Use of proton pump inhibitors and the risk of hepatocellular carcinoma: A systematic review and meta-analysis

Tien-En Chang[a,b], Yi-Shin Huang[a,b,*], Chin-Lin Perng[a,b], Yi-Hsiang Huang[a,b], Ming-Chih Hou[a,b]

[a]Dvision of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taiwan, ROC; [b]National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC

Abstract

Background: Worldwide, proton pump inhibitors (PPIs) are commonly used for the treatment of peptic ulcer and gastro-esophageal reflux disease. Recently, concern has arisen over the potential association between PPIs and hepatocellular carcinoma (HCC). The aim of the current study was to evaluate the influence of PPI use on the risk of HCC, through a systematic review and meta-analysis.

Methods: A review of all English-language literature was conducted, using the subject search terms: "hepatocellular carcinoma", "liver cancer", "hepatic tumor", and "proton pump inhibitor" in the major medical databases. A meta-analysis of the qualifying publications was then performed.

Results: A total of five studies, which had shown that PPIs were associated with HCC (crude risk ratio [RR] = 2.27, 95% confidence interval [CI]: 1.44-3.57; $p < 0.01$) when an unadjusted RR were adopted, were eligible for meta-analysis. It was observed that the cumulative dose of PPIs may increase the risk of HCC in a linear model ($p < 0.01$). However, when using data that were adjusted by comorbidities and concurrent medications, the association between PPIs and HCC became insignificant (adjusted RR = 1.62, 95% CI: 0.89-2.93; $p = 0.11$) and this result was consistent in the sensitivity analysis.

Conclusion: The current meta-analysis has shown that PPI use does not significantly increase the risk of HCC after adjusting for confounding factors. However, further studies are warranted to verify the association between PPIs and HCC in special populations, such as viral or alcoholic liver diseases.

Keywords: Hepatocellular carcinoma; Liver tumor; Proton pump inhibitor

1. INTRODUCTION

Proton pump inhibitors (PPIs) have been widely used in the treatment of peptic ulcer disease, gastroesophageal reflux disease, and in the eradication of *Helicobacter pylori*. PPIs were generally considered to be a safe and effective drug. However, adverse effects such as *Clostridium difficile*-associated diarrhea, vitamin and mineral malabsorption, hip fracture, and community-acquired pneumonia were noted in some patients following the long-term use of PPIs.[1–3] Furthermore, overprescription of PPIs has been reported lately.[4] PPIs were frequently used in patients with chronic liver diseases; however, 30% to 50% of patients may have been given inappropriate prescriptions.[5]

Although PPI-induced hepatotoxicity is rare,[6] the safety of PPIs in patients with chronic liver diseases has been challenged.[7–10] PPI use has been reported to be associated with the severity of cirrhosis and an increased risk of decompensation, such as ascites, spontaneous bacterial peritonitis (SBP), and hepatic encephalopathy (HE) among cirrhotic patients.[7–10] Previous studies have also revealed that PPIs may increase the rate of readmission and mortality in patients with chronic liver diseases.[7–10]

In addition, PPIs may be a potential carcinogenic agent. Long-term use of PPIs has been suspected to increase the risk of colorectal cancer, esophageal cancer, gastric cancer, and pancreatic cancer.[11–14] Chronic use of PPIs can induce hypergastrinemia and dysbiosis of the gut microbiome, which may lead to carcinogenesis in the gastrointestinal tract.[15–17] Recently, concern has arisen over whether long-term use of PPIs increases the risk of hepatocellular carcinoma (HCC). In an animal study, omeprazole was found to promote the formation of liver tumors,[18] and some clinical studies have also reported that PPIs may be associated with an increased risk of HCC.[19,20] However, there were also some recent studies that reached contradicting conclusions.[21–23]

Whether the use of PPIs increases the susceptibility of patients to HCC remains unclear. Therefore, the present study performed a systematic review and meta-analysis to assess the influence of PPI use on the risk of HCC.

2. METHODS

2.1. Identification and retrieval of studies

A literature search of English-language articles was conducted to evaluate the potential association between PPI use and HCC, in articles published up to January 2019 in PubMed, Medline,

*Address correspondence: Dr. Yi-Shin Huang, Division of Gastroenterology and Hepatology,Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: yshuang@vghtpe.gov.tw (Y.-S. Huang).

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Embase, and the Cochrane Database of Systematic Reviews, using the medical subject heading search terms: "hepatocellular carcinoma", "liver cancer", "hepatic tumor", and "proton pump inhibitor". Articles were selected for a full text review based on their title and abstract. Furthermore, the reference lists of the retrieved articles were manually searched to increase the number of possibly appropriate articles. A total of two researchers independently examined all of the retrieved articles and assessed their eligibility for inclusion within the present study. Discordant opinions were resolved by consensus with the other coauthors.

2.2. Inclusion and exclusion criteria

The included studies had to fulfill the following selection criteria: (1) patients received PPI treatment, including omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole, or dexlansoprazole; (2) had data on patients with or without PPI use, and with or without HCC; and (3) was published as a full-length article. The exclusion criteria were as follows: (1) repeated use of the same cohort in the second paper; (2) incomplete data on odds ratios, risk ratios (RR), hazard ratios, or standardized incidence ratios. Studies included in the analysis were reviewed for the following characteristics: authors and year of publication, ethnicity, prospective or retrospective case-control study, and type of PPI administered.

2.3. Statistical analysis

All statistical analyses were performed using Review Manager version 5.3.5 (RevMan for Windows, 2014; The Cochrane Collaboration, Oxford, UK). Inverse variance was used as the analysis method. RR with 95% confidence intervals (CIs) were calculated to determine the association between the incidence of HCC and PPI use. Heterogeneity between-studies was recognized with a cutoff value of ≥50% using I^2 statistics, or $p < 0.10$ using the χ^2 test for Cochran Q statistics. If significant heterogeneity was found, a random effect model was selected to analyze the pooled data. Funnel plots were used to assess the publication bias.

A dose-response meta-analysis was performed using the two-stage generalized least squares for trend (GLST) estimation of summarized dose-response data.[24,25] The GLST method first assessed study-specific slope lines and then obtained an overall average slope. The analysis was based on data for the median dose of PPI administered, the reported RRs, the 95% CIs for effect size, and the number of cases and controls in each quantitative group. If the median dose of PPI administered in different quantitative groups was not reported, the medians were estimated using the midpoint of the lower and upper limits. If the highest quantitative group was open-ended, the difference between the lowest range to the median was considered to be equivalent to the same difference in the closest adjacent category. The cumulative doses were allocated to each relevant RR. There were two studies that reported RRs with their corresponding 95% CIs, included in the GLST dose-response analysis.[20,23]

3. RESULTS

A total of 37 citations were identified following the initial main database search, from which five studies were eligible for meta-analysis (Fig. 1). Of the five included studies, three were performed in Asia, one was from the United States, and one was performed in Europe. Four of the studies were case-controlled studies and one was a prospective study; three studies documented the cumulative doses of PPI exposure (Table 1).

The meta-analysis showed that there was an association between PPI use and HCC (RR = 2.27, 95% CI: 1.44-3.57; $p < 0.01$; Fig. 2) when unadjusted RRs were used.

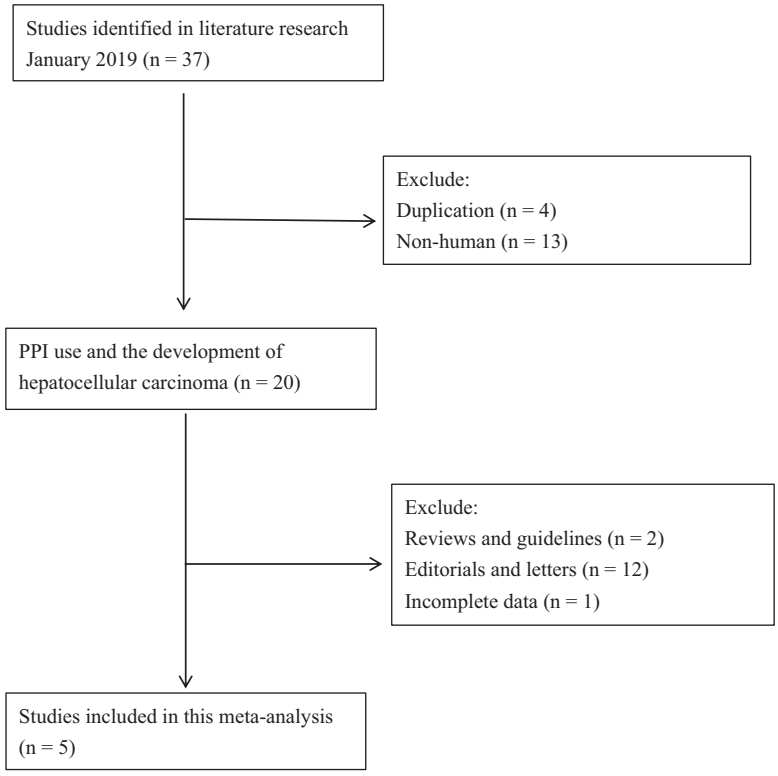

Fig. 1 Flow chart of the selection of eligible studies.

Table 1

Main characteristics of enrolled studies in the order of publication year (n = 5)

First author, year	Country	Study design	PPI/non-PPI	HCC/non-HCC	Patient population
Lai, 2013[21]	Taiwan	Case-control	1500/13 935	3087/12 348	Included patients with cirrhosis, viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease
Li, 2018[19]	USA	Case-control	5752/5774	Not documented	Noncirrhotic, hepatitis C
Shao, 2018[20]	Taiwan	Case-control	10 288/313 693	29 473/29 508	Excluded patients with viral hepatitis and cirrhosis
Tran, 2018[22]	UK	Prospective	Total: 471 851	88/471 763	Included patients with cirrhosis, hepatitis, alcoholism, and obesity
Kao, 2019[23]	Taiwan	Case-control	7492/7492	448/14 536	Hepatitis B or C

HCC = hepatocellular carcinoma; PPI = proton pump inhibitor.

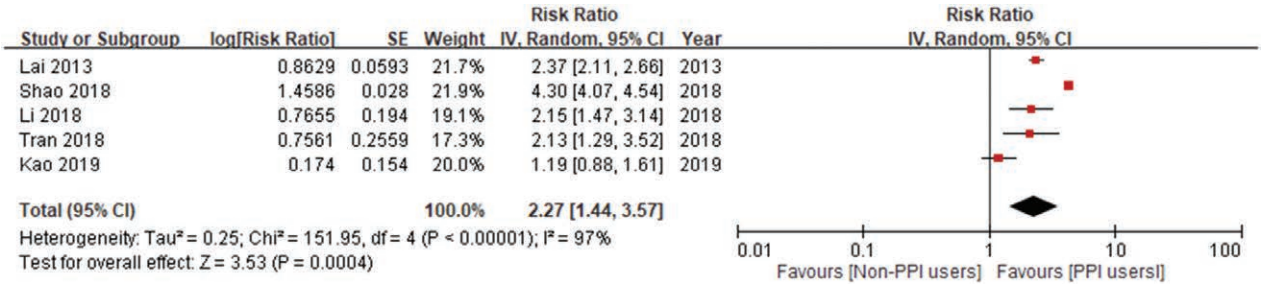

Fig. 2 Forest plot of association between PPI use and the risk of hepatocellular carcinoma in five eligible studies, using unadjusted risk ratio. Events denote patients with hepatocellular carcinoma. CI = confidence interval; IV = inverse variance; PPI = proton pump inhibitor.

In Li's study, the risk of HCC between non-PPI users and those with different cumulative defined daily dose (30-180, 181-540, 541-900, >900) was investigated.[19] However, the effect of the total cases of PPI on HCC was not obtainable from this study. Therefore, a cDDD of 181 to 540 was chosen to represent Li's data in the meta-analysis, as the cumulative doses in the other groups of Li's study were either too high or too low.

The dose-response relation was estimated in two studies that provided RRs with their corresponding 95% CIs.[20,22] Li's study was not included due to the lack of case numbers for HCC and PPI users.[19] The summary RR per 50 cumulative dose increases in PPI use was 1.24 (95% CI: 1.22-1.26; $p < 0.01$; Fig. 3) using the linear regression model. There was a dose-response relation between PPI use and HCC under long-term exposure.

In the studies by Lai et al, Tran et al, and Shao et al, both the crude RRs and adjusted RRs were presented.[20–22] The data were adjusted for age, cirrhosis, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), diabetes mellitus and concurrent medications, such as statins, metformin, and aspirin. When these adjusted RRs were used for the meta-analysis, the association between PPI use and HCC became insignificant (adjusted RR = 1.62, 95% CI: 0.89-2.93; $p = 0.11$; Fig. 4). A sensitivity analysis was performed due to high heterogeneity ($I^2 = 97\%$; $p < 0.01$), and the association remained insignificant, except when the study by Lai et al was removed (Table 2).

4. DISCUSSION

Recently there has been concern over the potential association between PPI use and the risk of HCC; however, it remains debated. The current study found that the use of PPIs may be associated with an increased risk of HCC, with a dose-response relationship. However, this association was not present after the data were adjusted for confounding factors.

PPIs can block the secretion of gastric acid by directly inhibiting hydrogen transport in the parietal cells of the stomach.[26]

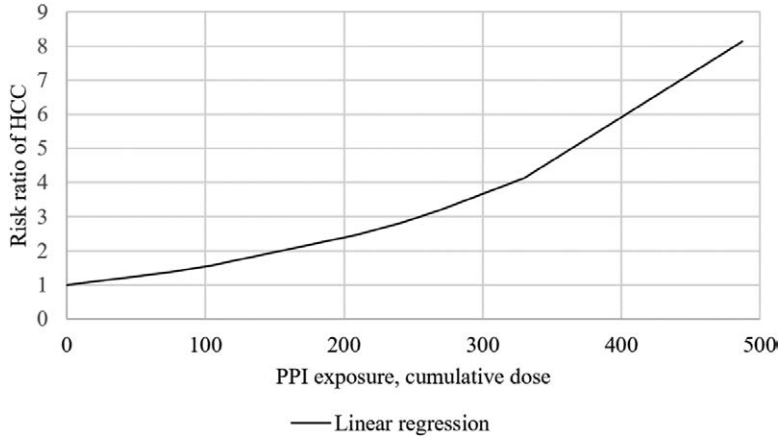

Fig. 3 Dose-response analysis shows significant relationship between dose of PPI and the risk of HCC in linear regression model (RR = 1.24, 95% CI: 1.22-1.26; $p < 0.01$). CI = confidence interval; HCC = hepatocellular carcinoma; PPI = proton pump inhibitor.

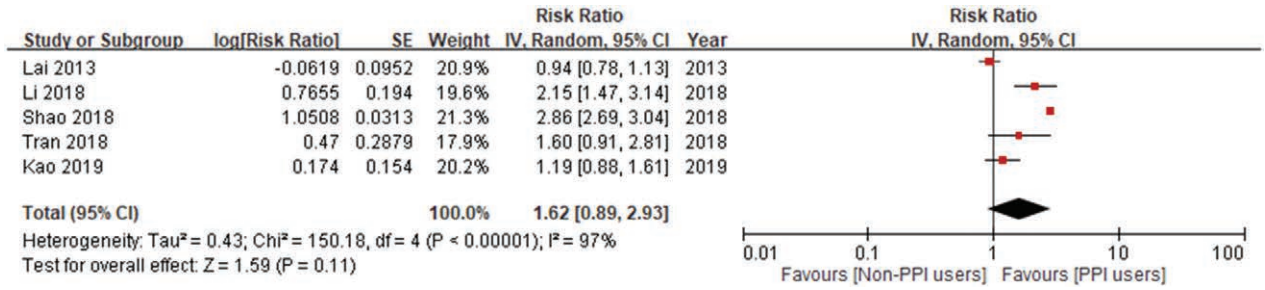

Fig. 4 Forest plot of association between PPI use and the risk of hepatocellular carcinoma in five eligible studies, using adjusted risk ratio. Events denote patients with hepatocellular carcinoma. CI = confidence interval; IV = inverse variance; PPI = proton pump inhibitor.

Table 2

Sensitivity analysis

	Risk ratio	95% CI	*p*
Lai et al[21]	1.88	1.15-3.07	0.01
Li et al[19]	1.51	0.74-3.07	0.26
Shao et al[20]	1.35	0.93-1.98	0.12
Tran et al[22]	1.62	0.83-3.18	0.16
Kao et al[23]	1.84	0.99-3.42	0.05

Sensitivity analysis was done by removal of included studies one by one.
CI = confidence interval.

Long-term use of PPIs causes hypergastrinemia as a response to the reduced acidity of the gastric juice.[27,28] Gastrin not only participates in the regulation of gastric acid secretion[29] but also plays a crucial trophic factor in the gastrointestinal tract.[30] Both gastrin and its receptor, cholecystokinin B receptor, were found to be expressed by HCC and may be associated with HCC tumor proliferation.[31,32]

Another possible mechanism of carcinogenesis by PPIs is alteration of the gut microbiota. Dysbiosis of gut microbiota may cause inflammation in the intestine, and the bacteria may translocate to the systemic circulation through a leaky gut and induce chronic inflammation in the body.[33] Both bacteria and their metabolites can enter the liver via the portal vein, and then activate the proinflammatory signaling pathway in the liver.[34] This process may induce hepatitis, fibrosis, and cancer.[34] Also, the gut microbiota plays an important role in modulating bile acids.[35] The deregulation of bile acids and increased fermented products from dysbiotic gut microbiota may be associated with the formation of HCC.[35,36] It has been shown that PPIs can induce dysbiosis of gut microbiota and increase the growth of potentially pathogenic bacteria, such as *Clostridium difficile*, genera *Enterococcus*, *Streptococcus*, *Staphylococcus*, and *Escherichia coli*.[16,37,38] Grąt et al from Poland discovered that patients with HCC had significantly increased fecal counts of *Escherichia coli* compared with non-HCC patients, but this association was not found for other enterobacteria.[39] Further studies are needed to confirm whether the alteration in the composition of the gut microbiome, which is induced by PPI use, can lead to carcinogenesis of the liver.

Furthermore, omeprazole, lansoprazole, and pantoprazole are CYP1A inducers, which may activate the aryl hydrocarbon receptor (*AhR*).[40,41] *AhR* is recognized as facilitating tumor promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin, also recognized as dioxin.[42] Some other CYP1A inducers are known to have the potential to promote hepatocellular tumors and increase oxidative stress in animal studies.[43,44] Omeprazole was found to be a hepatocellular tumor promoter in rats, with significant augmentation in the expression of *AhR* genes.[43,44]

Based on the above-mentioned hypothesis, Dultz et al found that PPI use was associated with a higher model of end-stage liver disease (MELD) score and ascites in cirrhotic patients, and was an independent risk for mortality in cirrhotic patients apart from MELD score, HCC and hepatic decompensation.[7] PPI use may also increase the risk of HE and SBP in patients with cirrhosis.[8,9] In a study by Llorente et al, it was demonstrated that PPIs may promote alcoholic liver disease by altering the gut microbiota.[38]

In 2013, Lai et al from Taiwan evaluated the association between PPIs and HCC, and they revealed that PPI use did not significantly increase the risk of HCC after adjusting for age, cirrhosis, alcoholic liver damage, NAFLD, viral hepatitis, diabetes mellitus, and the use of other medications.[21] In 2018, two different studies demonstrated that PPI use may be associated with the occurrence of HCC. Li et al from the United States found that PPI use increased the risk of HCC among patients with chronic hepatitis C infections.[19] Shao et al from Taiwan discovered that PPI use was associated with an increased risk of HCC in patients without viral hepatitis or cirrhosis, with a dose-response relationship (p for trend <0.0001).[20] Conversely, Tran et al, from the United Kingdom, analyzed two sets of data from the UK Biobank and Primary Care Clinical Informatics Unit (PCCIU), and found no significant correlation between PPI use and HCC after adjusting for age, gender, body mass index, alcohol, smoking, use of other medications and comorbidities, including cirrhosis, hepatitis, diabetes, and peptic ulcer disease.[22] Kao et al from Taiwan analyzed patients with chronic hepatitis B and C infections, and revealed that PPI use was not associated with HCC, even in patients with long-term use (>365 cumulative doses).[23] In 2018, a short report revealed that PPI use was not associated with HCC following a meta-analysis.[45] However, the meta-analysis enrolled patients with both HCC and cholangiocarcinoma, which may have distorted the results.[22,45] Although the current study included the same five studies, the data that were used was different, and included HCC patients only.[22]

In the present study, a significant association was found between PPI use and HCC when crude RRs were used. However, a high heterogeneity was found in the studied population. Lai et al included a heterogenous population with patients having viral hepatitis, cirrhosis, alcoholic liver disease, and NAFLD. Li et al included patients with Hepatitis C virus (HCV) infection who received anti-HCV therapy during the study period and excluded patients who had previous hepatic decompensation, HCC, or coinfection with human immunodeficiency virus or Hepatitis B virus (HBV).[19] However, patients who had been exposed to PPIs had higher baseline HCV RNA levels, lower sustained viral response rates, and increased alcohol abuse or a history of smoking compared with non-PPI users, which may have influenced the result.[19] Shao et al excluded patients with viral hepatitis or

cirrhosis at baseline.[20] Tran et al extracted two sets of data from the UK Biobank and PCCIU, and analyzed them separately. The data from the PCCIU was not analyzed in the present study because it included both HCC and intrahepatic cholangiocarcinoma patients and could not be properly used to assess the effect of PPI on HCC. Data from the UK Biobank included 0.1% patients with cirrhosis and 0.5% patients with hepatitis, and revealed that PPI use was not associated with HCC.[22] In the study by Kao et al, the included patients either had chronic HBV or HCV infection; however, patients with dual HBV and HCV infections were excluded.[23] They found that PPI use was not associated with HCC in both the HBV and HCV groups, even in patients with hepatic decompensation.[23] The association between PPI use and HCC was insignificant in the homogenous cohort of HBV or HCV carriers in Kao's group.[23] Viral hepatitis is known to be a risk factor for HCC, and the presence of viral hepatitis may overwhelm the effect of PPI. The association between PPI use and HCC was lost when the data were adjusted for concurrent liver disease and other medications during the meta-analysis. However, it was not possible to perform a subgroup analysis of coexisting liver diseases, such as viral hepatitis infection, due to the small study number and the lack of detailed information about the status of viral hepatitis in all of the studies.

A dose-response relationship between PPI and HCC was found in the present study. However, only two studies were corresponded to the analysis.[20,23] Therefore, further investigation is needed to confirm whether prolonged use of PPIs increases the risk of HCC.

There were several limitations to the present meta-analysis. First, the enrolled studies focused on different populations. Two of the studies focused on patients with viral hepatitis,[19,23] while one study excluded patients with HBV or HCV.[20] The status of hepatic function and the antiviral treatment were not well defined in most of the studies. Second, four of the included studies were case-controlled studies. There were unmeasurable confounding factors for HCC, such as alcoholic liver disease, NAFLD, smoking and family history. Third, some patients who bought PPIs over the counter may have been misclassified as non-PPI users.

In conclusion, the present meta-analysis has shown that PPI use was not significantly associated with an increased risk of HCC. However, limited studies have suggested that there may be a dose-response relationship between PPIs and HCC. Further studies are warranted to verify the association between PPI use and HCC.

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REFERENCES

1. Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, et al. Proton pump inhibitors therapy and risk of clostridium difficile infection: systematic review and meta-analysis. *World J Gastroenterol* 2017;**23**:6500–15.
2. Ding J, Heller DA, Ahern FM, Brown TV. The relationship between proton pump inhibitor adherence and fracture risk in the elderly. *Calcif Tissue Int* 2014;**94**:597–607.
3. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American gastroenterological association. *Gastroenterology* 2017;**152**:706–15.
4. Eid SM, Boueiz A, Paranji S, Mativo C, Landis R, Abougergi MS. Patterns and predictors of proton pump inhibitor overuse among academic and non-academic hospitalists. *Intern Med* 2010;**49**:2561–8.
5. Weersink RA, Taxis K, Drenth JPH, Houben E, Metselaar HJ, Borgsteede SD. Prevalence of drug prescriptions and potential safety in patients with cirrhosis: a retrospective real-world study. *Drug Saf* 2019;**42**:539–46.
6. Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. Multicenter, prospective study. *Hepatology* 2010;**52**:2065–76.
7. Dultz G, Piiper A, Zeuzem S, Kronenberger B, Waidmann O. Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis. *Aliment Pharmacol Ther* 2015;**41**:459–66.
8. Cole HL, Pennycook S, Hayes PC. The impact of proton pump inhibitor therapy on patients with liver disease. *Aliment Pharmacol Ther* 2016;**44**:1213–23.
9. 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;**64**:1265–72.
10. Bajaj JS, Acharya C, Fagan A, White MB, Gavis E, Heuman DM, et al. Proton pump inhibitor initiation and withdrawal affects gut microbiota and readmission risk in cirrhosis. *Am J Gastroenterol* 2018;**113**:1177–86.
11. Robertson DJ, Larsson H, Friis S, Pedersen L, Baron JA, Sørensen HT. Proton pump inhibitor use and risk of colorectal cancer: a population-based, case-control study. *Gastroenterology* 2007;**133**:755–60.
12. Brusselaers N, Engstrand L, Lagergren J. Maintenance proton pump inhibition therapy and risk of oesophageal cancer. *Cancer Epidemiol* 2018;**53**:172–7.
13. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for helicobacter pylori: a population-based study. *Gut* 2018;**67**:28–35.
14. Kearns MD, Boursi B, Yang YX. Proton pump inhibitors on pancreatic cancer risk and survival. *Cancer Epidemiol* 2017;**46**:80–4.
15. Dacha S, Razvi M, Massaad J, Cai Q, Wehbi M. Hypergastrinemia. *Gastroenterol Rep (Oxf)* 2015;**3**:201–8.
16. Freedberg DE, Lebwohl B, Abrams JA. The impact of proton pump inhibitors on the human gastrointestinal microbiome. *Clin Lab Med* 2014;**34**:771–85.
17. Smith JP, Fonkoua LK, Moody TW. The role of gastrin and CCK receptors in pancreatic cancer and other malignancies. *Int J Biol Sci* 2016;**12**:283–91.
18. Hayashi H, Shimamoto K, Taniai E, Ishii Y, Morita R, Suzuki K, et al. Liver tumor promoting effect of omeprazole in rats and its possible mechanism of action. *J Toxicol Sci* 2012;**37**:491–501.
19. Li DK, Yan P, Abou-Samra AB, Chung RT, Butt AA. Proton pump inhibitors are associated with accelerated development of cirrhosis, hepatic decompensation and hepatocellular carcinoma in noncirrhotic patients with chronic hepatitis C infection: results from ERCHIVES. *Aliment Pharmacol Ther* 2018;**47**:246–58.
20. Shao YJ, Chan TS, Tsai K, Wu SY. Association between proton pump inhibitors and the risk of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2018;**48**:460–8.
21. Lai SW, Liao KF, Lai HC, Lin CL, Sung FC. Proton pump inhibitors and risk of hepatocellular carcinoma: a case-control study in Taiwan. *Acta Gastroenterol Belg* 2013;**76**:348–50.
22. Tran KT, McMenamin ÚC, Hicks B, Murchie P, Thrift AP, Coleman HG, et al. Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies. *Aliment Pharmacol Ther* 2018;**48**:55–64.
23. Kao WY, Su CW, Chia-Hui Tan E, Lee PC, Chen PH, Tang JH, et al. Proton pump inhibitors and risk of hepatocellular carcinoma in patients with chronic hepatitis B or C. *Hepatology* 2019;**69**:1151–64.
24. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;**135**:1301–9.
25. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata Journal* 2006;**6**:40–57.
26. Shamburek RD, Schubert ML. Control of gastric acid secretion. Histamine H2-receptor antagonists and H+K(+)-atpase inhibitors. *Gastroenterol Clin North Am* 1992;**21**:527–50.
27. Lundell L, Vieth M, Gibson F, Nagy P, Kahrilas PJ. Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. *Aliment Pharmacol Ther* 2015;**42**:649–63.

28. Shiotani A, Katsumata R, Gouda K, Fukushima S, Nakato R, Murao T, et al. Hypergastrinemia in long-term use of proton pump inhibitors. *Digestion* 2018;**97**:154–62.
29. Wolfe MM, Soll AH. The physiology of gastric acid secretion. *N Engl J Med* 1988;**319**:1707–15.
30. Johnson LR. Effect of exogenous gut hormones on gastrointestinal mucosal growth. *Scand J Gastroenterol Suppl* 1982;**74**:89–92.
31. Caplin M, Khan K, Savage K, Rode J, Varro A, Michaeli D, et al. Expression and processing of gastrin in hepatocellular carcinoma, fibrolamellar carcinoma and cholangiocarcinoma. *J Hepatol* 1999;**30**:519–26.
32. Roy J, Putt KS, Coppola D, Leon ME, Khalil FK, Centeno BA, et al. Assessment of cholecystokinin 2 receptor (CCK2R) in neoplastic tissue. *Oncotarget* 2016;**7**:14605–15.
33. Giannelli V, Di Gregorio V, Iebba V, Giusto M, Schippa S, Merli M, et al. Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis. *World J Gastroenterol* 2014;**20**:16795–810.
34. Chassaing B, Etienne-Mesmin L, Gewirtz AT. Microbiota-liver axis in hepatic disease. *Hepatology* 2014;**59**:328–39.
35. Liu HX, Keane R, Sheng L, Wan YJ. Implications of microbiota and bile acid in liver injury and regeneration. *J Hepatol* 2015;**63**:1502–10.
36. Singh V, Yeoh BS, Chassaing B, Xiao X, Saha P, Aguilera Olvera R, et al. Dysregulated microbial fermentation of soluble fiber induces cholestatic liver cancer. *Cell* 2018;**175**:679–694.e22.
37. Imhann F, Bonder MJ, Vich Vila A, Fu J, Mujagic Z, Vork L, et al. Proton pump inhibitors affect the gut microbiome. *Gut* 2016;**65**:740–8.
38. Llorente C, Jepsen P, Inamine T, Wang L, Bluemel S, Wang HJ, et al. Gastric acid suppression promotes alcoholic liver disease by inducing overgrowth of intestinal enterococcus. *Nat Commun* 2017;**8**:837.
39. Grąt M, Wronka KM, Krasnodębski M, Masior Ł, Lewandowski Z, Kosińska I, et al. Profile of gut microbiota associated with the presence of hepatocellular cancer in patients with liver cirrhosis. *Transplant Proc* 2016;**48**:1687–91.
40. Masubuchi N, Li AP, Okazaki O. An evaluation of the cytochrome P450 induction potential of pantoprazole in primary human hepatocytes. *Chem Biol Interact* 1998;**114**:1–13.
41. Yoshinari K, Ueda R, Kusano K, Yoshimura T, Nagata K, Yamazoe Y. Omeprazole transactivates human CYP1A1 and CYP1A2 expression through the common regulatory region containing multiple xenobiotic-responsive elements. *Biochem Pharmacol* 2008;**76**:139–45.
42. Murray IA, Patterson AD, Perdew GH. Aryl hydrocarbon receptor ligands in cancer: friend and foe. *Nat Rev Cancer* 2014;**14**:801–14.
43. Coe KJ, Nelson SD, Ulrich RG, He Y, Dai X, Cheng O, et al. Profiling the hepatic effects of flutamide in rats: a microarray comparison with classical aryl hydrocarbon receptor ligands and atypical CYP1A inducers. *Drug Metab Dispos* 2006;**34**:1266–75.
44. Shimamoto K, Dewa Y, Kemmochi S, Taniai E, Hayashi H, Imaoka M, et al. Relationship between CYP1A induction by indole-3-carbinol or flutamide and liver tumor-promoting potential in rats. *Arch Toxicol* 2011;**85**:1159–66.
45. Zhao J, Hua L, Li N, An R, Liang C. Letter: proton pump inhibitors use and risk of hepatocellular carcinoma: a meta-analysis of observational studies. *Aliment Pharmacol Ther* 2018;**48**:886–8.