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PPI efficacy in the reduction of variceal bleeding incidence and mortality, a meta-analysis

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Abstract

Objective: To review the efficacy and safety of proton pump inhibitors (PPIs) in gastroesophageal varices (GEVs).

Methods: We searched PubMed MEDLINE, Scopus, and Web of Science for studies that measured the effect of PPI for prophylaxis and treatment of post-band ligation ulcers up to July 20, 2021. We included studies that measured the effect of PPI as treatment or prophylaxis for post-band ligation ulcers; articles that were published in peer-reviewed international journals and had enough data for qualitative and quantitative analysis were included with no language restriction. Heterogeneity was evaluated using the inconsistency (I^2) and chi-squared (χ^2) test. $I^2 > 50\%$ was considered substantial heterogeneity in the studies, and a P value less than 0.05 was considered statistically significant. The data was continuous, and we used the standardized mean difference (MD) and risk ratio (RR) with a 95% confidence interval to assess the estimated effect measure.

Results: A total of 7 studies with 2030 patients were included in our study of which 1480 participants were males (72%) and 550 females (18%). Mean age was 59.7 years old. Rebleeding post-band ligation was compared between PPI and placebo with significant favor for PPI ($p = 0.00001$). The pooled risk ratio was 0.53 (95% CI of 0.41, 0.68); furthermore, bleeding-related death at a 1-month period was compared between PPI and placebo with significant favor for PPI ($p = 0.00001$). The pooled risk ratio was significant at 0.33 (95% CI of 0.20, 0.53). The length of hospital stay postoperative was compared between PPI and placebo with cumulative mean difference of 0.13 (95% CI of -1.13 , 1.39), yet without significance.

Conclusions: The study suggests a twofold reduction in the risk of bleeding and a threefold reduction in the risk of bleeding-related death with the use of PPI following EVL.

Keywords: Gastroesophageal varices (GEVs), Proton pump inhibitors (PPIs), Variceal bleed

Introduction

Variceal hemorrhage is a serious complication of portal hypertension and represents approximately 60–65% of all bleeding episodes in patients with cirrhosis [1, 2]. The reported mortality rate during the first variceal hemorrhage

episode is 15–20%, with higher rates in advanced liver disease [3]. Despite the availability of effective treatment options for acute variceal hemorrhage, the risk for subsequent episodes of hemorrhage and mortality remains substantial. In one study, the risk of rebleeding following an initial variceal hemorrhage was 13% after 5 days and 17% at week 6 with reported mortality of 20% [4].

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Management of acute variceal hemorrhage consists of esophageal variceal band ligation (EBL) along with intravenous vasoconstrictors, antibiotics, and proton-pump inhibitor (PPI) followed by the initiation of secondary prophylaxis [5]. Combination therapy with EBL and nonselective beta-blockers are the current standard of care for secondary prophylaxis of variceal hemorrhage [6]. Despite the well-established effectiveness of PPI therapy in a variety of etiologies of upper gastrointestinal bleeding (UGIB), current data are insufficient to support its use in preventing variceal rebleeding or treating portal hypertensive gastropathy [7, 8].

Acid suppression therapy showed to benefit patients with cirrhosis by reducing the size of post-EVL esophageal ulcerations [9] and promoting gastric mucosal healing in peptic ulcer disease [10]. These benefits may explain the common clinical practice of prescribing oral PPI therapy in cirrhotic patients in the absence of supporting data and despite of published associations of long-term PPI use and spontaneous bacterial peritonitis as well as hepatic encephalopathy [11–13].

The role of PPI therapy in preventing UGIB in patients with cirrhosis after variceal hemorrhage remains unclear. Our study aimed to systemically analyze the role of PPI in post-band ligation ulcers.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was fulfilled in this systematic review and meta-analysis [14].

Search strategy

We searched PubMed MEDLINE, Scopus, and Web of Science for studies that measured the effect of PPI for prophylaxis and treatment of post-band ligation ulcers up to July 20, 2021.

The following search terms were used: (“PPI” OR “Proton pump inhibitors” OR “Proton pump inhibit*”) AND (“post band ligation” OR “ligation ulcers” OR “bleeding ulcers” OR “post band ulcers”); moreover, reviewing the reference lists of retrieved articles was used to complement the broad search.

Eligibility criteria

Studies that measured the effect of PPI as treatment or prophylaxis for post-band ligation ulcers and articles that were published in peer-reviewed international journals and had enough data for qualitative and quantitative analysis were included with no language restriction. We excluded conference papers, unpublished articles, reviews, letters to the editor, posters, and animal studies.

Data extraction

We extracted the following data from the included studies as baseline characteristics: name of the first author, publication year, country, study design, gender, mean age, and total sample size (Table 1). For qualitative and quantitative analysis, the received medical treatment, inclusion and exclusion criteria, and conclusion were extracted (Table 2).

Quality assessment

We used the Newcastle-Ottawa Scale (NOS) [22] to assess the observational studies and ROB-2 risk of bias version 2 for randomized control trials (RCT). The NOS tool judges the studies on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome. Furthermore, ROB-2 tool assesses the risk of biases in the following domains: (i) bias arising from the randomization process, (ii) bias due to deviations from intended interventions, (iii) bias due to missing

Table 1 Baseline characteristics

Author	Country	Study design	Age mean (SD)		Sex, male to female		Total number
			PPI	Placebo	PPI	Placebo	
Wu 2017 [15]	Taiwan	Prospective cohort	58.84 (16.97)	58.94 (16.57)	335: 146	106: 20	637
Ghoz 2020 [16]	USA	Retrospective cohort	62 (11.7)	57.7 (11.17)	53:37	49: 25	164
Kim 2015 [17]	Korea	Retrospective cohort	57.3 (10.7)	58.8 (11.5)	178: 41	100: 22	341
Hidaka 2012 [18]	Japan	RCT	64.7 (11.5)	61.5 (9.9)	10: 11	12: 10	43
Lau 2000 [19]	China	RCT	64 (17.2)	67 (15.9)	80: 40	80: 40	240
Lin 1997 [20]	Taiwan	RCT	57.75 (14.9)	63 (11.8)	46: 4	43: 7	100
Kang 2016 [21]	Korea	Retrospective cohort	53.6 (10.63)	55.2 (9.13)	375: 116	13: 1	505
							Total=2030

Table 2 Summary of included studies

Study	Received treatment	Inclusion criteria	Exclusion criteria	Conclusion
Wu 2017 [15]	Proton pump inhibitors	We enrolled only patients who received consecutive doses of acid suppression before the index endoscopy or during the index hospitalization. Patients receiving only a single dose were not included.	Patients with gastric variceal bleeding, patients with a failure to control the bleeding via emergent endoscopic treatments, patients with a history of endoscopy therapy (including sclerotherapy or ligation) less than one month prior to the index bleeding, moribund patients who died within 12 hours of enrollment (death event occurring in patients with a length of hospital stay less than 1 day), patients with a history of hepatocellular carcinoma or portal vein thrombosis found at any time before the index date, and patients with a history of gastric cancer any time before index date	The results of the current study suggest that adjuvant acid suppression prescription to patients who received endoscopic variceal ligation and vasoconstrictor therapy for bleeding esophageal varices may not change the rebleeding and mortality
Ghoz 2020 [16]	Proton pump inhibitor	We only included patients above the age of 18 years who had no documentation of prior endoscopic banding.	-	Post-EBL PPI therapy is associated with reduced risk of bleeding and death within 30 days after variceal hemorrhage in hospitalized patients.
Kim 2015 [17]	40 mg pantoprazole daily for at least 1 month from the day of hospital admission.	Patients who were diagnosed with bleeding GV and had undergone GVO using NBC at Chonnam National University Hospital (Gwangju, Korea) from January 2004 to July 2013	Patients who were diagnosed with bleeding GV and treated at other institutions before being referred to our center were excluded from the study. We also excluded isolated GV bleeding	The prophylactic use of PPIs reduces rebleeding after GVO using NBC in patients with gastric variceal hemorrhage. However, prophylactic use of PPIs does not reduce bleeding-related death.
Hidaka 2012 [18]	rabeprazole at a dose of 10 mg every morning for 2 years	Patients underwent variceal surveillance at the procedures unit of the Kitasato University East Hospital between March 2007 and September 2010.	Exclusion criteria were: (1) endoscopically confirmed existing varices 1 month after final EVL; (2) ongoing pharmacological therapy for portal hypertension with nonselective beta-blockers, nitrates, and angiotensin II type 1 receptor blockers (ARBs); (3) drinking alcohol within 3 months before the start of the study; (4) Child-Pugh score C10; (5) hepatocellular carcinoma (HCC); (6) portal thrombosis; (7) history of liver transplantation; and (8) pregnancy and allergy or past adverse reaction to PPIs.	Long-term administration of PPIs reduced the risk of treatment failure after EVL. Acid suppression therapy should also be considered as a treatment option after EVL.
Lau 2000 [19]	After endoscopic treatment, patients were randomly assigned to receive an intravenous infusion of placebo or omeprazole (Losec, Astra, Mjndal, Sweden), given as an 80-mg bolus injection followed by a continuous infusion of 8 mg per hour for a period of 72 h.	Patients who were older than 16 years and in whom endoscopic treatment of actively bleeding ulcers or ulcers with nonbleeding visible vessels had been successful were eligible for the study	Patients in whom endoscopic treatment was unsuccessful were not enrolled and instead underwent immediate surgery.	After endoscopic treatment of bleeding peptic ulcers, a high-dose infusion of omeprazole substantially reduces the risk of recurrent bleeding.

Table 2 (continued)

Study	Received treatment	Inclusion criteria	Exclusion criteria	Conclusion
Lin 1997 [20]	A 40 mg intravenous bolus of omeprazole was given followed by a 160 mg continuous infusion daily for 3 days. Thereafter, 20 mg of omeprazole was given orally once daily for 2 months	Patients were accepted for endoscopic therapy if a peptic ulcer with active bleeding or an NBVW was observed within 12 h of hospital admission.	Patients were excluded from the study if they were pregnant, did not give written informed consent, had bleeding tendency (platelet count <50 x 10 ⁹ /L, serum prothrombin <30% of normal, or were taking anticoagulants	The use of omeprazole is more effective than cimetidine in increasing intragastric PH and reducing rebleeding episodes in patients with bleeding peptic ulcer after successful endoscopic therapy.
Kang 2016 [21]	PPIs were initiated once a day at standard doses	Patients with liver cirrhosis who received elective EVL for primary prophylaxis of variceal bleeding between January 1998 and April 2011 at a tertiary hospital were included	Patients excluded if underwent emergency endoscopy for acute variceal bleeding, received EVL for secondary prophylaxis of variceal bleeding, underwent EVL for nonvariceal upper gastrointestinal bleeding such as Mallory-Weiss tearing, had hepatocellular carcinoma with portal vein thrombosis, had an allergic reaction to PPIs, had active peptic ulcers, or had a gastric varix only	We suggest that PPI therapy needs to be considered in patients receiving prophylactic EVL to reduce the risk of bleeding after prophylactic EVL.

outcome data, (iv) bias in measurement of the outcome, and (v) bias in selection of the reported result. A judgement of “low risk,” “some concerns,” or “high risk” was made for the risk of bias in each domain, allowing an overall risk of bias to be generated for each study using the tools algorithm. Two independent reviewers (A.A and A.A) screened the methodological quality of included studies and in case of discrepancies were resolved by discussion.

Data analysis

We conducted our double-arm meta-analysis using RevMan version 5. Random-effects meta-analysis models were employed to estimate the effect of PPI for bleeding, bleeding-related death, and hospitalization. Heterogeneity was evaluated using the inconsistency (I^2) and chi-squared (χ^2) test. $I^2 > 50\%$ was considered substantial heterogeneity in the studies, and a P value less than 0.05 was considered statistically significant. The data was continuous, and we used the standardized mean difference (MD) and risk ratio (RR) with a 95% confidence interval to assess the estimated effect measure.

Results

Search results

Our search strategy resulted in a total number of 127 studies. After removing the duplicates, 79 articles were screened for title and abstract screening, and 25 full-text articles were evaluated for eligibility. Following the full-text screening, 7 [15–21] papers met our criteria and were included in our meta-analysis (Fig. 1). Four studies were randomized control trials; three were retrospective cohort.

Baseline characteristics/summary of the included studies

A total of 2030 patients were included in our study of which 1480 participants were males (72%) and 550 females (18%). Mean age was 59.7 years old. Various types of proton pump inhibitors (PPI) were used including pantoprazole, rabeprazole, or omeprazole—the most used PPI. All PPI were used for treatment of post-band ligation ulcers occur for hospitalized patients (Tables 1 and 2).

Quality assessment

ROB-1 was performed assessing the risk of bias for randomized controlled trials; out of our 4 studies, 2 showed low risk of bias and 2 unclear (Figs. 2 and 3). While for cohort studies, judged by following New castle Ottawa (NOS) guidelines, our three cohort studies were of good quality due to matching of the cases and controls regarding the confounders and well selection of controls with detailed description (Table 3).

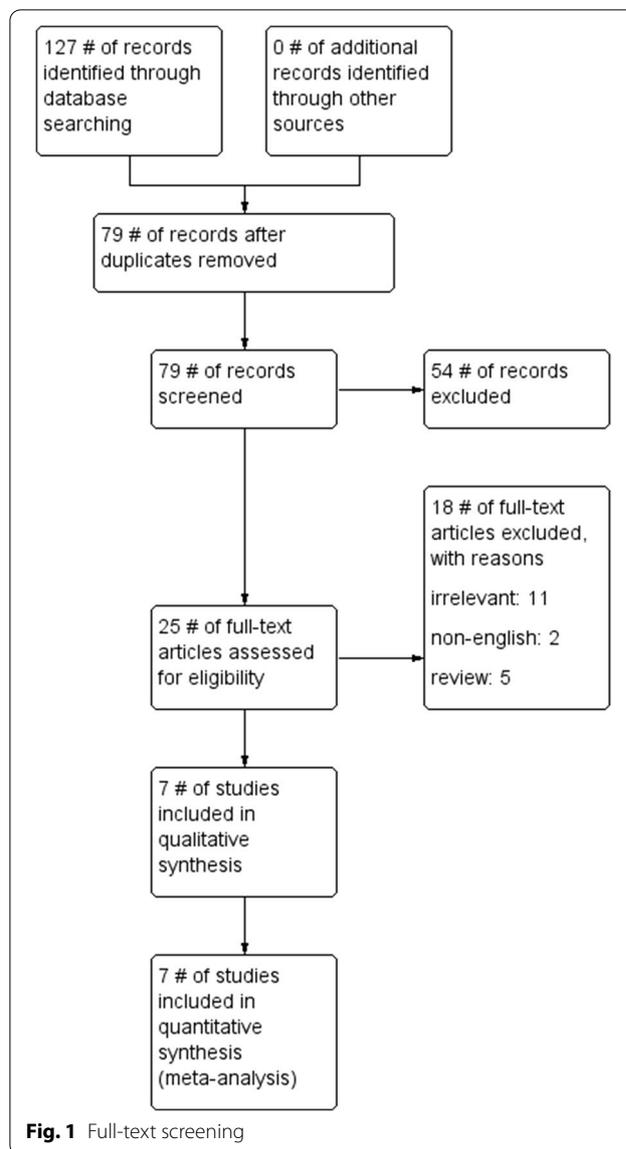


Fig. 1 Full-text screening

Data analysis

Forest plot of a random-effects meta-analysis on post-band ligation variceal bleed compares PPI with placebo. Values are risk ratios (95% CIs). The shaded boxes represent the point estimate for each individual trial, and the horizontal line extending from each box represents the upper and lower limits of the 95% CI. The size of the shaded circle indicates the relative weight of the trial in the meta-analysis. The diamonds represent the overall pooled risk ratio.

In our first analysis, all our seven studies including 2030 patients, rebleeding post-band ligation compared PPI and placebo with significant favor PPI ($p = 0.00001$). The pooled risk ratio was 0.53 (95% CI of 0.41, 0.68), showing

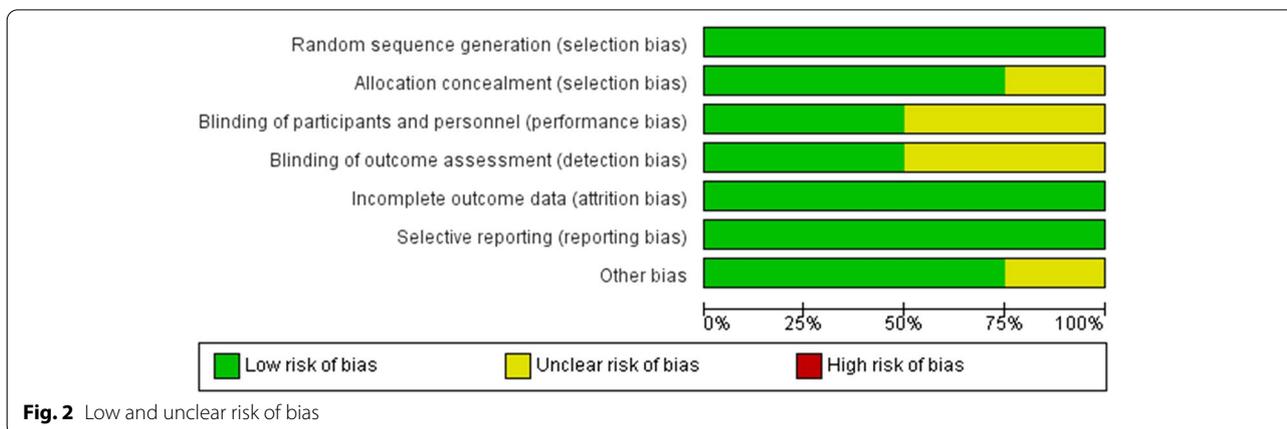


Fig. 2 Low and unclear risk of bias

a protective effect from rebleeding with PPI. Heterogeneity analysis demonstrated low-moderate statistical evidence for heterogeneity ($I^2 = 23\%$, $p = 0.26$) (Fig. 4).

In the second analysis, seven studies including 2030 patients bleeding-related death at a 1-month period compared PPI and placebo with significant favor for PPI ($p = 0.00001$). The pooled risk ratio was significant at 0.33 (95% CI of 0.20, 0.53), showing a protective effect from

bleeding-related death with PPI. No heterogeneity analysis was found as evidence for heterogeneity ($I^2 = 0\%$, $p = 0.69$) (Fig. 5).

In the third analysis, four studies including 1141 patients' length of hospital stay postoperative compared PPI and placebo. The cumulative mean difference was insignificant at 0.13 (95% CI of $-1.13, 1.39$), showing no effect either for PPI or placebo on length of hospital stay. Heterogeneity analysis demonstrated no evidence for heterogeneity ($I^2 = 0\%$, $p = 0.84$) (Fig. 6).

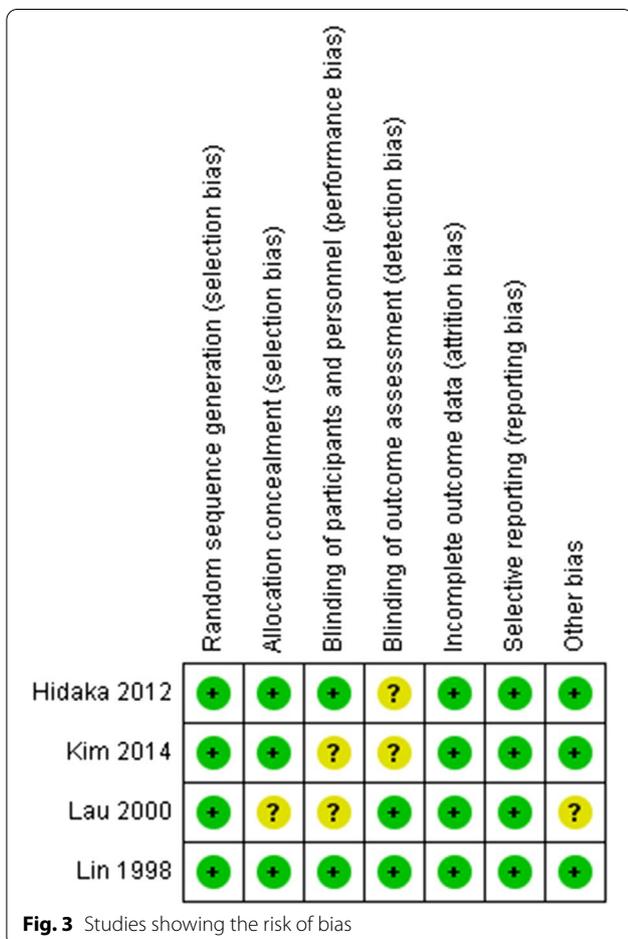


Fig. 3 Studies showing the risk of bias

Discussion

Our study demonstrates a significant reduction in the rate of bleeding and bleeding-related deaths with the use of PPIs rather than placebo following EVL. In addition, there is no evidence that this benefit comes at the cost of a longer hospital stay. Thus, our analysis shows that PPIs may be a valuable option following EVL as they are a cheap and widely available class of drugs that may significantly reduce complications and mortality following the procedure [22, 23].

Following EVL, bleeding due to ligation ulcers is a common complication occurring after 2.8 to 7.8% of procedures [24–27], although this rate varies depending on the setting (elective versus emergency) of the EVL session, with emergent EVL carrying a much greater risk of rebleeding [26]. Such bleeding is not only severely debilitating to the patient, but may also be fatal, with a 6-month mortality rate of 58.6% in one study [28].

One potentially important cause of post-EVL bleeding is acid reflux, which has been associated in one study with a significantly increased risk of post-EVL bleeding in patients receiving prophylactic ligation. Therefore, a possible mechanism by which PPIs may reduce post-EVL bleeding is the reduction of epithelial exposure to acid following the procedure.

Table 3 Newcastle-Ottawa Scale (NOS) for assessing the quality of observational studies

Study	Selection				Comparability	Exposure			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was followed up long enough for outcomes to occur	
Kang et al., 2016 [21]	*	*	*	*	*	*	*	*	8
Wu et al., 2017 [15]	*	*	*	*	*	*	*	*	8
Ghoz et al., 2020 [16]	*	*	-	*	**	*	*	*	8

Currently, there are no clear recommendations on the use of PPIs in patients with cirrhosis. For instance, the 2015 UK guidelines do not recommend proton pump inhibitor use for the control of an acute variceal bleed or for the prevention of post-EVL bleeding [29]. These recommendations are primarily based on data associating PPI use with severe adverse events. For instance, a 2014 propensity-matched cohort study showed a significantly higher rate of spontaneous bacterial peritonitis (SBP) in patients using PP [30]; however, findings on this risk have been conflicting, with two recent studies not reporting a positive association between PPI use and SBP [30, 31], and one study reinforcing the finding of the 2014 propensity matched cohort study by showing a positive association [32, 33]. In addition, an observational study linked PPI use in patients with cirrhosis to a higher mortality rate [34]. However, patients taking PPIs had a higher baseline severity of disease, and although the authors used multivariate models to adjust for potential confounders,

it is doubtful that all potential confounders were adequately adjusted for.

In addition to PPIs, another option for post-EVL bleeding prophylaxis is sucralfate. A study by Sakr et al. showed that sucralfate prophylaxis, compared to placebo, was associated with a nearly 50% relative reduction in the number of patients having post-banding ulcers [35]. Further, the mean size of ulcers in the sucralfate group was also significantly lower. Recently, a trial by Seo et al. showed that combination therapy with EVL and beta-blockers, for the primary prophylaxis of variceal bleeding, significantly reduced the 2-year recurrence rate of bleeding compared to either option alone by nearly four-folds [36]. However, there was no signal of a mortality benefit. To our knowledge, both studies are only available as abstracts and should accordingly be interpreted with caution. A small earlier randomized trial by Nijhawan et al. (30 patients) did not show that the use of sucralfate did not result in enhanced healing [37]. Another trial investigating simvastatin did not

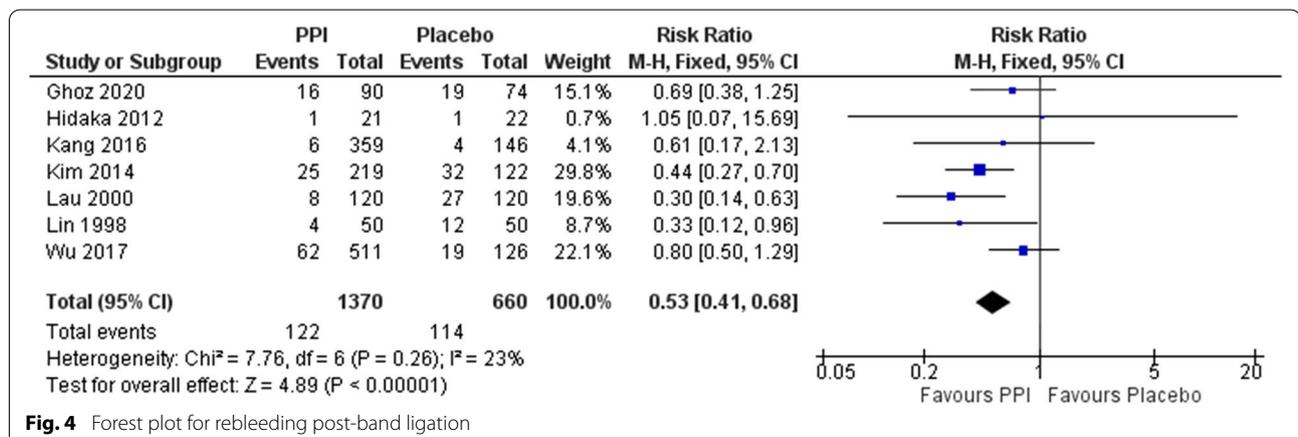


Fig. 4 Forest plot for rebleeding post-band ligation

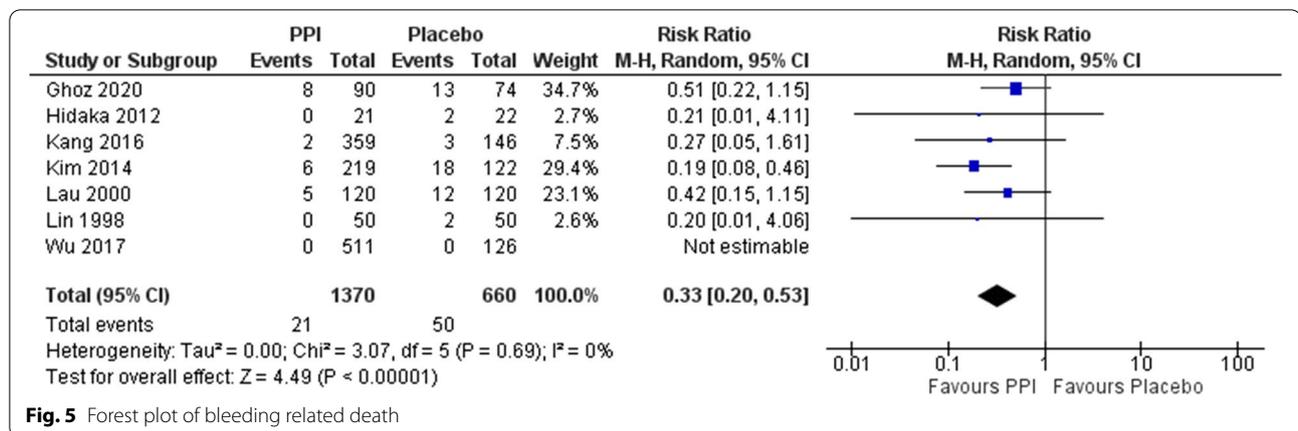


Fig. 5 Forest plot of bleeding related death

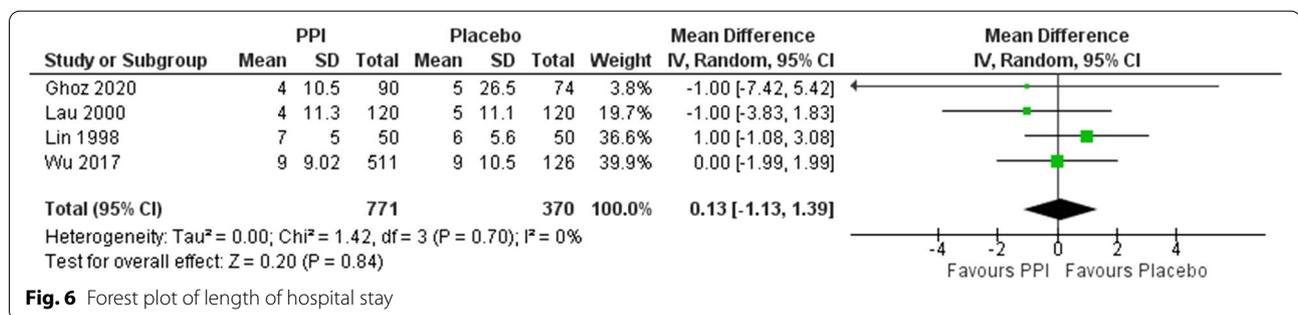


Fig. 6 Forest plot of length of hospital stay

show a significant reduction in the rates of bleeding; however, it was a relatively small trial of 59 patients, and the simvastatin group had significant reductions in portal pressure [38, 39].

Ultimately, because of the association of PPI with SBP, mortality, and a consequently unclear net clinical benefit, it may be rational to target high-risk patients for PPI therapy then to use them for all-comers. A number of risk factors have been associated with rebleeding after EVL, including Child-Pugh C status, bacterial infections, bilirubin levels, coagulation indices, the extent of ascites, varices, and the number of bands placed during EVL [40, 41]. In the future, randomized trials enrolling those patients at the highest risk of post-EVL rebleeding may show a net clinical benefit to the use of PPIs following EVL.

Our study has some limitations which ought to be acknowledged. First, a substantial portion of the evidence was derived from observational studies. Second, although statistical heterogeneity was low, there was some significant clinical heterogeneity as not all studies enrolled patients with a similar baseline severity or for the same purposes of primary vs secondary prophylaxis. Third, our meta-analysis cannot be used to determine the net clinical benefit to using PPIs, as side effects of PPI use were not evaluated in our analysis.

Finally, it is unclear from our analysis what the optimal duration of PPI therapy is.

In conclusion, our analysis suggests a twofold reduction in the risk of bleeding and a threefold reduction in the risk of bleeding-related death with the use of PPI following EVL. However, a significant portion of the evidence was derived from observational studies, and previous studies have raised concern about the association of PPIs with SBP. Accordingly, future randomized trials targeting high-risk patients are needed to inform clinical practice.

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Authors' contributions

SAE: study question, design, data analysis, and scientific writing. AS: study question, design, data analysis, and scientific writing. AKA: study question, design, data analysis, and scientific writing. DM: data collection, data extraction, and data analysis. AF: data collection, data extraction, and data analysis. AA: data collection, data extraction, and data analysis. MV: data collection and data extraction. ZZ: data collection and data extraction. Al: study review and appraisal. The authors read and approved the final manuscript.

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Availability of data and materials

All materials and data are available.

Declarations

Ethics approval and consent to participate

N/A.

Consent for publication

N/A.

Competing interests

The authors declare no competing interests.

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