Association of Spontaneous Bacterial Peritonitis and Use of Proton Pump Inhibitors among Patients with Liver Cirrhosis: A Systematic Review and Meta-Analysis

Sy-Janairo MLL[a]
Janairo JIB[b]
Mariano PMB[c]
Gopez-Cervantes JL[a]
Cua IHY[a]

[a]*Institute of Digestive and Liver Diseases St. Luke's Medical Center-Global City, Philippines*

[b]*Biology Department De La Salle University, Manila, Philippines*

[c]*Department of Medicine St. Luke's Medical Center-Quezon City, Philippines*

Correspondence:
Dr. Marianne Linley L. Sy-Janairo
mariannelinleyhsyjanairomd@gmail.com

Accepted for publication:
December 2020

Abstract

Background: Spontaneous bacterial peritonitis (SBP) is a frequent complication seen among cirrhotic patients resulting in increased hospitalization and has an estimated 30-day mortality of 33%. While the use of proton pump inhibitors (PPI) has been associated with higher incidence of SBP, previous studies provided conflicting conclusions. *Objective:* This study aims to re-assess the association between PPI use and SBP incidence with larger, updated data. *Methods:* Database of Medline, Cochrane, and Google scholar were used to search for relevant articles. Two reviewers independently assessed the quality of each paper. Disagreements were resolved by the third author. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was observed and complied with. Pooled odds ratios with 95% confidence intervals were calculated. Sub-group analysis was done to decrease heterogeneity. *Results:* Twenty-two studies (eight case-control, 13 cohort, and one randomized controlled trial) involving 10,828 patients were analyzed. Results showed a statistically significant association between SBP and PPI use (pooled odds ratio (OR): 2.03, 95% CI of 1.67-2.45), with substantial heterogeneity. Subgroup analysis involving cohort and randomized controlled trial revealed statistically significant association, although weaker (OR: 1.88 with 95% CI of 1.51-2.34, $p<0.00001$) and has substantial heterogeneity. For case-control studies, OR is 2.64 with 95% CI of 1.91-3.64. Pooled OR for high quality studies is 1.93 with 95% CI of 1.57-2.38, $p<0.00001$). The funnel plot was asymmetric suggesting publication bias. *Conclusion:* This meta-analysis showed there is statistically significant association, although weak, between higher incidence of SBP and PPI use. This updated meta-analysis suggests judicious use of PPI among cirrhotic patients with ascites.

Keywords: meta-analysis, peritonitis, proton pump inhibitor, liver cirrhosis

Introduction

Proton pump inhibitors (PPI) are one of the most commonly used medications. It is generally well-tolerated and safe, with few reported adverse effects. Studies have shown that there is an increasing overuse of PPIs in hospital and outpatient practices.[1-4] Because of this, there is now a growing concern regarding potential complications associated with long term use.[5-7]

Spontaneous bacterial peritonitis (SBP) is a common infection among patients with liver cirrhosis, and is associated with increased hospitalization and an estimated 30-day mortality of 33%.[8] Patients with liver cirrhosis are considered to be at higher risk for infection because of several factors, such as increased intestinal permeability resulting to bacterial translocation, and lower immune system due to complement deficiency, reticuloendothelial system depression, and leukocyte dysfunction.[9,10] The use of PPI among cirrhotic patients with ascites has been associated with higher incidence of SBP, possibly due to the suppression of the gastric acid secretion which may lead to increased bacterial colonization and altered gut flora. This may in turn

contribute to an even higher risk of bacterial overgrowth and translocation among this group of patients.[5,11,12] Furthermore, since PPIs are metabolized in the liver, changes in the pharmacokinetics among cirrhotic patients may occur, making them at higher risk for possible adverse effects.[13] Previous studies, however, including case control, cohort, and meta-analysis, provide conflicting results and conclusions. Several case control[14-16] and cohort studies[17,18] show association of SBP with PPI therapy among cirrhotic patients. In contrary, the study of Mandorfer et al.[19] and Terg et al.[20] conclude that there is no association between PPI use and higher risk of SBP. The latest meta-analysis by Yu et al.[21] also did not establish association between PPI use and higher incidence of SBP. After this meta-analysis, additional studies were published evaluating the association of PPI use and development of SBP. Considering the new data and information available, we aim to re-assess the association between PPI use and SBP incidence with larger and better quality data.

Methods

Literature Search

Two authors independently conducted a search for articles published until November 2019 in PUBMED (158 articles), the Cochrane Central Registry of Clinical Trials (four articles) and Google scholar (132 articles). The search entry terms used were: *proton pump or omeprazole or esomeprazole or lansoprazole or rabeprazole or pantoprazole AND spontaneous bacterial peritonitis OR peritonitis and cirrhosis*. The search was limited to human subjects. Different institutions from different countries were included to allow generalizability of the study. Bibliographies were also reviewed for articles which could qualify for the study.

Study Selection

All retrieved abstracts were independently reviewed by two authors. The full texts of potential articles were retrieved and reviewed by the same authors to determine eligibility. Disagreements were resolved by consensus with the third or, if necessary, by the fourth author. Inclusion criteria for the selection of relevant studies were: (i) those that reported the association between PPI therapy and SBP incidence (defined as ≥250 polymorphonuclear leukocytes/L in the ascitic fluid; (ii) randomized controlled trial (RCT), case–control or cohort articles; (iii) study population comprised adult patients (≥18 years); and (iv) articles reported relative risk (RR), odds ratio (OR), or hazard ratio (HR) at 95% confidence interval (CI), or the raw data to calculate them.

Exclusion criteria were as follows: (i) studies had no control group; (ii) studies included patients who experienced gastrointestinal bleeding, who were on antibiotic prophylaxis during the last two weeks prior to SBP, or liver transplant patients; (iii) papers were letters, commentaries, editorials, reviews and duplicate publications; and (iv) outcome is recurrent SBP. Outcome of interest is development of spontaneous bacterial peritonitis.

The study complied with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement[22].

Quality Assessment

Two reviewers independently graded the methodological quality of each included study using the Newcastle-Ottawa Scale (NOS)[23] for the non-randomized studies, and the Jadad scoring[24] system for the RCT article. Any disagreement about a particular study was resolved by consensus with a third and/or fourth investigator. NOS score ≥7 and Jadad score of 5 were considered high quality studies.

Statistical Analysis

Review Manager version 5.3 was used to conduct the meta-analysis. Results were presented as pooled ORs with 95% confidence interval. We assumed similarity between the OR and other relative measures, such as RR and HR, because SBP events and deaths were rare. When both the crude and the adjusted OR/RR values were offered, only the adjusted value was adopted for the meta-analysis. If only the raw data was reported, calculation for unadjusted OR was done. A random effects model was used with presumption of multiple potential sources of heterogeneity being present between the studies included. To address the heterogeneity from different study designs, subgroup analysis of studies was done. Statistical heterogeneity was evaluated using the Cochran Chi- square and the I^2 statistic. An I^2 value of >50% suggests significant heterogeneity.

Results

The search yielded 294 documents from database search, and four articles from bibliography search. After duplicates were removed, 194 articles were screened and full-text articles were reviewed. Out of the 55 screened-in articles, 31 were further excluded because they were either: a review/meta-analysis, no relevant data available, no standard definition of SBP, an abstract of an included study, and/or involved a different outcome. Two articles were published abstracts of conference proceedings. Twenty-two studies fulfilled eligibility criteria and were analyzed. **Figure 1** shows the flow of the selection process.

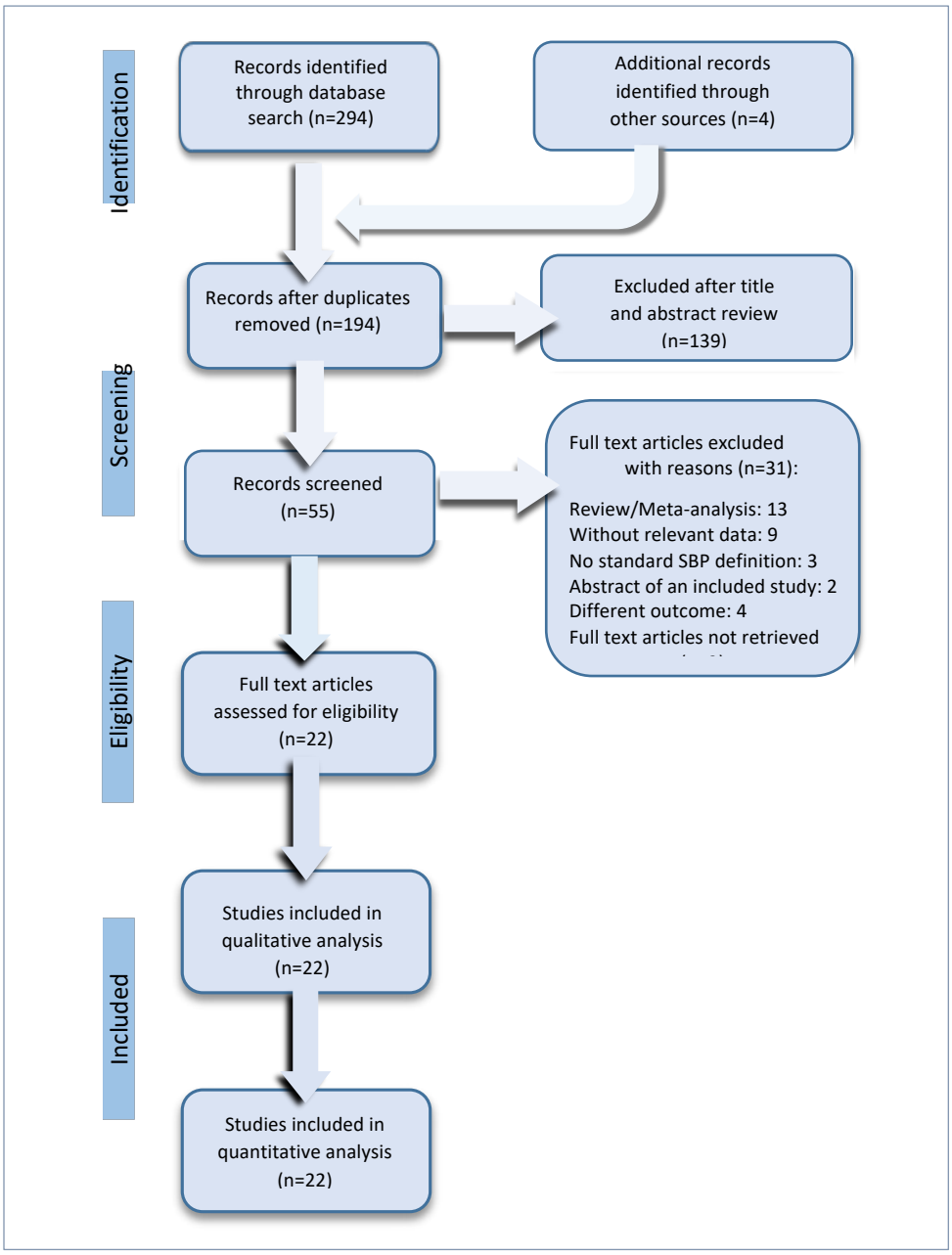


Figure 1. Flow diagram of the search strategy

Study Characteristics and Quality Assessment of Included Studies

The 22 studies included were published from 2008-2019, involving 10,828 patients. Most of the studies were conducted in the USA, Europe, and other studies were from Asia. The detailed characteristics of included studies are summarized in **Table 1**.

Table 1. Characteristics of included studies

Author	Year	Sample Size	# Patients on PPI Group	Single / Multi-Center	Follow Up (Months)	Adjusted/Matched Factors	Country
Case Control Studies (8)							
Bajaj[14]	2009	140	70	Single	-	CTP class, age, admission time period	USA
Campbell[25]	2008	116	43	Single	-	Age, bilirubin, INR, creatinine, MELD score, DM, gender, history of SBP, etiology of liver disease, race	USA
Choi[26]	2011	176	21	Single	-	CCTP class, age, MELD score, history of esophageal variceal bleeding	Korea
De Vos[27]	2013	102	38	Single	-	-	Belgium
Goel[16]	2011	130	91	Single	-	CTP class	USA
Kwon[15]	2014	1,140	129	Multi-	-	Age, MELD score	Korea
Miura[18]	2014	65	43	Single	-	Age, creatinine, platelets, albumin, total bilirubin	Japan
Ratelle[28]	2014	153	74	Single	-	Age, gender, year of admission, CTP class	Canada
Cohort Studies (13)							
Chang[29]	2015	947	-	Multi-	12	Age, sex, index date	Taiwan
Dam[30]	2016	865	340	Multi-	13	MELD, sodium, albumin, history of SBP	Denmark
Elzouki[31]	2018	333	171	Single	-	-	Qatar
Huang[32]	2016	3,060	1,870	Multi-	24	Age, sex, co-morbidities, ascites, hepatic encephalopathy, esophageal varices	Taiwan
Janka[33]	2019*	350	196	Single	60	Age, gender, co-morbidity, etiology of liver disease, MELD score, CTP class	Hungary
Mandorfer[19]	2014	607	520	Single	9.6	Age, HCC, history of variceal bleeding, varices, MELD score	Austria
Min[34]	2014	804	512	Single	25.1	Age, gender, etiology of liver disease, platelet count, AST, ALT,ALP, GGT, BUN, creatinine, serum sodium, serum albumin, total bilirubin, INR,CTP class	Korea
Miozzo[35]	2017	258	151	Single	60	CTP class	Brazil
O'leary[17]	2014	188	83	Multi-	6	-	N. America
Pacheco[36]	2017	113	44	Single	36	CTP class, ascites, chronic use of PPI, history of variceal bleeding	Mexico
Terg[37]	2015	384	165	Multi-	3	Age, gender, MELD score, CTP class, alcohol, HBV/HCV infection, encephalopathy, serum bilirubin, creatinine, peripheral leukocyte count, platelet count, protein in ascetic fluid	Argentina
Tergast[38]	2018	613	506	Single	0.9	-	Germany
Van Vlerken[10]	2012	84	52	Multi-	28	Age, CTP class	Netherlands
Randomized Control Trial (1)							
Hyat[39]	2018	200	100	Single	6	Age, gender	Pakistan

*published online

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CTP, Child-Turcotte-Pugh class; DM, diabetes mellitus; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCB, hepatitis C virus; HCC, hepatocellular carcinoma; INR, international normalized ratio (prothrombin time); MELD, model for end-stage liver disease

There was one randomized controlled trial, thirteen cohort studies, and eight case–control studies. Study duration ranged from 28 days to five years. Eighteen studies adjusted the impact of confounders when assessing the association between use of PPIs and development of SBP. Six studies were performed using a prospective cohort study design, five of which were conducted under multi-center settings. **Table 2** summarizes the risk of bias assessment for the included studies. Five out of the eight case-control studies were of high quality, and 12 out of 13 cohort studies were regarded as high quality. The only RCT trial was considered to have a moderate threat to validity, with a Jaded score of 2.

Table 2. Quality assessment of included studies

Author	Year	Quality Assessment Criteria	Score
Case Control Studies (8)			
Bajaj	2009	NOS*	7
Campbell	2008	NOS	6
Choi	2011	NOS	8
De Vos	2013	NOS	7
Goel	2011	NOS	7
Kwon	2014	NOS	8
Miura	2014	NOS	5
Ratella	2014	NOS	4
Cohort Studies (13)			
Chang	2015	NOS	8
Dam	2016	NOS	8
Elzouki	2018	NOS	6
Huang	2016	NOS	9
Janka	2019*	NOS	8
Mandorfer	2014	NOS	8
Min	2014	NOS	9
Miozzo	2017	NOS	8
O'leary	2014	NOS	8
Pacheco	2017	NOS	8
Terg	2015	NOS	9
Tergast	2018	NOS	7
Van Vlerken	2012	NOS	8
Randomized Control Trial (1)			
Hayat	2018	Jadad	2

*NOS: New Castle-Ottawa Scale

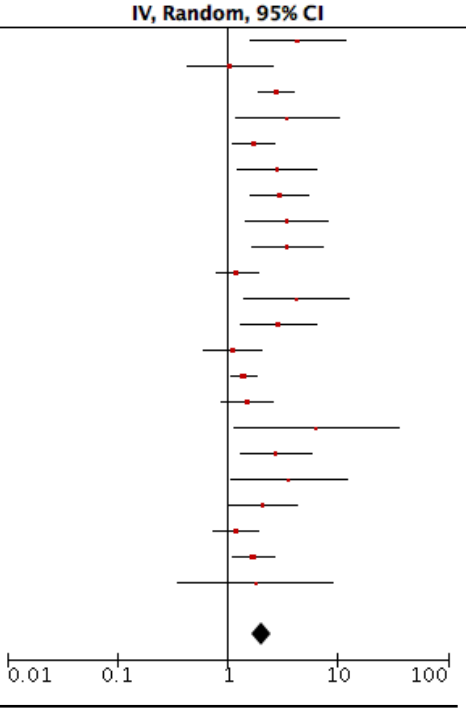
Meta-Analysis

The Forest plot (**Table 3**) showed pooled odds ratio of spontaneous bacterial peritonitis with proton pump inhibitor use among cirrhotic patients with ascites. The overall pooled odds ratio for the 22 studies is 2.03, with 95% CI of 1.67 to 2.45, and a statistically significant *p* value. Substantial heterogeneity was observed, as demonstrated by a significant Chi^2 *p*-value. Although the I^2 is less than 50%, moderate degree of heterogeneity was considered. Sensitivity analysis was done to decrease heterogeneity. One identified source of heterogeneity is the differences in the study design of the included articles, hence subgroup analysis for the different study design was done.

Table 3. Forest plot for association between PPI use and SBP incidence

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Bajaj, 2009	1.4609	0.5088	2.8%	4.31 [1.59, 11.68]
Campbell 2008	0.0488	0.4555	3.3%	1.05 [0.43, 2.56]
Chang, 2015	1.0188	0.1924	7.8%	2.77 [1.90, 4.04]
Choi, 2011	1.2355	0.5529	2.4%	3.44 [1.16, 10.17]
Dam, 2016	0.5423	0.2281	7.0%	1.72 [1.10, 2.69]
de Vos, 2013	1.033	0.426	3.6%	2.81 [1.22, 6.47]
Elzouki, 2018	1.0852	0.3104	5.3%	2.96 [1.61, 5.44]
Goel, 2011	1.2384	0.4353	3.5%	3.45 [1.47, 8.10]
Hayat, 2018	1.2389	0.375	4.2%	3.45 [1.66, 7.20]
Huang, 2016	0.1906	0.2231	7.1%	1.21 [0.78, 1.87]
Janka, 2019	1.4469	0.5583	2.4%	4.25 [1.42, 12.69]
Kwon, 2014	1.0543	0.403	3.9%	2.87 [1.30, 6.32]
Mandorfer, 2014	0.1044	0.3139	5.2%	1.11 [0.60, 2.05]
Min, 2014	0.3365	0.1419	9.1%	1.40 [1.06, 1.85]
Miozzo, 2017	0.4055	0.2773	5.9%	1.50 [0.87, 2.58]
Miura, 2014	1.8579	0.8722	1.1%	6.41 [1.16, 35.42]
O'leary, 2014	1.0001	0.3775	4.2%	2.72 [1.30, 5.70]
Pacheco, 2017	1.2809	0.6189	2.0%	3.60 [1.07, 12.11]
Ratelle, 2014	0.7372	0.3561	4.5%	2.09 [1.04, 4.20]
Terg, 2015	0.1823	0.2398	6.7%	1.20 [0.75, 1.92]
Tergast, 2018	0.5306	0.2266	7.0%	1.70 [1.09, 2.65]
van Vlerken, 2012	0.5878	0.8269	1.2%	1.80 [0.36, 9.10]
Total (95% CI)			**100.0%**	**2.03 [1.67, 2.45]**

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 39.99$, df = 21 (P = 0.007); $I^2 = 47\%$
Test for overall effect: Z = 7.24 (P < 0.00001)

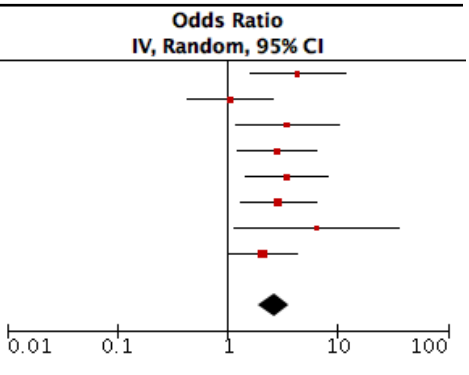


For case control studies (**Table 4**), the statistically significant pooled odds ratio of 2.64, with 95% CI of 1.91 to 3.64. Zero to minimal heterogeneity was observed in this subgroup analysis.

Table 4. Forest plot for association between PPI use an SBP incidence involving case controls

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Bajaj, 2009	1.4609	0.5088	10.2%	4.31 [1.59, 11.68]
Campbell 2008	0.0488	0.4555	12.7%	1.05 [0.43, 2.56]
Choi, 2011	1.2355	0.5529	8.7%	3.44 [1.16, 10.17]
de Vos, 2013	1.033	0.426	14.5%	2.81 [1.22, 6.47]
Goel, 2011	1.2384	0.4353	13.9%	3.45 [1.47, 8.10]
Kwon, 2014	1.0543	0.403	16.1%	2.87 [1.30, 6.32]
Miura, 2014	1.8579	0.8722	3.5%	6.41 [1.16, 35.42]
Ratelle, 2014	0.7372	0.3561	20.5%	2.09 [1.04, 4.20]
Total (95% CI)			**100.0%**	**2.64 [1.91, 3.64]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.16$, df = 7 (P = 0.41); $I^2 = 2\%$
Test for overall effect: Z = 5.91 (P < 0.00001)



For the cohort studies and one randomized controlled trial (**Table 5**), the pooled odds ratio is 1.88, with 95% CI of 1.51 to 2.34, with a statistically significant *p* value. However, significant and substantial heterogeneity was observed. Another subgroup analysis was done in which a forest plot (**Table 6**) was created involving the 17 high quality studies. The pooled odds ratio is 1.93 with 95% CI of 1.57 to 2.38, and a statistically significant *p* value. Again, substantial heterogeneity was observed as demonstrated by a significant Chi^2 *p*-value. The pooled odds ratio is 1.93 with 95% CI of 1.57 to 2.38, and a statistically significant p value. Again, substantial heterogeneity was observed as demonstrated by a significant Chi^2 p-value.

Table 5. Forest plot for association between PPI use an SBP incidence involving cohort studies and randomized controlled trial

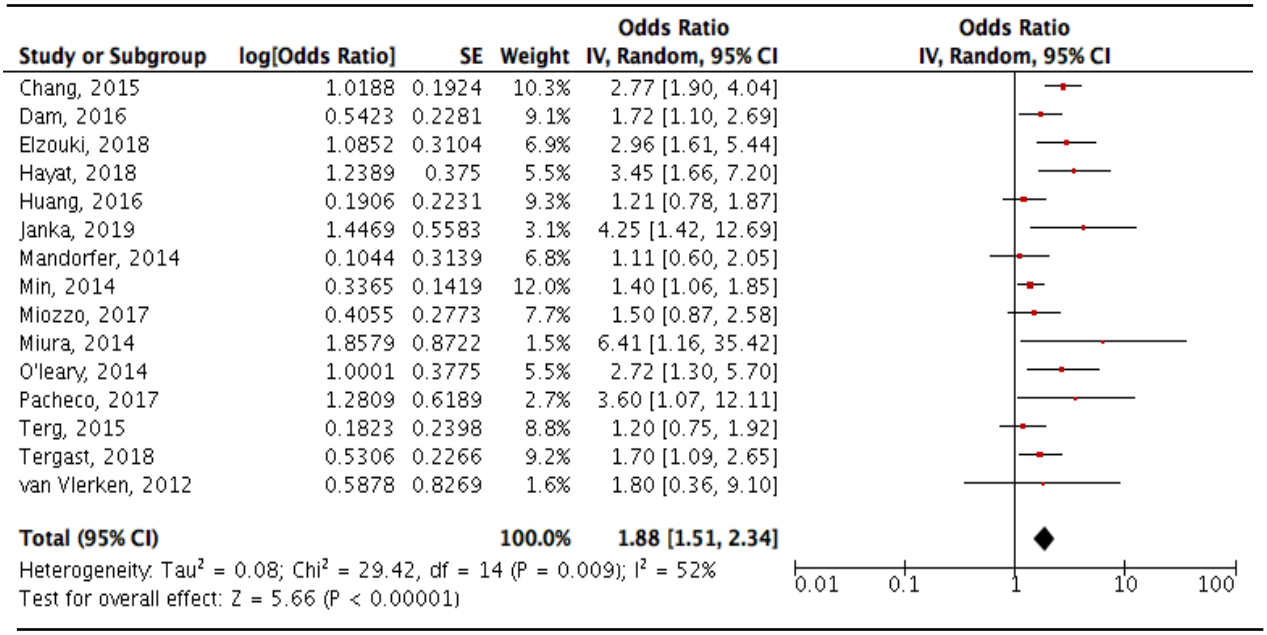
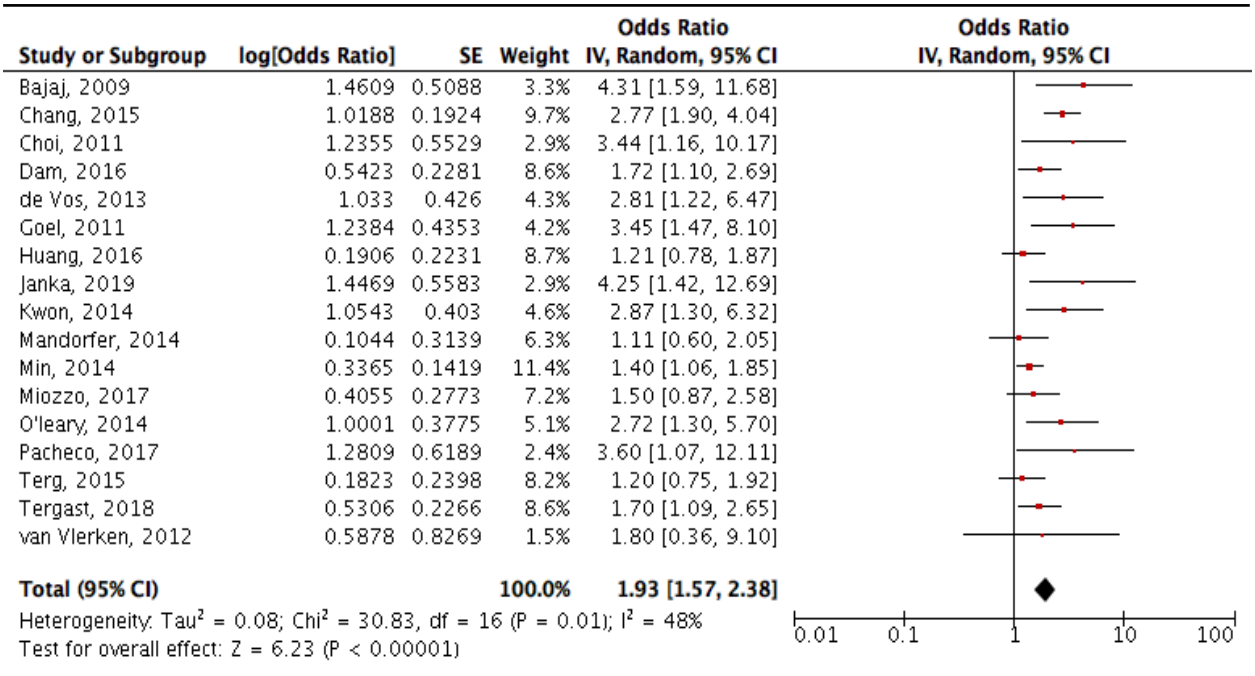


Table 6. Forest plot for association between PPI use an SBP incidence involving the 17 high quality studies



Publication bias was observed as seen in the asymmetrical funnel plot of included studies (**Figure 2**).

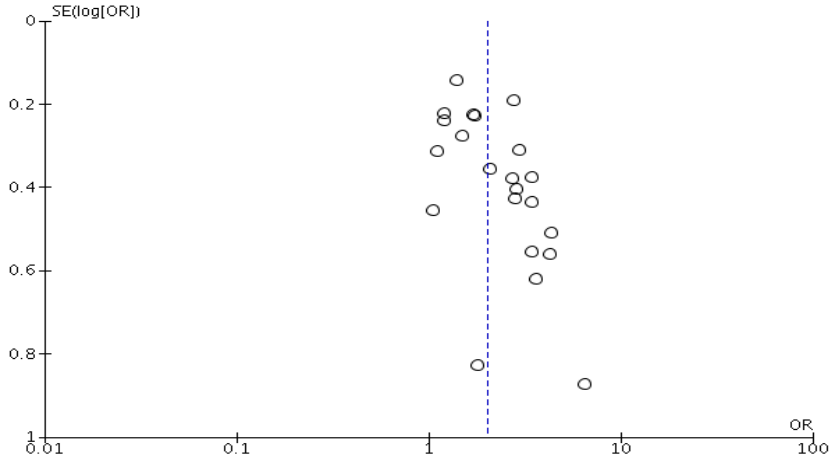


Figure 2. Funnel plot of included studies.

Discussion and Conclusion

One of the most commonly prescribed medications worldwide is proton pump inhibitors. Several studies have shown increasing inappropriate use of such drug. [1-1-4] Safety concerns regarding the use of PPIs have been raised especially among cirrhotic patients, one of which is the higher risk for bacterial peritonitis by increasing intestinal permeability predisposing to bacterial translocation, and lowering the immune system causing increased bacterial colonization in the gastrointestinal tract. Several studies were conducted in line with this but have shown inconclusive results. Newer studies were done to re-evaluate the causality of PPI use and development of SBP, hence an updated meta-analysis is important and warranted.

This study is the most updated and largest meta-analysis to date, including eight case-control studies, 13 cohort studies, and one randomized control trial. The meta-analysis of Yu et al.[21] included ten case control studies; however, the full text articles of the additional two studies were not retrieved; hence, was not included in this meta-analysis. The results of our study have demonstrated association of PPI with SBP occurrence with an overall pooled OR of 2.03, with 95% CI of 1.67 to 2.45, although a significant heterogeneity and publication bias was noted, as demonstrated by an asymmetrical funnel plot. To minimize the effect of heterogeneity and determine the robustness of the findings, sensitivity analysis was done. On the sensitivity analysis, the subgroup involving only the case-control studies has yielded the highest clinically significant pooled odds ratio with zero to minimal heterogeneity. Hence, the evidence for the observed association between PPI use and SBP occurrence remains to be weak, and could not establish causality. Since observations are made through time, results from cohort studies warrant more merit. Cohort studies may help determine potential causality on certain outcomes. For the cohort studies and one randomized controlled trial, a statistically significant pooled odds ratio of 1.88, with 95% CI of 1.51 to 2.34 was observed as compared to the statistically significant pooled odds ratio of 2.64, with 95% CI of 1.91 to 3.64 of the case control studies. Furthermore, the pooled OR for 17 high quality studies is 1.93 with 95% CI of 1.57 to 2.38, $p < 0.00001$. Hence, this systematic review and meta-analysis involving 10,828 patients from 21 observational studies and one randomized control trial has found statistically significant but quantitatively small associations between the use of PPI and SBP among cirrhotic patients with ascites. Our results reinforce the findings of previous meta analyses[21,40,41] that the association between incidence of SBP and PPI use is weak.

Several limitations were identified in our study. Most of the included studies were observational, and cannot establish causality with certainty. Hence,

more prospective studies are warranted to determine causal relationship of PPI use and SBP occurrence. Heterogeneity on the included studies and publication bias were observed. The differences in the population, such as age group of patients, Child-Pugh classification, and MELD score were possible confounders. Lastly, the indications for PPI use, and dosage and duration of PPI used were also not accounted for. It may be better if sensitivity analysis can be made according to duration and dosage of the PPI used. Further studies can be done to evaluate the association of PPI with SBP occurrence in comparison to the association of H2 receptor blocker with SBP occurrence, as to determine which gastric acid suppression therapy is safer to be given among cirrhotic patients.

In conclusion, this systematic review and meta-analysis showed that the evidence for PPI use leading to higher risk of SBP among cirrhotic patients with ascites is weak. Nevertheless, judicious use of PPI especially among this group of patients is highly recommended. Appropriate indication, duration, and dosage of PPI use is warranted.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Heidelbaugh JJ, Kim AH, Walker PC. Overutilization of proton-pump inhibitors: What the clinician needs to know. Therap Adv Gastroenterol. 2012; 5(4):219-32.
2. Chia CTW, Lim WP, Vu CKF. Inappropriate use of proton pump inhibitors in a local setting. Singapore Med J. 2014; 55(7):363-6.
3. Hálfdánarson Ó, Pottegård A, Björnsson ES, Lund SH, Ogmundsdottir MH, Steingrímsson E, et al. Proton-pump inhibitors among adults: A nationwide drug-utilization study. Therap Adv Gastroenterol. 2018 Jan 1; 11:1-11.
4. Haroon M, Yasin F, Gardezi SKM, Adeeb F, Walker F. Inappropriate use of proton pump inhibitors among medical inpatients: a questionnaire-based observational study. J R Soc Med Short Reports. 2013 Jul 31; 4(8).
5. Vaezi MF, Yang YX, Howden CW. Complications of Proton Pump Inhibitor Therapy. Gastroenterology [Internet]. 2017 Jul 1; 153(1):35-48. Available from: http://dx.doi.org/10.1053/j.gastro.2017.04.047.
6. Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: Understanding the complications and risks. Vol. 14, Nature Reviews Gastroenterology and Hepatology. Nature Publishing Group. 2017; 697-710.
7. Kinoshita Y, Ishimura N, Ishihara S. Advantages and disadvantages of long-term proton pump inhibitor use. J Neurogastroenterol Motil. 2018; 24(2):182-96.
8. Oey RC, de Man RA, Erler NS, Verbon A, van Buuren HR. Microbiology and antibiotic susceptibility patterns in spontaneous bacterial peritonitis: A study of two Dutch cohorts at a 10-year interval. United Eur Gastroenterol J. 2018 May 1; 6(4):614-21.
9. Scarpellini E, Valenza V, Gabrielli M, Lauritano EC, Perotti G, Merra G, et al. Intestinal permeability in cirrhotic patients with and without spontaneous bacterial peritonitis: Is the ring closed. Am J Gastroenterol. 2010 Feb; 105(2):323-7.
10. van Vlerken LG, Huisman EJ, van Hoek B, Renooij W, de Rooij FWM, Siersema PD, et al. Bacterial infections in cirrhosis : role of proton pump inhibitors and intestinal permeability. Eur J Clin Invest. 2012 Jul; 42(7):760-7.
11. Jackson MA, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC, et al. Proton pump inhibitors alter the composition of the gut microbiota. Gut. 2016 May 1; 65(5):749-56.
12. Jacobs C, Coss Adame E, Attaluri A, Valestin J, Rao SSC. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. Aliment Pharmacol Ther. 2013 Jun; 37(11):1103-11.
13. Weersink RA, Bouma M, Burger DM, Drenth JPH, Harkes-Idzinga SF, Hunfeld NGM, et al. Safe use of proton pump inhibitors in patients with cirrhosis. Br J Clin Pharmacol. 2018 Aug 1; 84(8):1806-20.
14. Bajaj JS, Zadvornova Y, Heuman DM, Hafeezullah M, Hoffmann RG, Sanyal AJ, et al. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. Am J Gastroenterol. 2009 May; 104(5):1130-1134.
15. Kwon JH, Koh SJ, Kim W, Jung YJ, Kim JW, Kim BG, et al. Mortality associated with proton pump inhibitors in cirrhotic patients with spontaneous bacterial peritonitis. J Gastroenterol Hepatol. 2014; 29(4):775-81.
16. Goel GA, Deshpande A, Lopez R, Hall GS, van Duin D, Carey WD. Increased Rate of Spontaneous Bacterial Peritonitis Among Cirrhotic Patients Receiving Pharmacologic Acid Suppression. Clin Gastroenterol Hepatol [Internet]. 2012 Apr; 10(4):422-7. Available from: http://dx.doi.org/10.1016/j.cgh.2011.11.019
17. O'Leary JG, Reddy KR, Wong F, Kamath PS, Patton HM, Biggins SW, et al. Long-term Use of Antibiotics and Proton Pump Inhibitors Predict Development of Infections in Patients With Cirrhosis. Clin

Gastroenterol Hepatol. 2014 Apr 1; 13(4):753-759.e2.
18. Miura K, Tanaka A, Yamamoto T, Adachi M, Takikawa H. Proton Pump Inhibitor Use is Associated with Spontaneous Bacterial Peritonitis in Patients with Liver Cirrhosis. Intern Med. 2014 May 15; 53(10):1037-42.
19. Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Summereder C, et al. Proton pump inhibitor intake neither predisposes to spontaneous bacterial peritonitis or other infections nor increases mortality in patients with cirrhosis and ascites. PLoS One. 2014 Nov 1; 9(11).
20. Terg R, Casciato P, Garbe C, Cartier M, Stieben T, Mendizabal M, et al. Proton pump inhibitor therapy does not increase the incidence of spontaneous bacterial peritonitis in cirrhosis: A multicenter prospective study. J Hepatol [Internet]. 2015 May 1; 62(5):1056-60. Available from: http://dx.doi.org/10.1016/j.jhep.2014.11.036.
21. Yu T, Tang Y, Jiang L, Zheng Y, Xiong W, Lin L. bacterial peritonitis incidence and mortality : A meta-analysis. Dig Liver Dis [Internet]. 2015; 1-7. Available from: http://dx.doi.org/10.1016/j.dld.2015.12.009.
22. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul; 6(7).
23. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. 2000.
24. Jadad AR, Andrew Moore R, Carroll D, Jenkinson C, John Reynolds DM, Gavaghan DJ, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Control Clin Trials. 1996; 17:1-12.
25. Campbell MS, Obstein K, Reddy KR, Yang YX. Association between proton pump inhibitor use and spontaneous bacterial peritonitis. Dig Dis Sci. 2008 Feb; 53(2):394-398.
26. Choi EJ, Lee HJ, Kim KO, Lee SH, Eun JR, Jang BI, et al. Association between acid suppressive therapy and spontaneous bacterial peritonitis in cirrhotic patients with ascites. Scand J Gastroenterol. 2011 May; 46(5):616-20.
27. de Vos M, De Vroey B, Garcia BG, Roy C, Kidd F, Henrion J, et al. Role of proton pump inhibitors in the occurrence and the prognosis of spontaneous bacterial peritonitis in cirrhotic patients with ascites. Liver Int. 2013 Oct; 33(9):1316-23.
28. Ratelle M, Perreault S, Villeneuve JJ, Tremblay L. Association between proton pump inhibitor use and spontaneous bacterial peritonitis in cirrhotic patients with ascites. Can J Gastroenterol Hepato. 2014; 28(6):330-5.
29. Chang SS, Lai CC, Lee MTG, Lee YC, Tsai YW, Hsu WT, et al. Risk of Spontaneous Bacterial Peritonitis Associated with Gastric Acid Suppression. Med (United States). 2015 Jun 7; 94(22):e944.
30. Dam G, Vilstrup H, Watson H, Jepsen P. Proton pump inhibitors as a risk factor for hepatic encephalopathy and spontaneous bacterial peritonitis in patients with cirrhosis with ascites. Hepatology. 2016 Oct 1; 64(4):1265-72.
31. Elzouki AN, Neffati N, Rasoul FA, Abdallah A, Othman M, Waness A. Increased Risk of Spontaneous Bacterial Peritonitis in Cirrhotic Patients Using Proton Pump Inhibitors. GE Port J Gastroenterol. 2019 Mar 1; 26(2).
32. Huang KW, Kuan YC, Luo JC, Lin CL, Liang JA, Kao CH. Impact of long-term gastric acid suppression on spontaneous bacterial peritonitis in patients with advanced decompensated liver cirrhosis. Eur J Intern Med [Internet]. 2016 Jul 1; 32:91-95. Available from: http://dx.doi.org/10.1016/j.ejim.2016.04.016.
33. Janka T, Tornai T, Borbély B, Tornai D, Altorjay I, Papp M, et al. Deleterious effect of proton pump inhibitors on the disease course of cirrhosis. Eur J Gastroenterol Hepatol. 2019 Aug; 1.
34. Min YW, Lim KS, Min BH, Gwak GY, Paik YH, Choi MS, et al. Proton pump inhibitor use significantly increases the risk of spontaneous bacterial peritonitis in 1965 patients with cirrhosis and ascites: A propensity score matched cohort study. Aliment Pharmacol Ther. 2014; 40(6):695-704.
35. Miozzo SAS, John JA, Appel-da-Silva MC, Dossin IA, Tovo C V., Mattos AA. Influence of proton pump inhibitors in the development of spontaneous bacterial peritonitis. World J Hepatol. 2017 Dec 18; 9(35):1278-85.
36. Lázaro-Pacheco IB, Servín-Caamaño AI, Pérez-Hernández JL, Rojas-Loureiro G, Servín-Abad L, Higuera-De La Tijera F. Proton pump inhibitors increases the overall risk of developing bacterial infections in patients with cirrhosis. Arq Gastroenterol. 2018 Mar; 55(1):28-32.
37. Terg R, Casciato P, Garbe C, Cartier M, Stieben T, Mendizabal M, et al. Proton pump inhibitor therapy does not increase the incidence of spontaneous bacterial peritonitis in cirrhosis: A multicenter prospective study. J Hepatol. 2015 May 1; 62(5):1056-60.
38. Tergast TL, Wranke A, Laser H, Gerbel S, Manns MP, Cornberg M, et al. Dose-dependent impact of proton pump inhibitors on the clinical course of spontaneous bacterial peritonitis. Liver Int. 2018 Sep 1; 38(9):1602-13.
39. Hayat MKF, Shah ZH, Hayat MKF, Imran MY, Qureshi IH. Comparative study of spontaneous bacterial

peritonitis in cirrhosis patients managed with and without proton pump inhibitors. Pakistan J Med Heal Sci. 2018 Apr 1; 12(2):598-601.

40. Khan MA, Kamal S, Khan S, Lee WM, Howden CW, Ali M, et al. Systematic review and meta-analysis of the possible association between pharmacological gastric acid suppression and spontaneous bacterial peritonitis. Eur J Gastroenterol Hepatol. 2015 Oct 1; 27(11):1327-36.
41. Xu HB, Wang HD, Li CH, Ye S, Dong MS, Xia QJ, et al. Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: A systematic review and meta-analysis. Genet Mol Res. 2015 Jul 3; 14(3):7490-501.