choi EJ (2011 [21])	Korea	176	55.5 (10.7)	138 (78.4)	CC
Campbell MS (2008 [11])	USA	116	54.6 (10.8)	78 (67.2)	CC
Bajaj JS (2009 [4])	USA	140	54.5 (13.0)	79 (56.4)	CC
Miura K (2014 [22])	Japan	65	66.1 (9.2)	44 (67.7)	CC
Goel GA (2012 [10])	USA	130	57.6 (11.1)	83 (63.9)	CC
Kwon JH (2014 [23])	Korea	1140	62.4 (10.0)	859 (75.4)	CC
de Vos M (2013 [24])	Belgium	102	58.4	70 (68.6)	CC
Min YW (2014 [25])	Korea	1554	57.9 (10.1)	1151 (68.3)	PC
Terg R (2015 [13])	Argentina	384	57 (12.0)	265 (69.0)	PC
Ratelle M (2014 [26])	Canada	153	60.6 (15.1)	114 (74.5)	CC
Mandorfer M (2014 [27])	Austria	607	57.5 (11.8)	426 (70)	CC

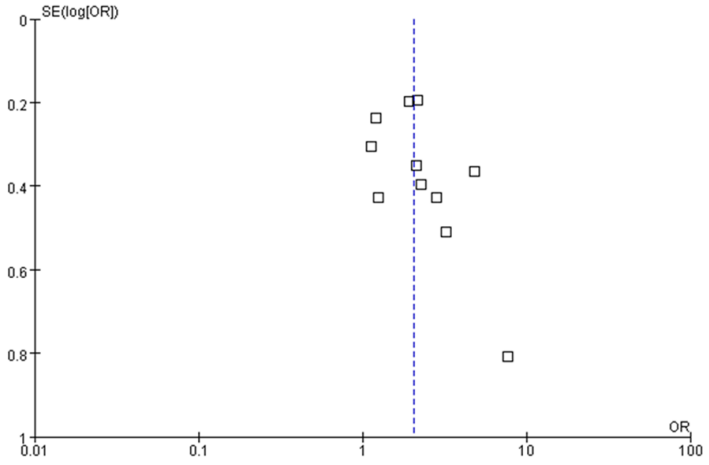

Figure 2. Funnel plot to assess publication bias.

used. Relative risk (OR) and 95% CI could be used for categorical data. When the heterogeneity could not be ascertained between the studies, the values of *P* and I^2 were in cutoff level, the reliability of the findings could be detected by fixed effect model and random effect model at the same time.

Assessment of risk of bias

We confirmed acid suppression therapy, the development of SBP, and other confounding factors on the occurrence of SBP in exposed group following the approach recommended by Cochrane Adverse Effects Methods Group and considered the population participated [18]. The literature was monitored for publication bias using funnel plot analysis to observe the symmetry and find out whether there was a publication bias. When a bias existed, the selection of the sensitivity analysis method was selected to recalculate the results of the effect of such document size [19, 20].

Results

Study characteristics

We searched PubMed, Medline, Embase, Web of Knowledge and other databases, and manually retrieved 559 documents, initially. By browsing the document title and summary, and removing duplicates, 41 literatures were selected according to the inclusion criteria and the exclusion criteria. After screening the abstracts of these potentially relevant articles, 29 were selected for full-text review based on relevance to study topic. Ultimately, 11 documents, related to PPI therapy and development of SBP, were included in the meta-analysis, involving 4567 patients in 9 case-control studies and 2 cohort studies. The reasons for exclusion of the remaining 18 documents are listed in **Figure 1**. General characteristics included in the study were shown in **Table 1**, and the screening flowchart of literatures was shown in **Figure 1**.

Quality assessment

Eleven studies were included by NOS quality score, seven of which were high quality researches, four of which were medium quality researches. All studies included the study population, results and evaluation of results. The most common confounders included age, complications and typing of advanced liver disease.

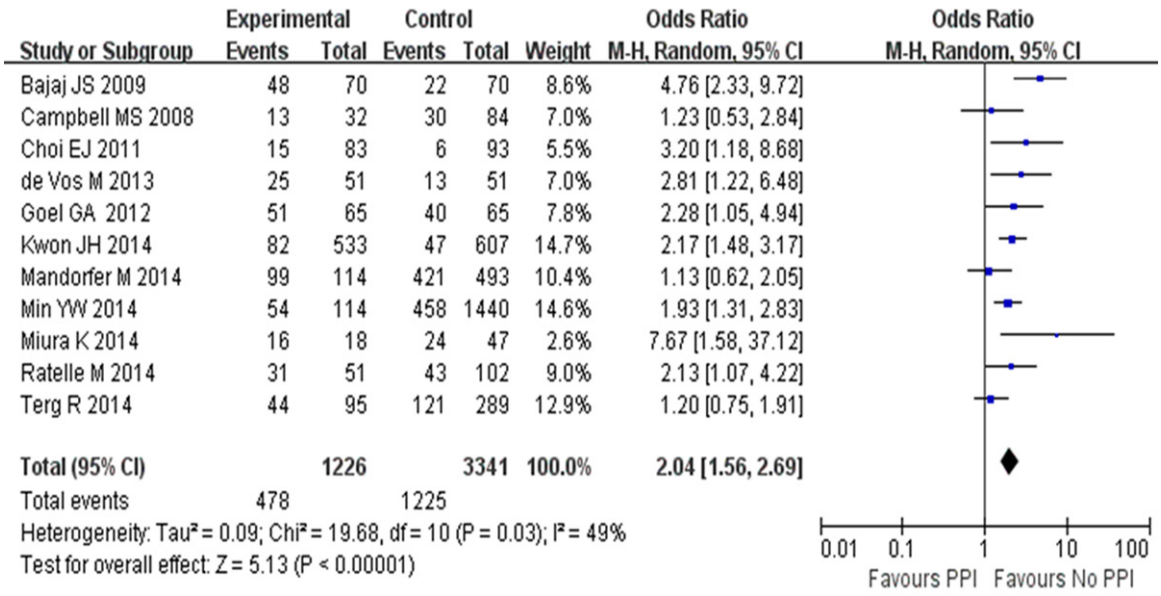

Figure 3. Forest plot of association between PPI and SBP. CI, confidence interval; df, degrees of freedom.

Before SBP being diagnosed, there was no relevant record information about patients taking the type of PPI, the dose and time of medication. After admission, there was also very small record information about the dose and time of PPI.

Publication bias

Using analysis software RevMan5.3, data were analyzed preliminarily by random effects model, and then the results were shown in funnel plot (**Figure 2**). By visual monitoring, the funnel plot was basically symmetrical, and suggested that publication bias was small. The result of test for heterogeneity, $P \leq 0.1$, $I^2 = 49\%$, indicated that there was low heterogeneity between studies.

Meta-analysis

The result of meta-analysis showed that there was a significant correlation between PPI therapy and SBP occurrence, and the incidence of SBP of PPI groups was significantly higher than non-PPI groups after administering PPI (OR = 2.04, 95% CI 1.56-2.69, $P < 0.00001$). The heterogeneity of study was $P \leq 0.1$, $I^2 = 49\%$. There was low heterogeneity, and the random effects model was used. The result was shown in **Figure 3**. In the eleven studies, eight studies showed significant relationship between PPI therapy and SBP occurrence, and three studies did not.

Subgroup analyzes

The result of meta-analysis, $I^2 = 49\%$, showed low heterogeneity among the studies. Because of different race, diet, lifestyle, genetic factors within study area, there were many differences, which might lead to heterogeneous in the study. So, we further stratified the study population in different regions.

Through comprehensive analysis of four groups of Asian populations, the results of heterogeneity: $P > 0.1$, $I^2 = 12\%$, showed that there were no heterogeneity among studies. The result of combined statistics using fixed effect model (OR = 2.22, 95% CI 1.72-2.87, $P < 0.00001$), was very close to the OR and 95% CI of the overall study. The incidence of SBP in Asian cirrhotic patients after using PPI was 2.22 times larger than that in non-PPI group. The result was shown in **Figure 4**.

Similarly, through separate analysis for European patients in two studies, the result, $P \leq 0.1$, $I^2 = 67\%$, showed that there was moderate heterogeneity among studies. Using random effects model (OR = 1.70, 95% CI 0.70-4.13, $P = 0.24$), the combined test statistic, $P = 0.24$, showed that there was no statistically significant. The result was shown in **Figure 5**.

Through separate analysis for American patients in five studies, the result, $P < 0.1$, $I^2 = 65\%$,

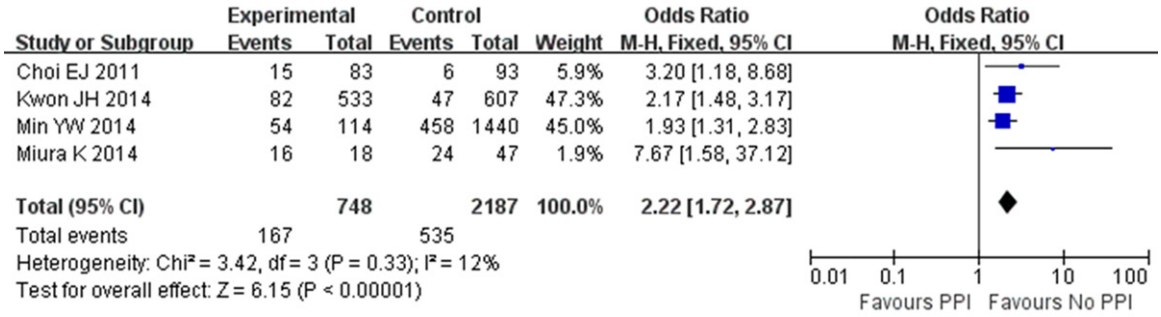

Figure 4. Forest plot of association between PPI and SBP in Asian. CI, confidence interval; df, degrees of freedom.

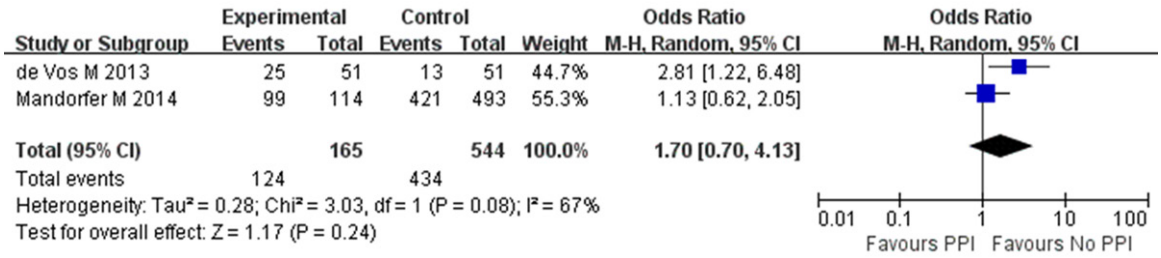

Figure 5. Forest plot of association between PPI and SBP in European. CI, confidence interval; df, degrees of freedom.

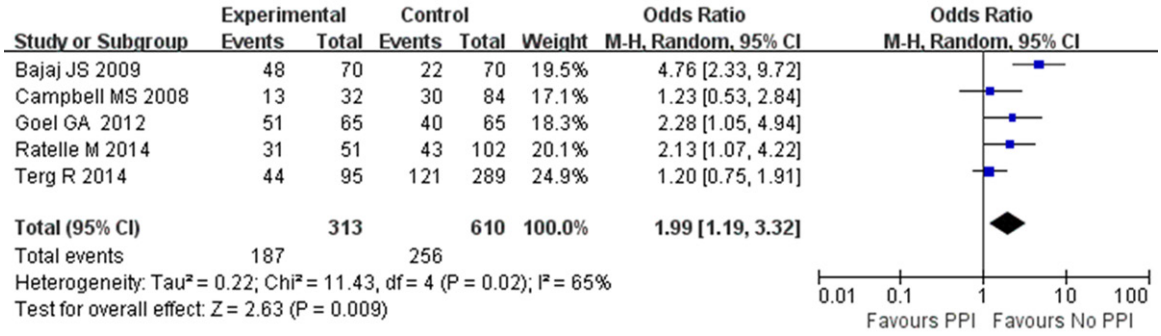

Figure 6. Forest plot of association between PPI and SBP in American. CI, confidence interval; df, degrees of freedom.

showed that there was less consistency among studies, and moderate heterogeneity. Using random effects model, (OR = 1.99, 95% CI 1.19-3.32, P = 0.009), there was significantly higher incidence of SBP in PPI group, compared with non-PPI group in the American cirrhotic patients. The result was shown in **Figure 6**.

Through analyzing the subgroup in different study areas, the result showed that there was significantly higher incidence of SBP in patients used PPI in Asian and American population. There was no heterogeneity in Asian patients. However, among Euro-American cirrhotic patients received PPI therapy, there was moderate heterogeneity. To some extent, the source of heterogeneity could be explained by these results. However, there were not adequate data to perform subgroup analysis for the type, the dose, and the medication time of PPI.

Discussion

This meta-analysis study included a total of 11 documents, involving 1226 patients who developed SBP. The results showed that the incidence of SBP was related to the application of PPI in cirrhotic patients. PPI therapy led to a

2.04 times increase of SBP as compared with those without PPI therapy. Thus, PPI was an inducer in SBP occurrence to some extent.

SBP is a common complication in cirrhotic patients with high morbidity and mortality. It was found that gastric acid inhibitor drugs, especially the most widely used PPIs, increased the incidence of SBP. Some retrospective control studies also showed that there was a correlation between the usage of gastric acid inhibitors and the incidence of SBP in some cases, even though the results in these correlation analyses contradicted other studies. Gati *et al.* and Bajaj *et al.* found that there was a significant correlation between PPI therapy and the development of SBP [4, 10], but Terg R *et al.* and Campbell *et al.* found that the use of PPI had nothing to do with the incidence of SBP [11, 13]. The difference may be due to the patients with significant liver damage in the former two studies. In addition, the mutant strains and its types, dosage of drugs may affect the results during treatment. So far, the mechanism associated with the incidence of SBP and PPI has remained unclear. There was a hypothesis that overgrowth of gastrointestinal flora after colonization during acid inhibitor therapy may be the cause of increasing SBP by acid inhibitor drugs. Regardless of the key mechanisms of SBP induced by PPI, the use of PPI may increase the incidence of SBP in cirrhotic patients in our study.

In our study, 11 literatures were evaluated in order to find a correlation between PPI use and the incidence of SBP. Trikudanathan *et al.* found that the use of PPI increased risks of SBP in treatment through meta-analysis [15], but only four observational studies were included in their study, involving 770 patients, and the projects and the samples were small. In another more comprehensive literature study, Deshpande *et al.* found that the incidence of SBP increased significantly in patients with PPI treatment, OR = 3.15 (95% CI 2.09-4.74, $P < 0.0001$) [14]. However, there are two literatures reported in the form of abstract only (involving 3034 patients) in this study, and the source of heterogeneity subgroup was not analyzed. Our results are similar to the above results, but included more literatures and more patients.

In the past two years, there has been a new progress about the correlation between the use of PPI therapy and the risk of SBP occurrence, and seven new literatures were involved in this issue. Therefore, our meta-analysis included the latest seven literatures in the last two years basing on the two previous studies. We evaluated the risk associated with PPI occurrence and the incidence of SBP. We found that the incidence of SBP was related to the use of PPI therapy, but there was certain heterogeneity in the results. Therefore, we performed subgroup analysis based on different regions of the study population, and investigated the relationship between PPI use and the incidence of SBP in order to find the source of the heterogeneity. The result of stratification suggested that there was a consistence between Euro-American patients' subgroup and overall patients in the risk of incidence of SBP after using PPI therapy. There was not heterogeneity in Asian regional patient's subgroup, and there was moderate heterogeneity in Euro-American patients' subgroup.

Three underlying factors may be related to the heterogeneity. (1) Heterogeneity may be related to the number of patients and research design included in the studies, such as the number of patients included in the Europe and America studies was relatively small compared with Asia studies. (2) Metabolism of PPI is mainly carried out by CYP2C19 metabolic enzymes, in which there are not only individual differences, but also significant differences in inter-ethnic [13]. Significant differences of CYP2C19 among different ethnic groups caused different metabolism, pharmacokinetics and pharmacodynamics about the same PPI.

To some extent, the results of moderate heterogeneity of the regional population that existed in Euro-American patients' subgroup could explain why the overall study heterogeneity exists.

There some limitations in this study. (1) Because the data of some literature were not available, relatively fewer studies have been included in the final meta-analysis. (2) Some limiting factors in research included in our meta-analysis, such as strains of bacteria, the type and dose of PPI, time of PPI therapy, and other factors including whether the patient accepted endoscopic variceal band ligation and other operations, may result in different outcomes. (3) Because of the lack of the type, dose and time of PPI, there were no adequate data for subgroup analysis.

In conclusion, PPI can be used in the treatment of peptic ulcer, gastroesophageal reflux, and other indications. However, PPI therapy should be administered with a caution in cirrhotic patients. Future studies maybe need to clarify the relationship between the occurrence of SBP and the type and dose of PPI in cirrhotic patients.

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Disclosure of conflict of interest

None.

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