Correlation Between Proton Pump Inhibitors and the Complications of Liver Cirrhosis: A Systematic Review and Meta-Analysis

Seong Jun Hwang[1], Dong Hyeon Lee[2], Seong-Joon Koh[2,3], Ji Won Kim[2,3], Hyun Sun Park[3,4], Byeong Gwan Kim[2], Kook Lae Lee[2]

[1]Department of Internal Medicine, Asan Medical Center, Seoul, South Korea
[2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea
[3]Laboratory of Intestinal Mucosa and Skin Immunology, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea
[4]Department of Dermatology, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

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ABSTRACT

Background: *Many studies and meta-analyses have investigated the associations among proton pump inhibitors (PPIs), spontaneous bacterial peritonitis (SBP), portosystemic encephalopathy (PSE), and other infections. However, these studies had limitations, including the omission of several relevant studies and drawing conclusions, based on the abstracts without consulting the full-text of the articles. To evaluate the association between PPIs and complications arising from cirrhosis and risks of PPI use in patients with cirrhosis.*

Methods: *Data were extracted from the EMBASE, PubMed, Cochrane, and Google Scholar databases. The Newcastle-Ottawa scale was used to assess the quality of the selected studies.*

Results: *A total of 29 studies (13 case–control and 16 cohort studies) involving 20,484 patients were included in the meta-analysis. The total relative risk (RR) for the 23 studies which investigated SBP was 1.31, and the 95% CI was 1.10-1.55 (I^2 = 73.0%). The total RR for the 7 studies which examined PSE was 1.25 (95% CI 0.85-1.84, I^2 = 96.1%). For the 7 studies which analyzed overall infection, the total RR was 1.37 (95% CI 1.07-1.76, I^2 = 79.3%). The RR for the 2 cohort studies that assessed mortality was 1.39 (95% CI 0.85-2.27, I^2 = 0.0%).*

Conclusion: *PPI use in cirrhosis patients increased the SBP and overall infection risk. PPIs should be considered with appropriate indications when the benefits exceed the risks in cirrhosis patients with ascites.*

Keywords: *Liver cirrhosis, proton pump inhibitors, peritonitis, hepatic encephalopathy, complications*

INTRODUCTION

Proton pump inhibitors (PPIs) are effective gastric acid suppressors. They play pivotal roles in the treatment of peptic ulcer disease, gastric bleeding, GERD, and *Helicobacter pylori* infection.[1,2] PPIs are the most commonly prescribed medication for the suppression of gastric acid because of their safety and effectiveness.[3,4] However, recent studies have reported that PPIs are associated with increased risk of pneumonia and *Clostridium difficile* infection.

Gastric acid aids digestion and sterilizes the digestive tract by removing pathogenic microorganisms that enter the tract.[5] The absence of this sterilizing action appears to have a more detrimental effect when the immune system is compromised and normal bacterial defense mechanisms are impaired. In addition to these effects on the immune system, PPIs alter the oral and intestinal microbiota.[6]

Patients with cirrhosis show delayed intestinal transit and intestinal dysfunction.[7] Immune dysfunction is marked in patients with cirrhosis because of the reduction of hepatic mononuclear cells in the liver and biosynthesis of soluble pathogen-recognition receptors and complement.[8,9] Furthermore, bacterial translocation occurs frequently with mucosal barrier dysfunction, resulting in infectious diseases such as spontaneous bacterial peritonitis (SBP).[10] In cirrhosis patients, the half-life of PPIs is increased, leading to increased concentrations and the

Corresponding author: ***Dong Hyeon Lee*** *or* ***Seong-Joon Koh****, e-mail:* ***donghyeonlee83@gmail.com*** *or* ***jel1206@snu.ac.kr***
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risk of toxicity. Therefore, the continuous use of PPIs in patients with cirrhosis may increase the risk of infectious diseases such as SBP and *C. difficile*.[11,12] Studies have suggested that gut microbes modified by PPIs may increase the risk of portosystemic encephalopathy (PSE) risk by increasing ammonia levels.[13,14]

Many studies and meta-analyses have investigated the association between PPIs, SBP, PSE, and other infections. However, these studies have limitations, including the omission of several relevant studies and drawing conclusions based on abstracts alone, without consulting the full-text of the articles. These studies focused on a single complication in patients with cirrhosis. Here, we aimed to conduct a large-scale meta-analysis assessing the association between PPIs and multiple cirrhosis-related complications, including mortality. This study is the largest meta-analysis of its type among the available literature and, to the best of our knowledge, the largest meta-analysis on this subject.

MATERIALS AND METHODS

Our meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[15]

Study Selection

A comprehensive search of published articles was conducted using the MEDLINE/PubMed, EMBASE, and Cochrane databases. We conducted structured search using the following keywords: "proton pump inhibitor," "PPI," "*prazole," "anti-acid," "cirrhosis," "LC," "hepatic fibrosis," "portal hypertension," "complication," "ascites," "spontaneous bacterial peritonitis," "SBP," "hepatorenal syndrome," "HRS," "portosystemic shunt," "PSE," "hepatic encephalopathy," "HE," "jaundice," "varix," "varices," "variceal bleeding," "hepatopulmonary syndrome," "HPS," "liver cancer," "liver malignancy," "hepatocellular carcinoma," "HCC," and "mortality". The inclusion criteria were as follows: availability of a full-text version of the article; participants had cirrhosis; availability of PPI prescribing data; and outcomes resulting from the complications of cirrhosis were reported. The study searches were not restricted based on language. The exclusion criteria were as follows: absence of a control group; patients reported prior complications; use of antibiotic prophylaxis; and history of brain function impairments. When duplicated publications were identified, the most recently published study was included. We manually reviewed the bibliographies of all studies included in the meta-analysis.

Data Extraction

After the initial screening of abstracts, 2 investigators (S.J.H. and D.H.L.) extracted all data independently using a predefined information sheet in accordance with the PRISMA statement.[15] For each study, the following characteristics were extracted: first author, year of publication, country, institution, study design, complications of cirrhosis, types of PPIs, participant information, and the number of exposed participants among the cases and controls. Independently extracted data did not differ between reviewers.

The Newcastle–Ottawa scale (NOS) was used to assess the quality of the selected studies,[16] and quality assessments were performed independently. A paper with a NOS score below 6 was classified as inadequate, and a subgroup analysis was conducted.

Statistical Analysis

All statistical analyses were performed using STATA software (version 15; Stata Corporation, College Station, TX, United States). The relative risk (RR) or odds ratio (OR) with the associated 95% CI was considered the effect size. ORs were considered similar to RRs because of the low incidence of cirrhosis-related complications. The random-effects method was used when comparing results between studies. Heterogeneity among studies was evaluated using Cochran's *Q*-test and Higgins' I^2.[17,18] *P* values < .1 indicated heterogeneity between studies using the *Q*-test. Heterogeneity was defined using I^2 as follows: I^2 < 25%, no heterogeneity; 25% < I^2 < 50%, mild heterogeneity; 50% < I^2 < 75%, moderate heterogeneity; and I^2 > 75%, high heterogeneity. Publication bias was assessed using Begg's rank correlation test and Egger's regression test. *P* values < .05 indicated significant publication bias.

RESULTS

The study selection and inclusion process are shown in Figure 1. A total of 1455 citations were identified after searching the databases. After the removal of duplicates, the title and abstract of 1265 citations were screened, and 1060 were excluded. A total of 205 articles were then assessed according to predefined eligibility criteria, and 178 were excluded. This left a total of 27 studies, and 2 additional studies were added after manual review. Thirteen articles reported the results of case–control studies[19-31] and 16 reported results of cohort studies.[12,13,32-45] Figure 1 summarizes the study selection process, and Table 1 displays the characteristics of the

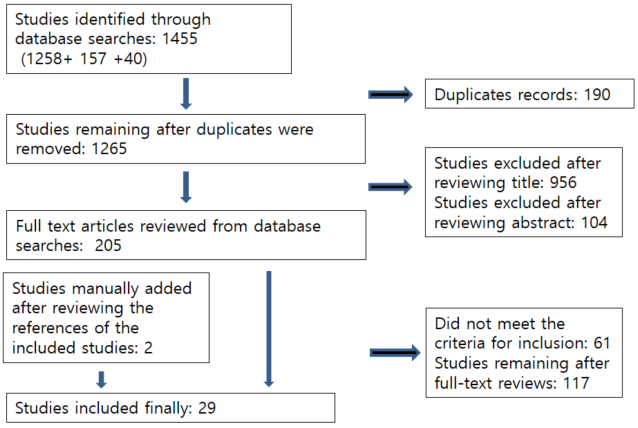

Figure 1. The process of inclusion or exclusion of records based upon predetermined selection parameters.

studies involved. A total of 20 484 participants from the 29 studies were included in the meta-analysis. All studies focused on the use of PPIs in patients with cirrhosis. Twenty-two studies evaluated the correlations between PPIs and SBP, 7 studies reported associations between PPIs and overall infection (pneumonia, urinary tract infection, enterocolitis, sepsis), 6 studies assessed the use of PPI and PSE, and 2 studies evaluated the risk of mortality with PPIs use.

Spontaneous Bacterial Peritonitis

The pooled analysis of all the studies showed a significant association between PPI use and the risk of SBP in patients with cirrhosis (RR = 1.31, 95% CI = 1.10-1.55, *P* = .002 [OR were considered similar to RR]; OR = 1.56, 95% CI = 1.21-2.02, *P* = .001 [RR was considered similar to OR]), with moderate heterogeneity among studies (I^2 = 73.0 and 71.9 in each model) (Table 2). The pooled data of case–control studies also indicated that PPI users had a significantly increased risk of SBP (OR = 2.69, 95% CI = 2.11-3.43, *P* < .001) (Figure 2 and Table 2).

Portosystemic Encephalopathy

The overall analysis of all 7 studies found that PPI use was not significantly associated with risk of PSE (RR = 1.25, 95% CI = 0.85-1.84, *P* = .253 [OR was considered similar to RR]; OR = 1.51, 95% CI = 0.79-2.88, *P* = .210 [RR was considered similar to OR]), with high heterogeneity across studies (I^2 = 96.1 and 96.2 in each model; Table 2). The harmful association was limited to the 2 case–control studies (OR = 5.18, 95% CI = 2.97-9.01, *P* < .001) (Figure 2 and Table 2). No significant association was noted in cohort studies (RR = 0.98, 95% CI = 0.64-1.51, *P* = .921) (Figure 3 and Table 2). Analysis conducted using Begg's and Egger's test showed no evidence of publication bias (all *P* > .05).

Overall Infection

The pooled data showed a significant association between PPI use and risk of overall infection (RR = 1.37, 95% CI = 1.07-1.76, *P* = .012 [OR was considered similar to RR]; OR = 1.56, 95% CI = 1.12-2.19, *P* = .009 [RR was considered similar to OR]), with high heterogeneity among studies (I^2 = 79.3 and 80.8 in each model) (Table 2). When only cohort studies were analyzed separately, the heterogeneity was markedly reduced (I^2 = 51.1). However, the association was not statistically significant (RR = 1.13, 95% CI = 0.96-1.33, *P* = .147) (Figure 3 and Table 2). All studies were of moderate-to-high quality. Potential publication bias was observed in Egger's regression test (*P* = .018 and .022 in each model).

Mortality

There were 2 cohort studies that also evaluated the relationship between PPI use and mortality in patients with cirrhosis. The aggregated data showed that PPI use was not significantly associated with a risk of mortality (RR = 1.39, 95% CI = 0.85-2.27, *P* = .184) (Figure 3 and Table 2). There was no evidence of heterogeneity (I^2 = 0.0) or publication bias (*P* = .317).

DISCUSSION

Proton pump inhibitors are often prescribed inappropriately to patients with cirrhosis; recent studies suggest up to 60% of PPIs are prescribed inappropriately.[22,46] There have been meta-analyses investigating the association between PPIs and cirrhosis-related complications; however, there are few meta-analyses exploring cirrhosis-related complications comprehensively. We found that PPIs were associated with increased risk of SBP and overall infection. However, no significant associations between the use of PPIs and PSE or mortality were identified. To the best of our knowledge, this is the largest meta-analysis on the association between PPI use and complications from cirrhosis. The meta-analysis included 20 484 patients from 29 studies looking at the association between PPI use and complications of cirrhosis. This is the first meta-analysis assessing the association between PPIs and cirrhosis-related mortality. This study provides valuable insight, especially considering that randomized controlled trials cannot be used to study adverse drug-related events.

We found that PPIs are associated with an increased risk of SBP and overall infection. This is consistent with

Table 1. Details of the Participants Included in the Meta-analysis Based on 29 Studies (13 Case–Control and 16 Cohort)

No.	Author	Year	Country	Study Design	Center	Events	Kinds of PPI	Male (%)	Mean Age	No.		NOS
										PPI (+)	PPI (–)	
1	Campbell et al.	2008	US	Case–control	Single	SBP	-	67.2	54.6	43	73	8
2	Bajaj et al.	2009	US	Case–control	Single	SBP	-	56.4	54.5	70	70	7
3	Choi et al.	2011	Korea	Case–control	Single	SBP	Esomeprazole, Pantoprazole, Rabeprazole	78.4	55.5	21	155	8
4	Goel et al.	2012	US	Case–control	-	SBP	-	63.9	57.6	91	39	7
5	de Vos et al.	2013	Belgium	Case–control	-	SBP	-	68.6	58.4	38	64	7
6	Matsumoto et al.	2014	Japan	Case–control	Single	SBP	Lansoprazole, Omeprazole, Rabeprazole	61.8	63.1	55	102	5
7	Ratelle et al.	2014	Canada	Case–control	Single	SBP	-	74.5	60.6	74	77	7
8	Miura et al.	2014	Japan	Case–control	Single	SBP	Lansoprazole, Omeprazole, Rabeprazole	67.7	66.3	43	22	7
9	Meril et al.	2015	Italy	Case–control	Single	SBP	Esomeprazole, Omeprazole, Pantoprazole, Rabeprazole	70.3	61.5	127	40	6
10	Hayat et al.	2018	US	Case–control	Single	SBP	-	48.0	42.6	100	100	7
11	Lin et al.	2014	China	Case–control	Single	PSE	-	78.2	44.0	119	46	5
12	Zhu et al.	2018	Canada	Case–control	Single	PSE	-	36.3	56.1	85	71	7
13	Elzouki et al.	2018	Qatar	Case–control	Single	Infection	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	78.1	52.8	171	162	8
14	van Vlerken et al.	2012	Netherland	Cohort	Multi	SBP	Omeprazole, Pantoprazole	67.0	55.0	17	34	6
15	Mandorfer et al.	2014	Austria	Cohort	Single	SBP, Infection	-	70.0	57.5	520	87	8
16	Min et al.	2014	Korea	Cohort	Single	SBP	Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole	68.3	57.9	402	402	8
17	Kwon et al.	2014	Korea	Cohort	Multi	SBP	Pantoprazole	75.4	62.4	129	1011	9
18	Terg et al.	2015	Argentina	Cohort	Multi	SBP, PSE, Infection	-	69.0	57.0	165	219	7

(*Continued*)

Table 1. Details of the Participants Included in the Meta-analysis Based on 29 Studies (13 Case–Control and 16 Cohort) (*Continued*)

No.	Author	Year	Country	Study Design	Center	Events	Kinds of PPI	Male (%)	Mean Age	No.		NOS
										PPI (+)	PPI (–)	
19	O'Leary et al.	2015	US	Cohort	Multi	SBP	-	54.4	56.3	116	72	8
20	Dam et al.	2016	Denmark	Cohort	Multi	SBP, PSE, Death	-	68.7	57.4	340	525	8
21	Huang et al.	2016	Taiwan	Cohort	Multi	SBP, PSE	-	76.2	54.1	1870	1190	9
22	Kim et al.	2017	Korea	Cohort	Single	SBP, Death	Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole	77.9	57.7	58	149	8
23	Miozzo et al.	2017	Brazil	Cohort	Single	SBP	Omeprazole	63.0	53.6	151	107	9
24	Lázaro-Pacheco et al.	2018	Mexico	Cohort	Multi	SBP, PSE, Infection	-	42.5	62.1	44	69	9
25	Tergast et al.	2018	Germany	Cohort	Single	SBP	Pantoprazole	62.0	56.1	506	107	8
26	Tsai et al.	2017	Taiwan	Cohort	Multi	PSE	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	74.2	53.1	693	1639	9
27	Bajaj et al.	2012	US	Cohort	Single	Infection	-	98.6	-	1256	1256	8
28	Dultz et al.	2015	Germany	Cohort	-	Infection	Esomeprazole, Omeprazole, Pantoprazole	66.9	57.0	213	59	9
29	Hung et al.	2018	Taiwan	Cohort	Multi	Infection	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	67.5	62.6	1004	4016	9

No., number; PPI, proton pump inhibitor; NOS, Newcastle–Ottawa scale; SBP, spontaneous bacterial peritonitis; PSE, portosystemic encephalopathy.

Table 2. Details of the Meta-analysis of the Relationship Between Proton Pump Inhibitor Use and Complications Resulting from Cirrhosis

Complications of LC	Study Design	Studies No.	Heterogeneity		Effect Size					Publication Bias	
			I^2 (%)	P_H	M	RR	OR	(95% CI)	P_{ES}	P_{Begg}	P_{Egg}
SBP											
Cohort study		12	58.0	0.006	R	1.14	-	(0.95-1.37)	.152	.217	.203
Case–control study		11	0.0	0.581	R	-	2.69	(2.11-3.43)	<.001	.815	.810
Total		23	56.6	<0.001	R	1.40	-	(1.22-1.61)	<.001	.303	.685
			65.9	<0.001	R	-	1.69	(1.34-2.14)	<.001	.096	.149
PSE											
Cohort study		5	97.0	<0.001	R	0.98	-	(0.64-1.51)	.921	1.000	.539
Case–control study		2	0.0	0.785	R	-	5.18	(2.97-9.01)	<.001	.317	-
Total		7	96.1	<0.001	R	1.25	-	(0.85-1.84)	.253	.652	.980
			96.2	<0.001	R	-	1.51	(0.79-2.88)	.210	.652	.552
Infection											
Cohort study		6	51.1	0.069	R	1.13	-	(0.96-1.33)	.147	.015	.001
Case–control study		1	-	-	R	-	3.90	(2.26-6.73)	<.001	-	-
Total		7	79.3	<0.001	R	1.37	-	(1.07-1.76)	.012	.051	.018
			80.8	<0.001	R	-	1.56	(1.12-2.19)	.009	.099	.022
Death											
Cohort study		2	0.0	0.582	R	1.39	-	(0.85-2.27)	.184	.317	-
Case–control study		0	-	-	R	-	-	-	-	-	-

LC, liver cirrhosis; No., number; P_H, *P* value for heterogeneity; M, model for meta-analysis; R, random-effect model; RR, relative risk; OR, odds ratio; P_{ES}, *P* value for effect size; P_{Begg}, *P* value for Begg's test; P_{Egg}, *P* value for Egger's test.

previous meta-analyses[47-50] that support the correlations. However, the heterogeneity between our samples was high; therefore, we performed subgroup analyses. Subgroup analyses of SBP, overall infection, and PSE were performed, and the cohort study achieved an RR > 1 (Table 2), suggesting that PPIs affected each complication but not to a significant degree ($P > .05$). Heterogeneity was moderate-to-high for SBP, PSE, and overall infection (Table 2). When subgroup analysis was performed on the case–control studies, the OR of PPI users was significant ($P < .001$), and there was no heterogeneity ($I^2 = 0$). Cohort studies did not produce significant results but rather showed a tendency, and the case–control studies did show significance, providing support for the tendencies seen in the cohort studies. This may be a result of differences in research methods. Selection bias may have been present in the case–control studies because patients were chosen based on the presence of cirrhosis-related complications before PPI use was determined. In addition, cohort studies rely on follow-up assessments of complications to determine PPI use. It is possible that complications may have appeared if the follow-up period was longer.

Previous meta-analyses demonstrated significant correlations between PPI and PSE; however, PSE and mortality were not significantly related to PPI use.[51] Bian et al.[51] only included 3 studies: Tsai et al.,[42] Dam et al.,[13] and Lin et al.[29] in their meta-analysis associating PPIs with PSE. Perhaps some articles may have been omitted because they did not meet inclusion criteria, or there might have been publication bias. In the case of both cohort and case–control studies, the correlation between PPI and PSE tended to be lower. However, subgroup analysis showed significant results in case–control-only studies, suggesting that there was controversy in the meta-analysis results. If

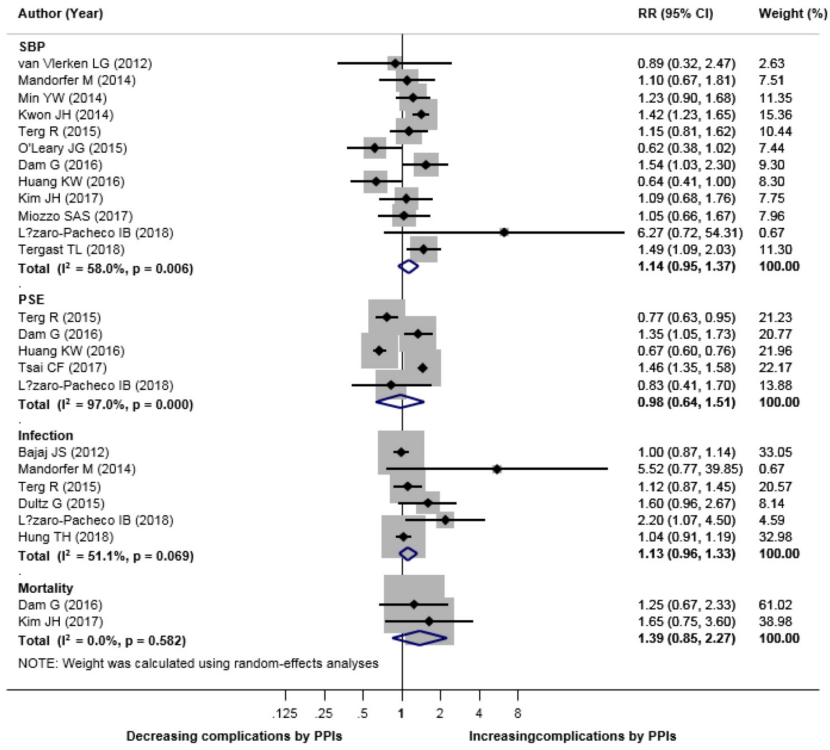

Figure 2. Forest plots for unadjusted overall infection at a 95% CI for complications of cirrhosis in individuals using proton pump inhibitors for 14 case–control studies. SBP, spontaneous bacterial peritonitis; PSE, portosystemic encephalopathy; PPI, proton pump inhibitor.

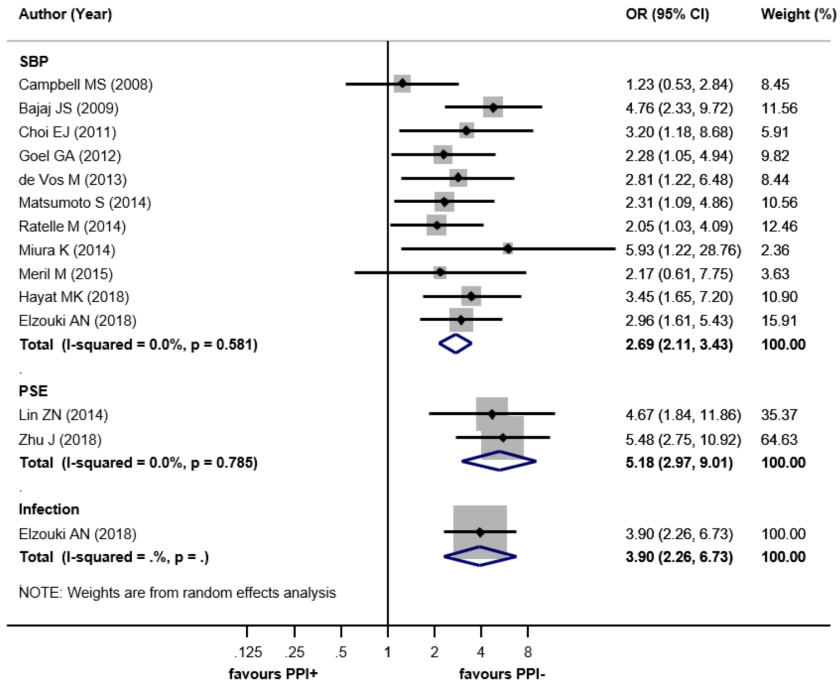

Figure 3. Forest plots of unadjusted relative risk at a 95% CI for complications of cirrhosis in individuals using proton pump inhibitors for 25 cohort studies. RR, relative risk; SBP, spontaneous bacterial peritonitis; PSE, portosystemic encephalopathy; PPI, proton pump inhibitor.

further studies of PSE and PPI are added, meta-analysis may need to be performed again.

A limitation of this meta-analysis was that many of the source articles did not clearly state information regarding patients' use of PPIs, including the type of PPI used and the duration of use. Furthermore, there was no information on the follow-up period in many of the studies, possibly 1 of the variables contributing to differences in outcomes between case–control and cohort studies. *H. pylori* infection status and antibiotic use, both of which may contribute to increased blood ammonia levels resulting in an increased risk of PSE, were not reported in many of the papers, and this relationship may be a confounding factor.

Our study is significant because it explored the relationship between PPIs and SBP and other cirrhosis-related complications. To the best of our knowledge, no other studies have investigated this combination of variables. PPIs are often inappropriately prescribed to patients with cirrhosis. Recent studies suggest that up to 60% of PPIs are inappropriately prescribed.[22,46] Therefore PPIs should be considered with appropriate indications when the benefit exceeds the risk in patients with ascites. A large systematic cohort study that controls for the type of PPI, duration of use, and follow-up interval is warranted to clarify the correlation between cirrhosis-related complications.

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Informed Consent: N/A.

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