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Proton pump inhibitors and risk of liver cancer and mortality in patients with chronic liver disease: a systematic review and meta-analysis

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Abstract

Background—Epidemiological studies investigating the use of proton pump inhibitors (PPI) on the risk of liver cancer and/or mortality among persons with chronic liver disease (CLD) have reported conflicting results. We conducted a systematic review and meta-analysis to determine the impact of PPI-use on liver cancer and/or death among patients with CLD.

Methods—The core databases including MEDLINE, EMBASE, and Cochrane library were searched through January 2020. We included studies, evaluating the association between PPIs and liver cancer or mortality among patients with CLD including randomized controlled, nonrandomized controlled, and observational studies. We used inverse-variance random-effects models to estimate the pooled relative risk (RR) and 95% confidence interval (CI) for liver cancer or mortality.

Results—Eleven studies including 173,894 patients were selected. In three studies, individuals with CLD who used PPIs had a 67% greater risk of developing hepatocellular carcinoma (HCC) compared to nonusers (RR, 1.67; 95% CI, 1.12–2.50; I^2=92%). Combining data from the eight

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studies relating PPI to overall mortality, we observed a 57% increased risk of mortality in PPI users with CLD compared to CLD nonusers (RR: 1.57; 95% CI, 1.24–1.99; I^2=69%).

Conclusion—PPI-use was associated with an increased risk of HCC and mortality in patients with CLD suggesting that PPI prescriptions in patients with CLD should be considered carefully.

Keywords

proton pump inhibitor; mortality; liver cancer; hepatocellular carcinoma; chronic liver disease; systematic review; meta-analysis

Introduction

Proton pump inhibitors (PPIs) were first introduced in 1989 to treat gastroesophageal reflux disorder (GERD) by blocking acid production by irreversibly inhibiting Hþ/Kþ-adenosine triphosphatase in gastric parietal cells. By 2015, PPIs in the United States ranked among the top 10 national health-related drug expenditures [1–4]. However, in recent years, concern has been raised for potential serious adverse events associated with PPI-use including gastric cancer, pancreatic cancer, major adverse cardiovascular events, and death [5–9]. The most recent research suggests that when PPIs are used appropriately, they are safe medications but should be used for the shortest time period at the smallest effective dose [10,11].

As in the general population, PPIs are also among the most commonly prescribed classes of drugs among patients with cirrhosis [12]. However, PPIs are only recommended in a few specific situations such as during the immediate post variceal banding period and only for short-term use [13]. In fact, PPI is not routinely recommended for patients with decompensated cirrhosis and not even for primary or secondary prophylaxis against gastrointerestinal bleeding among those with significant esophageal varices [14].

Recently, several observational studies examining the association between the use of PPIs and the risk of hepatocellular carcinoma (HCC), a well-known complication of cirrhosis whether due to viral hepatitis or alcoholic or nonalcoholic liver disease [15–18], but they reported conflicting results [18–21]. Therefore, we performed a systematic review and meta-analysis of the relevant published literature to evaluate the association between PPI-use, liver cancer development, and mortality among patients with CLD.

Methods

Literature search

We searched relevant full-text articles using the MEDLINE, EMBASE, and Cochrane library databases through January 31, 2020. The search strategy included “liver disease,” “liver neoplasm,” and “liver cancer” as patient-related terms, and “proton pump inhibitor” as the main drug-related term (Supplementary Table 1). Both MeSH terms and text words were applied to each database as applicable. PPI drug names included in the search strategy were omeprazole, esomeprazole, pantoprazole, rabeprazole, dexlansoprazole, tenatoprazole, and benatoprazole as well as their brand and chemical names.

Study selection

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [22]. We included studies that met the following inclusion criteria: they (1) presented original data from randomized controlled studies, nonrandomized controlled studies, or observational studies that evaluated the association between PPIs and liver cancer or mortality among patients with CLD; (2) included clearly defined outcomes of liver cancer incidence and/or mortality; (3) provided quantitative risk estimates (hazard ratio [HR], relative risk [RR], or odds ratio [OR]) and associated 95% confidence intervals (CI); and (4) were written in English. We excluded non-comparative studies, non-peer reviewed studies, conference abstracts, and review studies. Two investigators independently conducted the study selection, data extraction, and quality assessment (HJS and XJ). When discordance occurred and a consensus could not be reached through discussion by the two primary reviewers, discussion and adjudication with the third investigator (HP) was carried out.

Quality assessment

Since all eligible studies of this systematic review were observational studies, we used the risk of bias assessment tool for non-randomized studies (ROBANS) to assess the quality for all articles included in this study [23]. ROBANS consists of six items (selection of participants, confounding variables, measurement of intervention, blinding for outcome assessment, incomplete outcome data, and funding resources) evaluated on the three levels of bias (low, unclear, or high risk of bias).

Data extraction

Data were extracted using a data frame with predefined variables: country of study, study design, data source, inclusion and exclusion criteria of patients, the number of patients in each group, and cohort characteristics (e.g., mean age, sex, and etiology of liver disease), PPI name with dosage, criteria to define liver cancer incidence and mortality outcomes, study follow-up duration, and other relevant confounders if regression analysis was performed. The study protocol was registered to PROSPERO (CRD42018116354) prior to the study execution.

Data analyses

Our primary outcome was the adjusted estimates of the risk of liver cancer incidence or mortality rates associated with PPI-use among patients with CLD. For studies that reported multiple risk estimates, we used the best-adjusted estimates to obtain the pooled estimate. The summary estimate of the adjusted risk ratio of outcome was generated by weighting the study-specific risk ratios by the inverse of their variance. We considered HRs as RRs [24,25], and we converted ORs to RR using the Zhang and Yu method [26]. We included eight studies that reported HRs and two studies that reported ORs in our analysis to estimate the pooled RR [27,28]. If the included study reported the number of deaths for each group, we pooled the unadjusted RR using inverse-variance random effect models.

Heterogeneity was assessed using the I^2 tests and the Q statistic [29]. Significance of the Q-statistic test ($P<0.05$) indicates a substantial level of heterogeneity. The I^2 statistic describes the percentage of the variability in estimates resulting from heterogeneity rather than

sampling error, with I^2 values of 50% or higher indicating the presence of a significantly high level of heterogeneity [29]. Due to the high level of heterogeneity observed in the preliminary analysis of this study, we used a random-effects model to analyze the pooled estimates.

In addition, we performed subgroup analyses according to the type of CLD (cirrhosis or hepatitis), follow-up period (≤1 year versus >1 year), and study location (Asia versus non-Asia) when there was data available for at least two studies. We used the funnel plot to assess possible publication bias. All statistical analyses were performed using the Review Manager Software version 5.3 (RevMan v5.3, The Cochrane Collaboration, Oxford, UK).

Results

Literature search

Our search strategy initially yielded 9,002 articles for review and screening (Fig. 1). After excluding duplicates, 8,575 articles remained for title or abstract screening. Excluded studies included: no CLD patients, no PPI group, papers not written in English, case reports or series, editorials, reviews, and abstracts. After these articles were excluded, 683 full text articles were reviewed and 672 studies were then excluded. Eleven articles (173,894 patients) met our study inclusion/exclusion criteria and were included in the meta-analysis: three studies provided data for liver cancer incidence analysis [20,21,30] and eight studies for mortality rate analysis [12,18,19,31–35]. No studies provided both liver cancer and mortality outcomes.

General characteristics of the included studies

Table 1 describes the characteristics of the included studies and their patient cohorts. There were three studies from Taiwan and one from each of the following countries: United States, United Kingdom, Germany, Austria, Italy, Hungary, Singapore, and South Korea. Ten used a cohort study design and one used a nested case-control study design. The etiologies/types of CLD of the study cohorts included ALD, NAFLD, viral hepatitis, cirrhosis of any etiology, autoimmune disease, and other miscellaneous liver diseases. The exposure to PPIs was based on prescribed medications (e.g. omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole). Table 2 describes the ascertainment methods of exposures and outcomes employed by the included studies.

Quality assessment

We assessed the risk of bias for ten cohorts from nine studies since Kao et al. included two separate cohorts (hepatitis B virus [HBV] cohort and hepatitis C virus [HCV] cohort) [30]. All included studies had low risk of bias in the selection of study participants, blinding for outcome assessment, and funding resources (Fig. 2). Since the outcomes of liver cancer and mortality were not associated with subjective judgement, we considered low risk for blinding for outcome assessment. Most (>80%) of the studies also had low risk of bias in the category of confounding variables and incomplete outcome data, while two were considered high risk of bias because the study participants' demographic data were not included as confounders [12,37]. For bias regarding measurement of intervention, half of the included

studies were considered low risk, while the risk was not ascertainable in the remainders because the studies could not identify over-the-counter medications that patients may have purchased.

Association between PPI-use and liver cancer

Three studies including two from Asia comprising 166,301 patients and evaluating the association between PPIs and HCC were included [20,21,30]. As Kao et al. reported patients with HBV and HCV separately [30]; we had a total of four cohorts in our analysis: one HBV cohort, two HCV cohorts, and one cirrhosis cohort. Overall, the patients' mean age ranged from 48 to 59 years, with about 48% to 96% male and 6%−19% diabetic patients. Notably, the vast majority of the patients had CLD related to HBV (n=11,154), HCV (n=15,356), or cirrhosis (n=139,791) and less than 3% of HBV and HCV patients had ALD (n= 319) or NAFLD (n=256). All three studies adjusted for relevant demographic, comorbidity and/or concomitant medication covariates in their regression analysis relating HCC outcomes to PPI exposure and showed similar etiology/types of CLD between PPI user and nonuser groups. The Kao et al. and Shao et al. studies defined PPI users by cumulative daily drug dose (cDDD), calculated as the number of pills dispensed by the prescribed dose divided by the recorded days' supply), of 28 or 30 mg or greater [20,30] while the Li et al. study classified PPI users as those who took at least one PPI prescription at any time during the study period [21] (Table 2). Over a median follow-up time ranging from one to eight years, there were 1,452 cases of incident HCC in 13,037 PPI users (11.1%) and 11,744 cases of incident HCC in 141,738 nonusers (8.3%) from three studies (RR, 1.42; 95% CI 0.68–2.95) (Fig. 3a).

The pooled risk estimates indicated that PPI users with CLD had a 67% greater risk of developing HCC compared to nonusers (aRR, 1.67; 95% CI, 1.12–2.50) (Fig. 3b). There was evidence of significant heterogeneity (I^2=92%, P<0.001), but not publication bias (Fig. 4a). In the subgroup analysis, significantly higher HCC risk was observed in PPI users with hepatitis (PPI users: n=13,244, nonusers: n=13,266) compared to nonuser counterparts (aRR, 1.45; 95% CI, 1.03–2.03). This association was observed among patients with cirrhosis although this finding was not statistically significant (aRR, 1.14; 95% CI, 0.32–4.01) (PPI users: n=5,878, nonusers: n=133,328) (Table 3). We observed that the longer the follow-up of HCC after PPI-use, the higher the pooled RR. Notably, the association between PPI-use and higher HCC risk was not statistically significant in the Asia study.

Association between PPI-use and mortality

Eight studies investigated the relationship between PPI-use and mortality among patients with CLD (n=7,593 patients: 2,492 PPI users and 5,101 nonusers) [12,18,19,31–35]. One included patients with all types of liver disease [31] whereas seven included patients with cirrhosis [12,18,19,32–35]. Some of the cirrhotic patients from the seven studies also had other liver diseases such as viral hepatitis, ALD or NAFLD, or HCC and the proportion of liver disease among the two groups was similar (Table 1). The majority of the study patients were male (54–77%) with mean age ranging 56 to 63 years. For CLD patients, the model for end-stage liver disease (MELD) score ranged from 11 to 20. Regarding liver disease etiology, ALD accounted for 8–55% among the included studies, NAFLD 3–18%, HBV 13–

75%, and HCV 12–27%. Of note, about half of Hung et al. (45%) and Kwon et al. (54%) study patients had HCC [18,32]. The median follow-up time ranged from 30 days to 3.4 years (Table 2). Among eight studies, five reported the number of deaths and adjusted HR [18,19,32,34,35] and three reported mortality data only as adjusted HR [12,31,33]. In the five studies, there were 1,062 deaths among 1,705 PPI users (62.2%) and 2,718 deaths among 4,803 nonusers (56.6%) (RR, 1.82; 95% CI, 1.22–2.72) (Fig. 5a).

Pooled estimates from the eight included studies indicated that PPI users had a 57% increased risk of (RR) mortality compared to PPI nonusers (aRR, 1.57; 95% CI, 1.24–1.99). There was significant heterogeneity (I^2=69%, P=0.002) (Fig. 5b) but not publication bias (Fig. 4b). We found a significant association between PPI-use and increased mortality among patients with cirrhosis in seven studies (aRR, 1.59; 95% CI, 1.23–2.06). There was insufficient data to perform sub-analysis for patients with hepatitis. When investigating the effect of follow-up duration, the association between PPI-use and increased mortality was highly significant (aRR, 2.05; 95% CI, 1.63–2.58), while the association was only modest and trending towards significance among those with a one-year follow-up or shorter duration (aRR, 1.20; 95% CI, 0.97–1.48) (Table 3). The significant association between PPI-use and mortality appeared consistent among studies from Asia (aRR, 1.43; 95% CI, 1.08–1.89) and non-Asia (aRR, 1.69; 95% CI, 1.12–2.54).

Discussion

To the best of our knowledge, this is first meta-analysis to evaluate and quantify the association between PPI-use and the risk of liver cancer and mortality among patients with CLD. Overall, we found that patients with CLD who used PPIs had a 67% increased risk of HCC and a 57% increased risk of mortality compared to nonusers, though there were some differences among the various subgroups.

Investigations of the association between PPI-use and hepatic encephalopathy in patients with liver dysfunction [36] and PPI-use and HCC in general population (i.e. people with or without liver disease) [37] reported varied results. One meta-analysis reported that PPIs were associated with a higher hepatic encephalopathy risk among patients with chronic and acute liver dysfunction (OR, 1.76; 95% CI, 1.15–2.69) [36]. Another reported that there was no significant association between PPI-use and the risk of HCC (OR, 1.58; 95% CI, 0.91–2.76) [37]. The differences in our findings may be due to previous studies not considering the impact of CLD as an important risk factor for the incidence of HCC [38]. In fact, HCC almost exclusively occurs in the setting of CLD.

Therefore, to further investigate our findings, we performed subgroup analyses and found that patients with hepatitis were at a higher risk for HCC than nonusers. In addition, patients with >1 year follow-up after initiating PPIs had a two times greater risk for HCC than those with ≤1 year. Unfortunately, we were unable to analyze PPI dosage as only two studies (Li et al. and Shao et al.) reported dose-dependent risk. They found that an increased cumulative daily dose was associated with an increased risk of HCC [20,21]. Though we also found that PPI-use was associated with increased risk of HCC among cirrhotic patients, this finding

was not statistically significant, probably due to small sample sizes of PPI users among cirrhotic patients.

Besides the observed increased risk for mortality, we also found that PPI-use was significantly associated with increased risk of death in CLD patients (aRR, 1.57; 95% CI, 1.24–1.99). The association remained significant among patients with cirrhosis and those with >1 year follow-up. Several meta-analyses evaluated the association between PPIs and risk of death in patients with other chronic medical conditions (e.g., spontaneous bacterial peritonitis [SBP]) and their findings are somewhat different [39–42]. Yu et al. conducted a meta-analysis of PPI-use and the risk for mortality among cirrhotic patients with SBP. They reported that the association was not statistically significant. However, they noted that their meta-analysis included only four observational studies including one of low quality and cautioned readers that their results were unstable and further studies were needed [39]. The results of systematic reviews about the association between PPIs and mortality in patients taking clopidogrel were also controversial [40–42].

Although the pathophysiologic mechanism between PPI-use and the risk of liver cancer and death are not well understood, several plausible mechanisms have been suggested. Since PPIs are metabolized in the liver, PPI toxicity may occur in liver impaired patients which could lead to hypergastrinemia causing carcinogenic effects, especially on liver cells [43,44]. In addition, the use of cultured cells from the human liver have exhibited a genetic expression similar to well-known carcinogens in the liver after exposure to PPIs [45,46]. Reducing gastric acid with PPIs also leads to bacterial overgrowth of the stomach by increasing various microbes [48,49]. It has been shown that primary bile acid of the intestine transforms to secondary bile acid contributing to liver disease exacerbation in mice [50–52]. High levels of secondary bile acid in liver and bile duct cells may cause inflammatory, toxic, and deoxyribonucleic acid (DNA) damage that may contribute to HCC and cholangiocarcinoma [53,54]. Furthermore, PPI-use was found to lead to the proliferation of cells with fatal mutations through the induction of oxidative stress and the production of reactive oxygen species that further damage DNA and increases the mutation rate, tumor suppressor genes and oncogenes-increasing the risk of cancers [55–58]. Others have suggested that PPI-use limits the regenerative capacity of livers, reduces proteostasis and lysosomal acidification, and may promote oxidative stress, dysfunction, telomere shortening, aging of human endothelial cells, blockage of the antigen-presenting pathway, inhibiting synthesis and secretion of cytokines, as well as effecting the complement component proteins and coagulation factors. However, the mechanism of the association between changing gene expression and the risk of death is not entirely clear, requiring further study [59–62].

Our study has several strengths. First, this study, to the best of our knowledge, is the first systematic review and meta-analysis to examine the association between PPI-use and liver cancer and mortality in patients with CLD. The results of each observational study were controversial so now we are able to offer the best available evidence through our systematic and meta-analytic approach. Another strength of this study was that the present meta-analysis included a large sample size and high-quality studies. Thus, the precision of the meta-analysis was increased and the results more reliable. Third, we could identify PPI as an

independent risk factor for liver cancer or mortality in patients with CLD since we used the best-adjusted estimates to obtain the pooled estimate after controlling for confounders including demographic characteristics, comorbidities, and/or concomitant medications.

Several limitations need to be considered in the interpretation of our findings. First, the number of included studies was small, so we could not examine the magnitude of the association in detail or stratify by dose or different types of CLDs or different categories of PPI. Only two studies reported the dose-related association and found a PPI associated with an increased risk of HCC in a dose-dependent manner. There was one study that investigated a dose-dependent risk for mortality. Second, there was substantial heterogeneity in the population and quality of the original studies. The methods used to ascertain PPI-use and population varied widely across studies, likely contributing to the high degree of heterogeneity in the results. Although a random-effects meta-analysis, which takes into account study variability and confounders, was used to obtain a pooled estimate of studies, unknown factors can affect our results. Third, the included studies of this meta-analysis were cohort or case-control studies. Thus, we could only investigate the association between PPI-use and liver cancer or mortality and the casual relationship could be not confirmed. Fourth, there could be a confounding effect by indication of PPI use among “sicker” patients at higher risk for gastrointestinal bleeding. However, except for the few specific situations such as the immediate postendoscopic variceal banding period, there are generally no proven benefit or recommendation for PPI use in sicker or decompensated liver patients. In addition, PPI use in such situations is usually short-term. Therefore, it is likely that the vast majority of PPI use among cirrhotic patients are for indications that would be similar to the widespread use of PPI in the non-CLD population. Fifth, residual confounding is possible because no information was available for the duration of liver disease.

Conclusion

This systematic review and meta-analysis found that PPI-use was associated with an increased risk for HCC and mortality in CLD patients. We discussed various pathophysiologic mechanisms for these findings to include the direct damage to the liver cells and the impact of the liver disease itself in perhaps hastening liver disease progression. However, these theories require further study before conclusions can be drawn. Therefore, we conclude that PPIs should be used cautiously in patients with CLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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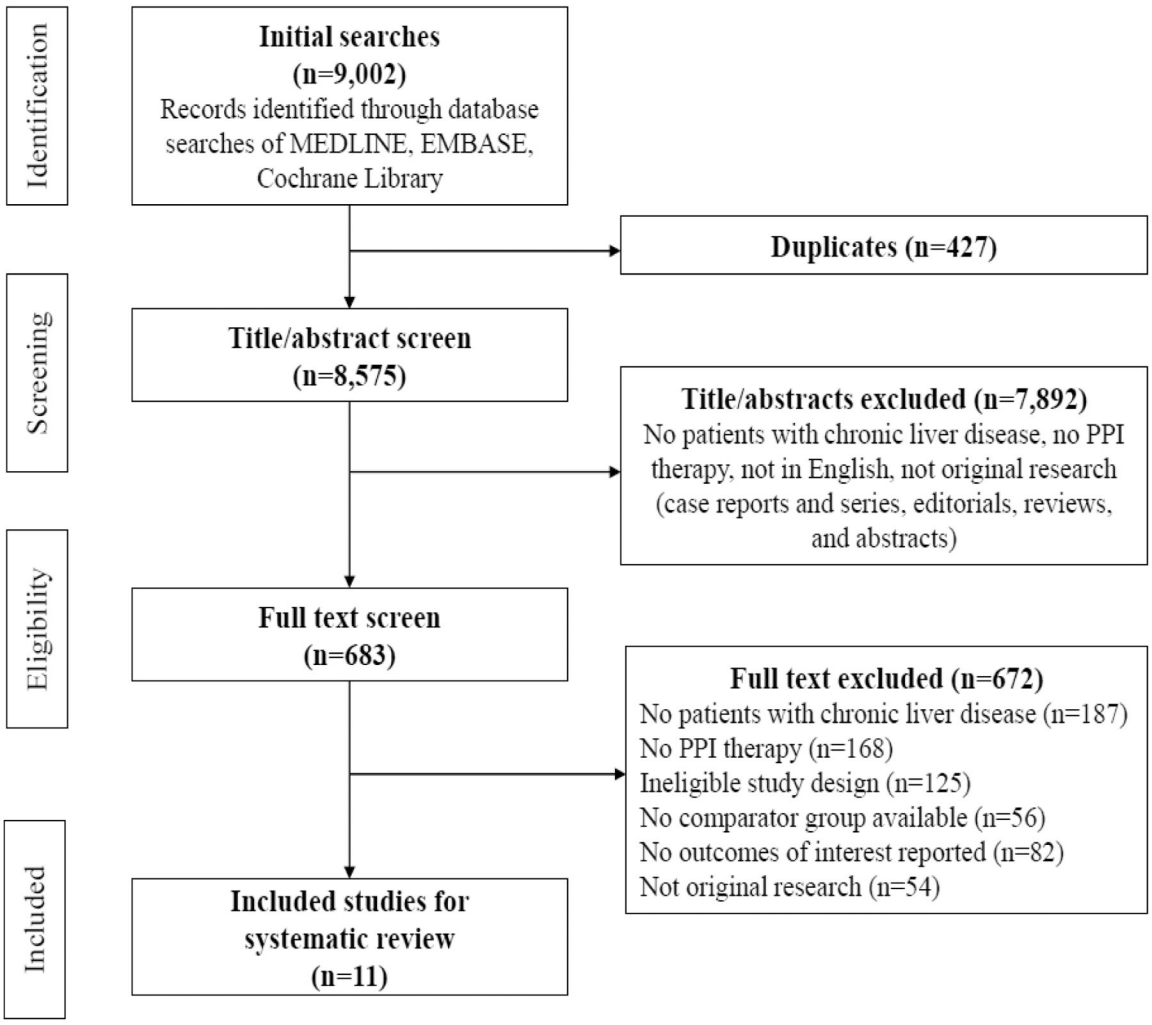

Fig. 1.
PRISMA flow diagram of study selections

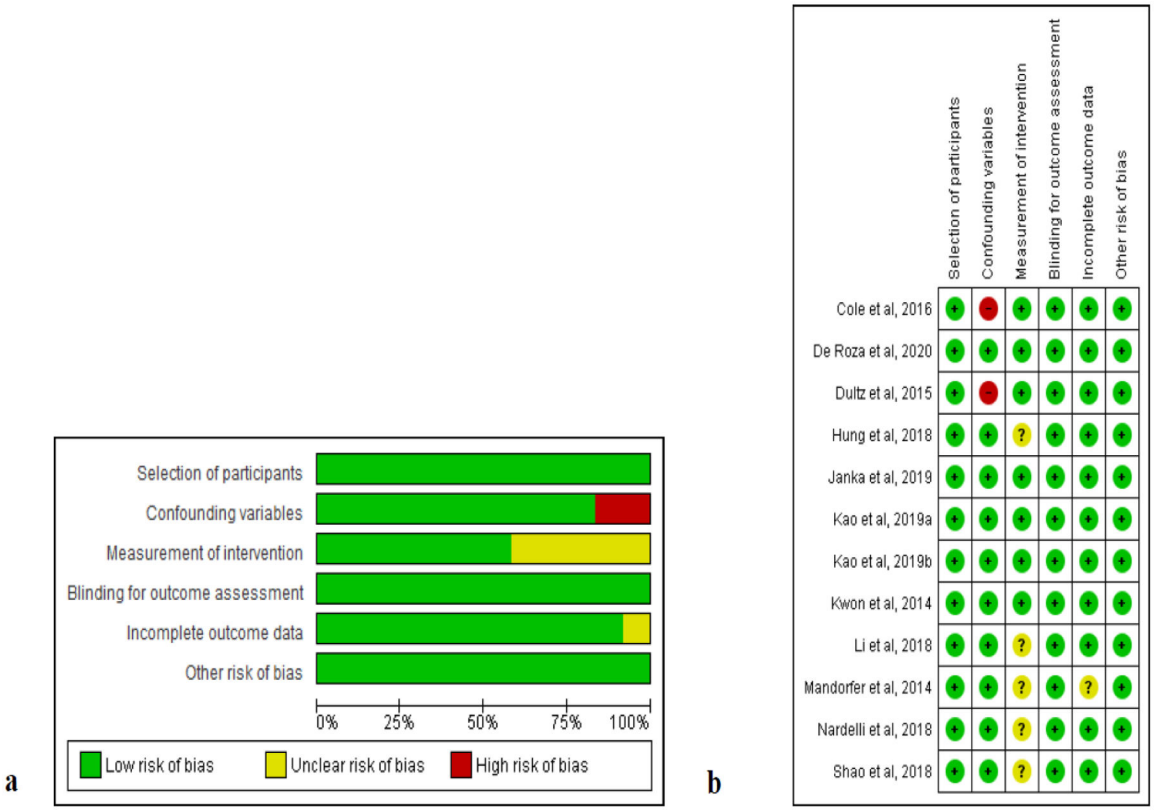

Fig. 2.

Quality assessment of included studies using Risk of Bias Assessment tool for Nonrandomized Studies (ROBANS) **a** ROBANS graph and **b** ROBANS summary +: low risk of bias; ?: unclear risk of bias; −: high risk of bias

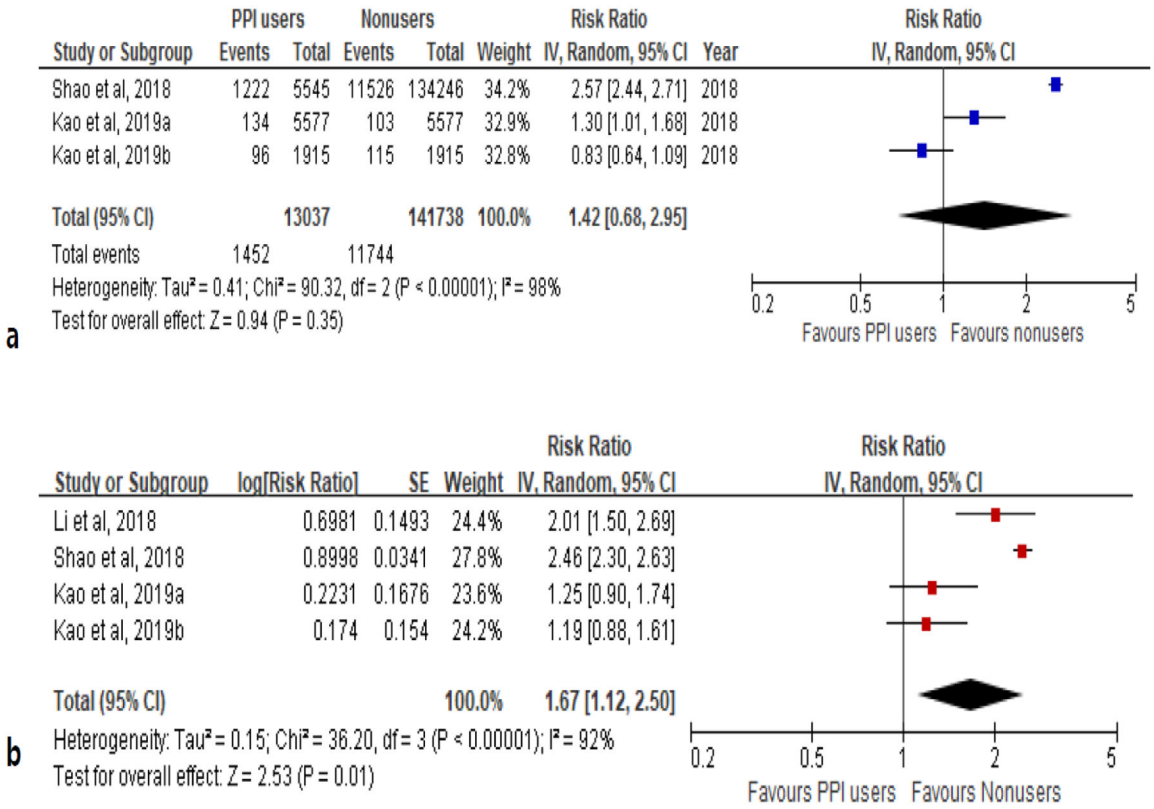

Fig. 3.

The association between proton pump inhibitor use and the risk of liver cancer in patients with chronic liver disease **a** unadjusted relative risk and **b** adjusted relative risk

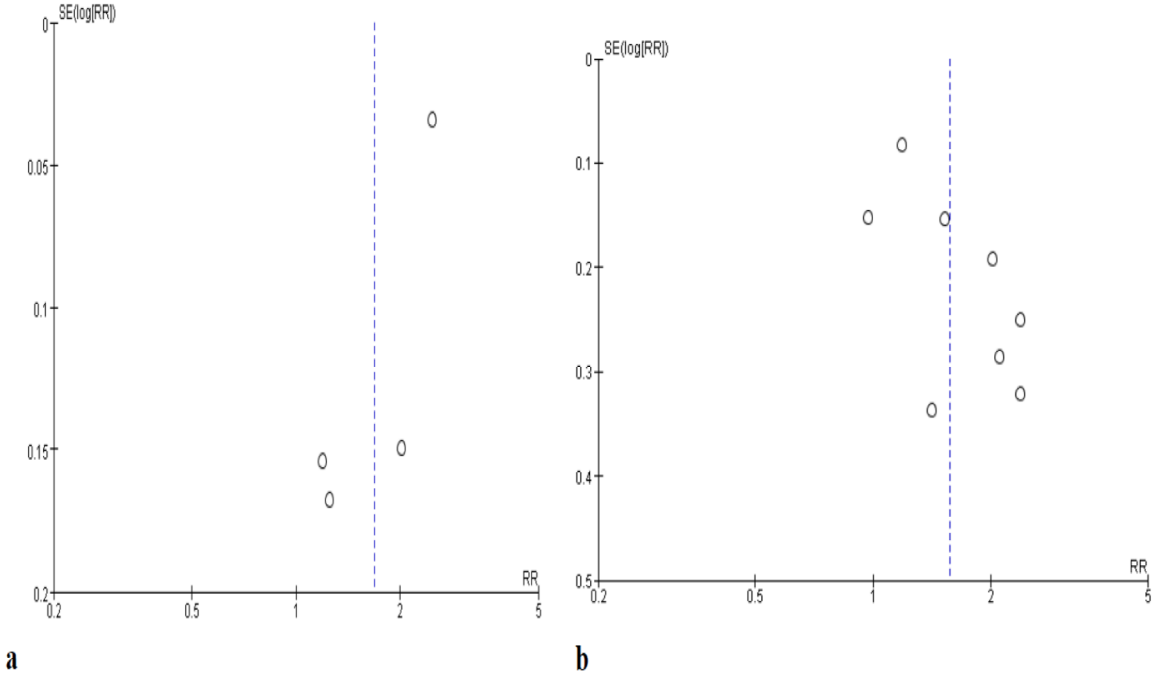

Fig. 4.
Funnel plot of included studies **a** liver cancer **b** mortality

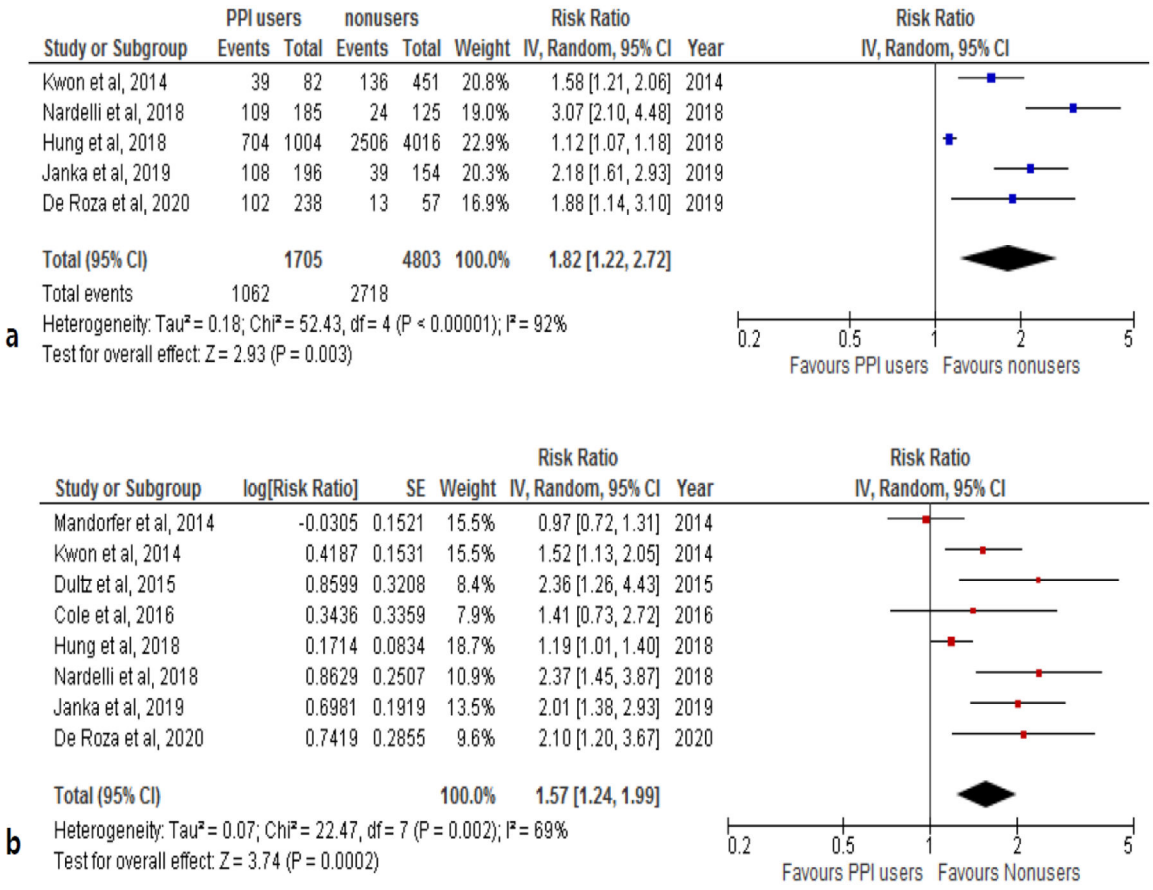

Fig. 5.

The association between proton pump inhibitor use and the risk of mortality in patients with chronic liver disease **a** unadjusted relative risk and **b** adjusted relative risk

Table 1

Study characteristics of included studies

Author, year	Country	Study design/ Data source	Patients	Number of participants	Mean age (SD)	Male	Diabetes	Etiology of liver disease/MELD score, median (range) or mean ± SD
Proton pump inhibitor use and liver cancer								
Kao et al. 2019 [30]	Taiwan	Cohort study/ Longitudinal H ealth Insuranc e Database (LH ID), 2003–2013	**1** Patients with HBV infection **2** Patients with HCV infection • Inclusion: Adult patients with HBV or HCV infection, three or more ambulatory claims or one inpatient • Exclusion: patients with dual HBV and HCV infection, diagnosed with other forms of cancers, follow-up duration of less than one year, PPI use before 2003, diagnosed with HCC before 2003 or within a year of the cohort entry date, diagnosed with HCC after using PPIs for less than a year	**1** HBV cohort 11,154 (5,577 PPI users, 5,577 nonusers) **2** HCV cohort 3,830 (1,915 PPI users, 1,915 nonusers)	**1** HHBV cohort PPI 48.9 (12.8), no PPI 48.9 (13.9) **2** HHCV cohort PPI 59.0 (13.7), no PPI 58.9 (14.4)	• HBV cohort PPI 61.7% • HCV cohort PPI 47.7%	**1** HBV cohort 9.0% **2** HCV cohort 19.0%	**1** HBV cohort • ALD: 1.9% • NAFLD: 1.4% • Cirrhosis: 3.2% **2** HCV cohort • ALD: 2.8% • NAFLD: 2.5% • Cirrhosis: 6.8%

Author, year	Country	Study design/ Data source	Patients	Number of part icipants	Mean age (SD)	Male	Diabetes	Etiology of liver disease/MELD score, median (range) or mean ± SD
Li et al. 2018 [21]	US	Cohort study/ Electronically retrieved cohort of HCV-infected veterans (ERCHIVES), 2001–2015	Patients with HCV infection • Inclusion: Non-cirrhotic patients with HCV infection, at least 14 days of treatment for HCV • Exclusion: coinfection with HIV, positive test for HBV surface antigen (HBsAg), diagnosis of cirrhosis, hepatic decompensation event prior to baseline or known gastr oesophageal v arices, HCC any time before or up to within 6 months of baseline, missing a baseline HCV RNA or FIB- 4 score, at least one FIB-4 was not available at least 24 months after completion of HCV therapy, exposed to both PPI and H2RA, first prescription of PPI after first diagnosis of cirrhosis	11,526 (5,752 PPI users, 5,774 nonusers)	Median 53 (IQR 49–57)	96.1%	6.1%	N/A
Shao et al. 2018 [20]	Taiwan	Nested case-control study/ National Health Insurance Research Dataset (NHIRD) linked the Death Registry, 2000–2013	Patients with cirrhosis • Inclusion: Patients with cirrhosis and without HBV or HCV • Exclusion: younger than 20 years, any diagnosis of cancer, HBV or HCV or cirrhosis before 2002, received any anti-viral therapy for hepatitis throughout the study period, PPI prescription before 2001, less than 365 days of follow- up, less than 180 days follow-up after first dose of PPIs	139,791 (5,545 PPI users, 134,2 46 nonusers)	N/A	N/A	N/A	N/A
Proton pump inhibitor use and mortality								
Cole et al. 2016 [31]	UK	Cohort study/ Scottish Liver	Patients with liver disease	206 (114 PPI us ers, 92 nonusers)	Median 56 (range 50–63)	65.5%	N/A	• ALD: 37.9%

Author, year	Country	Study design/ Data source	Patients	Number of participants	Mean age (SD)	Male	Diabetes	Etiology of liver disease/MELD score, median (range) or mean ± SD
		Transplant Unit (SLTU), 2013	• Inclusion: 2013 discharge list for all patients with liver disease on the Hepatology ward • Exclusion: non-hepatic illness, liver transplant, significant comorbidity such as HCC					• HBV, HCV, and HEV: 24.8% • NAFLD: 18.4% • Autoimmune hepatitis: 4.9% • Encephalopathy 34.5% • MELD: 18 (1324)
De Roza et al. 2020 [34]	Singapore	Cohort study/ Changi General Hospital, 2013–2017	Patients with cirrhosis • Inclusion: liver cirrhosis confirmed by histology, imaging or transient elastography and hospital admissions for hepatic decompensation • Exclusion: patients without hepatic decompensation	295 (238 PPI users, 57 nonusers)	PPI 63.3 (12. 4), nonusers 60.0 (13.3)	68.1%	Type 2 diabetes 53.2%	• HBV: 18.0% • HCV: 21.4% • Alcohol: 19.7% • NASH: 28.1% • Autoimmune: 2.7% • Median MELD: PPI 10.5 (range 8.0–14.3), nonusers 11.0 (range 8.0–14.5)
Dultz et al. 2015 [12]	Germany	Cohort study/ German University hospital, 2009–2011	Patients with cirrhosis • Inclusion: out- and in-patients with cirrhosis (confirmed by liver histopathological examination or pathognomonic results in ultrasound, CT, or MRI) • Exclusion: history of cancer other than HCC within the last 5 years, history of solid organ transplantation	272 (213 PPI users, 59 nonusers)	Median 57 (range 25–84)	66.9%	N/A	• ALD: 50.0% • HCV: 27.2% • HBV: 12.9% • NAFLD: 2.6% • Autoimmune hepatitis: 1.1% • MELD: 15 (6–40)
Hung et al. 2018 [18]	Taiwan	Cohort study/ National Health Insurance Research Database (NHIRD), 2010–2013	Patients with cirrhosis • Inclusion: patients with cirrhosis and HE, patients discharged with a main or accessory diagnosis of cirrhosis (ICD-9-CM code 571.5 or 571.2), use only first HE episode data (572.2) • Exclusion: esophageal variceal bleeding,	5,020 (1,004 PPI users, 4,016 nonusers)	PPI users 62. 5 (13.3), nonusers 62.6 (13.6)	67.5%	N/A	• HCC: 45.4% • Alcoholic cirrhosis: 20.5%

Author, year	Country	Study design/ Data source	Patients	Number of participants	Mean age (SD)	Male	Diabetes	Etiology of liver disease/MELD score, median (range) or mean ± SD
			panendoscopy examinations, intravenous PPI treatment during hospitalization, patients with an aDD of more than 1					
Janka et al. 2019 [35]	Hungary	Cohort study/ Referral Hepatology Center (Division of Gastroenterology, Department of Internal Medicine, Clinical center, University of Debrecen), 2006–2010	Patients with cirrhosis • Inclusion: patients with diagnosis of cirrhosis based on clinical, biochemical, imaging, and histological data and no signs of acute decompensation • Exclusion: patients with a single specialist consultation only, follow up regularly elsewhere, and follow up shorter than 3 months	350 (196 PPI users, 154 nonusers)	Median 56 (IQR 50–64)	53.7%	N/A	• HCC: 9.4% • MELD: 11.5 (816)
Kwon et al. 2014 [32]	South Korea	Cohort study/ Seoul National University Hospital, Seoul National University Boramae Medical Center, 2003–2010	Patients with cirrhosis • Inclusion: cirrhotic patients with SBP, cirrhotic patients with ascites who had undergone diagnostic paracentesis after admission, cirrhosis was established by liver biopsy or clinical evidence such as varices or radiological evidence in ultrasound, CT, MRI • Exclusion: gastrointestinal bleeding within 14 days prior to carcinomatosis, HIVadmission, organ transplantation, unclear medical record, antibiotic use within 2 weeks prior to admission, tuberculosis peritonitis, carcinamatosis, HIV	533 (82 PPI users, 451 nonusers)	PPI users 61. 9 (9.9), nonusers 62.9 (9. 4)	76.9%	18.9%	• HBV: 75.4% • HCV: 11.6% • ALD: 8.1% • HCC: 53.7% • MELD: PPI users 20.0±9.7, nonusers 18.8±8.9

Author, year	Country	Study design/ Data source	Patients	Number of participants	Mean age (SD)	Male	Diabetes	Etiology of liver disease/MELD score, median (range) or mean ± SD
Mandorfer et al. 2014 [33]	Austria	Cohort study/ Medical University of Vienna, 2006–2011	Patients with cirrhosis • Inclusion: patients with cirrhosis who underwent their first paracentesis • Exclusion: other causes of ascites such as severe cardiovascular disease, renal insufficiency, extra-hepatic malignancies and noncirrhotic portal hypertension	607 (520 PPI users, 87 nonusers)	57.5 (11.8)	70.0%	N/A	• ALD: 55% • Viral hepatitis: 19% • ALD and viral hepatitis: 8% • HCC: 21% • MELD: 17.5 (10.6)
Nardelli et al. 2019 [1 9]	Italy	Cohort study/ Center for the Study of Portal Hypertension i n Rome, 20142016	Patients with cirrhosis • Inclusion: in- and out-patients with cirrhosis, the diagnosis of liver cirrhosis was based on clinical, biochemical and radiological signs • Exclusion: alcohol/ psychoactive drug intake, unrelated neurological disease, lack of compliance with psychometric evaluation, dementia, advanced HCC, not suitable for Milan criteria	310 (125 PPI us ers, 185 nonusers)	62.2 (11.8)	71.3%	N/A	• Viral hepatitis: 61.0% • Alcohol: 27.1% • DCC: 66.8% • MELD: 12.7±4.9

aDD: average number of defined doses, ALD: alcoholic liver disease, CT: computed tomography, DCC: decompensate cirrhosis, FIB-4: fibrosis-4, H2RA: histamine-2 receptor antagonist, HBV: hepatitis B virus, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, HE: hepatic encephalopathy, HEV: hepatitis E virus, HIV: human immunodeficiency virus, IQR: interquartile range, MELD: model of end-stage liver disease, MRI: magnetic resonance imaging, N/A: not available, NAFLD: non-alcoholic fatty liver disease, PPI: proton pump inhibitor, RNA: ribonucleic acid, SBP: spontaneous bacterial peritonitis, NASH: non-alcoholic steatohepatitis

Table 2

The definition of exposure and outcome in included studies

Study	Exposure	PPI/no PPI use defined as	Mortality/Liver ca ncer defined as	Follow-up	The number of events, n/N (%)	Covariates included in ana lysis (Case-control matched var iables)
Proton pump inhibitor use and liver cancer						
Kao et al. 2019 [30]	Omeprazole, pant oprazole, lansoprazole, rabeprazol e, esomeprazole, dexlansoprazole	PPI use: ≥28 cDDD (cDDD: 027, 28–119, 120–364, ≥352), c umulative dose = (the numb er of pills dispensed by the p rescribed dose dividing by th e recorded days' supply, no exposure to PPI for <28 c DDD	• Liver cancer: an ambulatory visit or admission to a hospital for HCC (ICD-9- CM: 155.0 and 155.2) /	• 1 year after initial PPI use or cohort entry date	**1** HBV cohort PPI users 134/5,577 (2.4%), nonusers 103/5,577 (1.8%) **2** HCV cohort PPI users 96/1,915 (5.0%), nonusers 115/1,915 (6.0%)	• Age, gender, year of cohort entry • Comorbidities: cirrhosis, nonalcoholic liver disease, alcoholic liver disease, hypertension, chronic kidney disease, hyperlipidemia, diabetes • oncomitant medication: interferon/ nucleotides, non-aspirin NSAIDs, histamine 2 receptor antagonist, aspirin, statin, fibrate, insulins, metformin
Li et al. 2018 [21]	Omeprazole, eso meprazole, lanso prazole, dexlanso prazole, pantopra zole, rabeprazole	PPI prescription in any Veter ans pharmacy during the stu dy observation; ≥30 cDDD (c DDD: 30–180, 181–540, 541–900, >900), no PPI: <30 cDDD	• Liver cancer: At least 2 ICD- 9-CM for a chronic liver disease plus 2 ICD-9-CM codes(ICD-9-CM: 155.0) for hepatocellular carcinoma	• Median follow-up: 93.4 months (IQR 62.8125.9) among PPI users and 89.5 months (IQR 62.8–125.9) for nonusers, median duration of PPI exposure among PPI users: 27.25 months (IQR 8–69)	N/A	• Age, sex, race • Diabetes, obesity, alcohol abuse history, smoking history, statin use • HCV genotype, HCV RNA, baseline ALT, AST, platelet count, FIB-4 score, attainment of SVR
Shao et al. 2018 [20]	omeprazole, pant oprazole, lansopr azole, rabeprazol e, esomeprazole	PPI prescriptions in pharmac eutical claims between the i ndex date through 1 year pri or to	• Liver cancer: Patients who were diagnosed as having primary	• Mean follow-up duration:	PPI users 1,222/5,545 (22.0%), nonusers 11,526/134,246 (8.6%)	• Hypertension, diabetes, COPD, acute coronary syndrome,

Study	Exposure	PPI/no PPI use defined as	Mortality/Liver ca ncer defined as	Follow-up	The number of events, n/N (%)	Covariates included in ana lysis (Case-control matched var iables)
		cancer diagnosis, no PP 1: no prescription in pharmac eutical claims between the i ndex date and 1 year prior to the cancer diagnosis date of their matched cases, cumula tive DDD: sum of the dispens ed DDDsof any PPI	malignancy of the liver (ICD-9-CM: 155.0); did not include patients diagnosed as having intrahepatic bile duct tumors or whose primary tumors were not specified	60 months (SD 48)		cerebrovascular accident, peptic ulcer disease, GERD, hyperlipidemia • H. pylori eradication therapy, H2-receptor antagonists, aspirin, NSAIDs • (Age, sex, duration of follow-up from cohort entry to the date of cancer diagnosis)
Proton pump inhibitor use and mortality						
Coleetal.20 16 [31]	Omeprazole, lans oprazole, esomep razole, pantopraz ole	Discharge on a PPI from 2013 on the Track medical recor ds database, indication for P PI prescription: no indication (73.7%), Barrett's oesophagu s (6.1%), gastric or duodenal ulcer (7.0%), oesophagitis, g astritis, duodenitis (6.1%), G ERD (7.0%)	• Mortality: the time from assessment until death or present day (1/7/2015), the date of last recorded contact (if no date of death detailed)	• Median follow-up time 712 days (range 0–1216)	N/A	• MELD score, UKELD score,ALD
De Roza et al. 2020 [34]	PPI	Landmark period of 3 month s before and 6 months after i ndex hepatic decompensatio n admission, PPI users with a cDDD≥28 within the landma rk period	• Overall survival: from the end of the designated landmark period until the census date of 31th December 2017	• Median follow up period: PPI 551 days (IQR 231–1017), nonusers 584 days (IQR 289–1152)	PPI users 102/238 (42.9%), nonusers 13/57 (22.8%)	• Demographics • Etiology of liver cirrhosis, history of HCC, previous decompensation (ascites, variceal bleed, SBP, HE, hepatorenal syndrome), medical comorbidities, baseline MELD score, baseline medication use
Dultzetal. 2015 [12]	PPI	PPI treatment based on the assessment at the day of ad mittance to the hospital, PPI treatment was given for stro ng indications (gastrointestinal bleeding, PUD, GERD,	• Mortality: time from inclusion into the study until death or last contact	• 1250 days follow-up	N/A	• Decompensation, HCC, MELD

Study	Exposure	PPI/no PPI use defined as	Mortality/Liver ca ncer defined as	Follow-up	The number of events, n/N (%)	Covariates included in ana lysis (Case-control matched var iables)
		end oscopic variceal ligation) or s ymptomatically for epigastri c pain, nausea or vomiting				
Hunget al. 2018 [18]	Omeprazole, rabe prazole, lansopraz ole, pantoprazole, esomeprazole	The average number of defin ed doses (aDD) of PPI was ca lculated as ‘total number of defined doses of PPI’ divided by ‘total number of hospitali zation days’, defined dosage s: omeprazole 20mg, rabepr azole 20mg, lansoprazole 30 mg, pantoprazole 40mg, eso meprazole 40mg	• Mortality: starting point is the date of hospital admission	• 30-day • 30- to 90-day mortality • 90-day to 1-year mortality	PPI users 704/1,004 (70.1%), nonusers 2,506/4,016 (62.4%)	• Age, sex • Alcoholic cirrhosis, ascites, HCC, renal function impairment, bacterial infection
Janka et al. 2019 [35]	PPI	Taking drug for at least 80% of the follow-up period	• Mortality: follow up until death	• Median time to death 575 days (IQR 286–885), median follow up for patients alive 1155 days (IQR 646–1741)	PPI users 108/196 (55.1%), nonusers 39/154 (25.3%)	• Age • comorbidity, alcohol, other liver disease, MELD score
Kwon et al. 2014 [32]	PPI	The use of any PPIs form ore than 2 days	• Mortality: patient who died during hospitalization or within 30 days after SBP	• 30 days after SBP	PPI users 39/82 (47.6 %), nonusers 136/451 (30.2%)	• Age, sex • MELD score, HCC
Mandorfer e tal.2014[33]	PPI	Information on PPI intake fro m patient’s medical record	• Mortality: transplant-free survival; until the time to liver transplantatio n, death or end of follow-up	• 486 person-year follow-up for 607 patients	N/A	• Age • MELD score, HCC, history of variceal bleeding, varices
Nardelli etal. 2019 [19]	Omerazole, lanso prazole, pantopra zole, esomeprazol e	Physician admission notes fo r inpatients and medication 1 ists in outpatients notes, PPI treatment at least 4 weeks p rior to the admission, strong	• Mortality: follow-up until death, liver transplantatio n or to the last available outpatient review	• Median follow-up 14.1 months (SD 12.3)	• PPI users 109/185 (58.9%), nonusers 24/125 (19.2%) It	• Age • Sodium, MELD score, albumin, MHE, development of overt HE, previous HE

Study	Exposure	PPI/no PPI use defined as	Mortality/Liver ca ncer defined as	Follow-up	The number of events, n/N (%)	Covariates included in ana lysis (Case-control matched var iables)
		indication (gastrointestinal b leeding, PUD, GERD, endosc opic variceal ligation) or sym ptomatically for epigastric pa in, nausea or vomiting, stand ard dosages: omeprazole 20 mg, lansoprazole 30mg, pant oprazole 40mg, esomeprazol e 40mg				

ALT: alanine aminotransferase, AST: aspartate aminotransferase, cDDD: cumulative daily drug dose, CHD: chronic heart disease, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, FIB-4: Fibrosis-4, GERD: gastro-oesophageal reflux disease, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, HE: hepatic encephalopathy, HF: heart failure, HIV: human immunodeficiency virus, ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, MELD: model for end-stage liver disease, MHE: minimal hepatic encephalopathy, MI: myocardial infarction, N/A: not available, NSAIDs: nonsteroidal anti-flammatory drugs, PPI: proton pump inhibitor, PUD: peptic ulcer disease, PVD: peripheral vascular disease, RNA: Ribonucleic acid, SBP: spontaneous bacterial peritonitis, SD: standard deviation, SVR: sustained virologic response, UKELD: UK model for end-stage liver disease

Table 3

Subgroup analysis of the impact of proton pump inhibitor use on mortality and liver cancer in patients with chronic liver disease

Subgroup	Studies, n	PPI users, n	Nonusers, n	Random effects, Risk Ratio [95% CI]	Effect, P-value	I^2	Heterogeneity, P-value
Proton pump inhibitor use and liver cancer							
Liver disease							
Non-cirrhotic patients with HBV or HCV	3	13,244	13,266	1.45 [1.03, 2.03]	0.03	72%	0.03
Cirrhotic patients	3	5,878	134,328	1.14 [0.32, 4.01]	0.84	83%	<0.01
Follow-up							
1 year or less	2	7,492	7,492	1.22 [0.97, 1.52]	0.08	0%	0.83
More than 1 year	2	11,298	140,020	2.34 [1.98, 2.77]	<0.01	42%	0.19
Region							
Asia	3	13,037	141,738	1.57 [0.89, 2.74]	0.12	94%	<0.01
Study design							
Cohort study	3	13,244	13,266	1.45 [1.03, 2.03]	0.03	72%	0.03
Proton pump inhibitor use and mortality							
Liver disease							
Patients with cirrhosis	7	2,378	5,009	1.59 [1.23, 2.06]	<0.01	73%	<0.01
Follow-up							
1 year or less	3	1,606	4,554	1.20 [0.97, 1.48]	0.09	54%	0.11
More than 1 year	5	786	547	2.05 [1.63, 2.58]	<0.01	0%	0.77
Region							
Asia	3	1,324	4,524	1.43 [1.08, 1.89]	0.01	60%	0.08
Non-Asia	5	1,168	577	1.69 [1.12, 2.54]	0.01	75%	0.003

HBV: hepatitis B virus, HCV: hepatitis C virus