The Efficacy of Proton Pump Inhibitor in Cirrhotics with Variceal Bleeding: A Systemic Review and Meta-Analysis

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Keywords

Proton pump inhibitor · Gastroesophageal variceal bleeding · Re-bleeding rate · Mortality

Abstract

Background and Aims: Proton pump inhibitor (PPI) was widely used in cirrhotic patients with variceal bleeding empirically rather than evidence-based practice. We aimed to evaluate the plausible indication of PPI use in variceal bleeding cirrhotic patients and figure out whether it can decrease the re-bleeding rate after endoscopic therapy. Furthermore, we also investigated the association between PPI and bleeding-related mortality in these patients. **Methods:** We have searched in PubMed, Medline, Web of Science, Google Scholar, Cochrane and Embase prior to May 2019. Pooled OR and 95% CI were calculated by random-effects model. **Results:** A total of 11 original articles including 1,818 cirrhotic patients were analyzed. The overall meta-analysis highlighted that PPI use may decrease the re-bleeding rate after endoscopic therapy (OR 0.52, 95% CI 0.35–0.77). The conclusion was irrespective of study methods, endoscopic purpose and hemorrhage sites. However, the conclusion speculated that PPI should be prescribed >1 month. Meanwhile, PPI use may not impact the bleeding-related mortality. **Conclusions:** PPI, used for >1 month, can decrease re-bleeding rate

after endoscopic therapy in cirrhotic patients for prophylaxis or emergency treatment purpose. No matter how long it takes, PPI use is not associated with bleeding-related mortality.

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Introduction

Esophagogastric variceal bleeding (EGVB) is one of the most common and fatal complications occurring in cirrhotic patients. As for acute EGVB, the first-line therapy is endoscopic hemostasis combined with pharmacologic treatment [1, 2]. Endoscopic hemostasis, mainly including endoscopic variceal ligation (EVL), gastric variceal obliteration (GVO) and sclerotherapy, has achieved a high success rate nowadays; however, post-procedural re-bleeding has been taken into consideration gradually. Life-threatening post-ligation ulcer bleeding occurs in 2–5% of cirrhotic patients who underwent EVL [3, 4]. Due to ischemia and acid reflux, esophageal ulceration often develops after EVL procedure, which might cause secondary bleeding [5]. As we known, proton pump in-

L.L. and B.C. contributed equally to this work.

hibitor (PPI) is widely used in the department of gastroenterology considering its potent antacid efficacy. However, the indication of PPI administration during EGVB remains unclear. Guidelines did not indicate whether PPI should be used in patients with acute variceal hemorrhage. Furthermore, British guideline in 2015 has clearly stated that PPI is not recommended in this situation except for existing peptic ulcer [2]. However, there are still many physicians using PPI or H₂ receptor inhibitor in patients with variceal hemorrhage. Several studies demonstrated that PPI can delay re-bleeding episode or reduce early bleeding risk after endoscopic hemostasis, and also minimize ulcer sizes through acid suppression and promoting ulcer healing process [6–9]. In contrary, some other reports showed that PPIs were not effective for re-bleeding prophylaxis or treatment [10, 11]. Meanwhile the conclusion of whether PPI could reduce mortality also remains elusive. After searching for related literatures, we found only 3 meta or systemic reviews concerned about the role of adjuvant PPI in EGVB [12–14]. Lodato et al. [13] figured out that PPI overuse in cirrhotics may be empirical rather than evidence-based practice. Meanwhile, the previous works of Lo and Lodato [12, 13] just systematically reviewed the published data but without synthesized them. Although Zhu et al. [14] have investigated this issue with 9 articles involved; they enrolled conference abstract, which may decrease data quality.

In this study, we aimed to evaluate the role of PPI in patients with EGVB. Furthermore, we also analyzed the association between PPI and bleeding-related mortality in these patients.

Methods

Search Strategy

The systematic review and meta-analysis was adhered to the PRISMA statement and was registered in the PROSPERO international prospective register of systematic reviews (CRD42019139073). A search of PubMed, Medline, Web of Science, Google Scholar, Cochrane and Embase was conducted. This search was performed in May 2019. Language was limited to English because of our language limitation.

The search terms were as follows: (proton pump inhibitor OR H₂ receptor inhibitor OR acid suppression therapy) AND (variceal band ligation OR endoscopic variceal ligation OR sclerotherapy) AND (esophageal varices OR gastroesophageal varices OR variceal hemorrhage OR variceal bleeding).

Inclusion and Exclusion Criteria

Two reviewers (L.L. and B.C.) screened the titles and abstracts of the literature from the electronic databases independently using the following inclusion criteria to identify all eligible studies: (1)

original articles with full text; (2) assessed the association between PPI use and EGVB in cirrhotic patients; (3) including patients >18 years old; (4) re-bleeding or bleeding-related death were evaluated as endpoints; (5) the value of OR with 95% CIs, or raw data were available for the comparison of PPI use and endpoints. We selected adjusted estimates for analyzing if possible, otherwise the raw data was used by calculating the unadjusted effect estimates.

Exclusion criteria were as follows: (1) conference abstracts without full texts or unpublished papers, (2) articles were duplicate publications, reviews, letters, commentaries, editorials, (3) no control group involved, (4) involving non-adult, (5) experimental studies, (6) other language except English. All disagreements were solved by discussion or consultation with the corresponding author (C.S.).

Data Extraction and Outcome Assessment

Two investigators (L.L. and B.C.) extracted the data independently by reading the full texts involved. Data extraction included author; publication year; country; study design; grade of evidence; clinical characteristics; inclusion and exclusion criteria; intervention and comparison; death or mortality; side effects such as ulcer size, ulcer healing time; doses and duration of PPI and follow-up. Any disagreements or discrepancies were resolved in consensus.

Quality Assessment

The quality of enrolling studies was assessed independently by 2 authors (Y.D. and X.J.). Observational articles like cohort study or case-control study were evaluated by Newcastle-Ottawa Scale (NOS) [15], which was measured according to the following parameters: selection, comparability, and exposure/outcome. The maximum of NOS was 9 points, and >6 point was determined as high-quality, otherwise, as low-quality.

The quality of randomization controlled trial (RCT) was assessed by the Cochrane Risk of Bias Tool [16]. The tool was consistent in 7 particular domains, sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Any disagreement was solved by consensus.

Statistical Analysis

Stata software, version 14 (Stata Corporation, College Station, TX, USA) was used for data analysis. Estimates like pooled OR and 95% CIs were chosen for meta-analysis. We would choose adjusted estimate value for meta-analysis if possible. Otherwise the raw data was used by calculating the unadjusted effect estimates. We used a random effects model for conservative consideration. Statistical heterogeneity was performed by using I^2 statistic. An I^2 value of <25% was considered to be low heterogeneity, while >75% was considered high heterogeneity, the value between 25 and 75% was considered moderate [17]. And we considered a $p < 0.05$ to indicate the presence of heterogeneity. The test for overall effect of meta-analysis was performed by a Z value with $p < 0.05$, which was considered to be statistically significant. We generated funnel plots and used Egger's asymmetry test [18] for publication bias assessment. A threshold of $p < 0.1$ was considered that publication bias existed. If asymmetry was detected, we would evaluate the potential effect of publication bias by using the nonparametric "trim-and-fill" test to recalculate the effect size.

Fig. 1. Results from literature search for studies relating to PPI and gastroesophageal variceal bleeding published prior to May 2019.

Results

Study Characteristics and Quality

We have searched 235 publications which involving PPI and endoscopic therapies in EGVB in electric databases. After discarding 56 duplicate publications and 160 articles which did not meet our requirements, we reviewed the remaining 19 original articles thoroughly. We discarded 2 non-related articles, 3 articles published in 90's which without comparison, 1 was poster without full text, 1 missed necessary data and 1 was lack of related endpoint. Finally, eleven original researches including 1,818 cirrhotic patients were identified in our analysis [6–11, 19–23] (Fig. 1).

The main material and clinical characteristics of the included studies were documented in Table 1. Most patients involved in separate studies were elderly male. The proportion of male patients ranged from 45.7 to 81.5%. The re-bleeding rate after endoscopic therapy was 16.3%, 310 patients (17.5%) died during follow-up period. Among 11 researches, there were 4 articles designed as RCTs, 4 retrospective cohort studies, the remaining 3 were retrospective case-control studies. There were 6 ar-

ticles concerned about esophageal varices bleeding by performing EVL for treatment or prophylaxis, and 4 researches clearly identified to perform sclerotherapy or GVO for gastric variceal bleeding. Only one of them did not mention the related endoscopic therapy in their study [11]. Nine out of 11 researches were published by Asian, especially in South Korea and Japan.

Meanwhile, there were 9 of 11 articles unveiling the relationship between PPI and post-procedural-related re-bleeding rate. And 6 of 11 researches explored the impact of PPI on the mortality of cirrhotic patients with gastroesophageal varices.

The assessment of study quality was conducted in all eligible researches. Most of studies (8 out of 11) have moderate quality. Five out of 7 observational studies have quality according to NOS. Meanwhile, 3 out of 4 RCTs were acceptable by Cochrane Collaboration tool assessment (Fig. 1).

Meta-Analysis

Association between PPI and Post-Procedural-Related Re-bleeding Rate

The meta-analysis revealed that routinely using PPI after endoscopic therapy for EGVB was a protective fac-

Table 1. Characteristics of the included studies in the current meta-analysis

Study, year	Country	Design	Number	Male, n (%)	Age, years	Endoscopic therapy	Intervention group	Control group	Grade of evidence	
									NOS	cochrane risk of bias tool
Wu et al. [22], 2017	Taiwan, China	RC	637	471 (73.9)	Intervention group: 58.84±16.97 control group: 58.94±16.57	EVL	Vasoconstrictors + PPI/H ₂ RA	Vasoconstrictors only	8	
Cho et al. [10], 2017	South Korea	CC	430	363 (84.4)	59.5±11.1	EVL	Vasoconstrictors + pantoprazole 40 mg × 3 day + antibiotics + EVL	NA	5	
Kang et al. [19], 2016	South Korea	RC	505	388 (76.8)	53.6±10.58	EVL	Standard dosage of PPI	No PPI	8	
Lo et al. [9], 2013	Taiwan, China	RCT	118	98 (83.1)	PPI group: 54.2±9.7 Vasoconstrictor group: 52.5±14.4	EVL	Omeprazole/pantoprazole 40 mg intravenously per day during hospitalization and pantoprazole 40 mg oral per day × 10 days	Vasoconstrictors (somatostatin or terlipressin)		C
Hidaka et al. [6], 2012	Japan	RCT	43	22 (51.0)	61 (55–70)	EVL	Rabeprazole oral 10 mg/day	No PPI		B
Shaheen et al. [21], 2005	USA	RCT	42	24 (57.1)	50.5	EVL	Pantoprazole 40 mg/day	No PPI		A
Garcia Saenz-de-Sicilia et al. [11], 2010	México	RC	105	48 (45.7)	58 (26–87)	Not mention	Omeprazole 20 mg/day (or an equivalent dose of any other PPI)	No PPI	7	
Garg et al. [23], 1995	India	RCT	44	33 (75.0)	Intervention group: 42.90±16.81; control group: 29.10±15.92	Sclerotherapy	Omeprazole 20 mg/day	No PPI		B
Kim et al. [8], 2015	South Korea	CC	341	278 (81.5)	57.79 (22–96)	GVO	PPI + antibiotics + vasoactive drugs	Antibiotics + vasoactive drugs	6	
Jang et al. [7], 2014	South Korea	RC	16	9 (56.3)	61.8±11.7	GVO	PPI full dosage orally	No PPI	5	
Komori et al. [20], 2017	Japan	CC	42	29 (69.0)	64.9 (48–62)	GVO	Not mention	Not mention	6	

RC, retrospective cohort study; CC, case-control study; RCT, randomization controlled trial; EVL, esophageal variceal ligation; GVO, gastric variceal obliteration; PPI, proton pump inhibitor; H₂RA, H₂ receptor inhibitor; NOS, Newcastle-Ottawa Scale.

tor, with a pooled OR 0.52 (95% CI 0.35–0.77, $Z = 3.21$, $p = 0.001$). The heterogeneity was moderate ($I^2 35.3\%$, $p = 0.135$). In the other words, using PPI after endoscopic therapy may reduce almost 50% re-bleeding rate in cirrhotics with variceal bleeding.

Because different procedures would be performed for variceal bleeding arising from different sites, while the postoperative re-bleeding rate tend to be higher in gastric variceal bleeding. We subsequently sub-analyzed the data according to esophageal and gastric varices. Both of them supported the conclusion that PPI use after EVL or GVO can reduce the re-bleeding rate (pooled OR 0.43 [0.22–

0.82] vs. 0.52 [0.35–0.85]; Fig. 2a). Studies involving esophageal varices have a higher heterogeneity than gastric ones ($I^2 58.2$ vs. 0%).

No matter the purpose for endoscopic therapy was prophylaxis or urgent hemostasis, patients administrated with PPI had a significantly lower risk of re-bleeding. The efficacy was more effective in prophylaxis studies in particularly (pooled OR 0.29 [0.09–0.88] vs. 0.59 [0.42–0.83]; Fig. 2b). The heterogeneity was 59.9 and 0% respectively.

We also analyzed the result based on research design methods. Both observational researches and RCTs identi-

Fig. 2. Forest plots and funnel plot of PPI administration after endoscopic therapy in cirrhotics with gastroesophageal variceal bleeding. The overall meta-analysis revealed that routinely using PPI after endoscopic therapy for variceal bleeding was a protective factor. **a** Sub-analysis classified with hemorrhage sites. **b** Sub-analysis depended on prophylaxis or emergency treatment purpose.

c Sub-analysis depended on different research design methods. **d** Sub-analysis according to the duration of PPI administration; short-term use was defined as using <10 days and long-term use was >4 weeks. Weights are from random effects analysis. RCT, randomization controlled trial.

(Figure continued on next page.)

fied a significant difference in PPI use and re-bleeding rate (pooled OR 0.61 [0.39–0.94] vs. 0.25 [0.1–0.6]; Fig. 2c). It may lead to 75% reduction in re-bleeding rate in patients who use PPI after endoscopic therapy in RCTs. As expected, RCTs retain better heterogeneity than observational studies (I^2 0 vs. 47.8%).

According to the duration of PPI use defined in registration studies, we manually classified the PPI use into short-term use (<10 days), and long-term use (>4 weeks). In conclusion, we speculated that long-term use of PPI after endoscopic procedure was recommended (pooled OR 0.47, 95% CI 0.26–0.84, $p < 0.05$; Fig. 2d). Administra-

tion of PPI <10 days may not reduce the re-bleeding rate then (pooled OR 0.52, 95% CI 0.24–1.14, $p = 0.11$). The effect of PPI use between 10 days and 4 weeks should be evaluated in the future. Meanwhile, exactly duration of PPI usage also concerns.

Sensitivity Analysis and Publication Bias

The funnel plot for possible publication bias demonstrated asymmetrical on visual inspection and confirmed by Egger's asymmetry test ($p = 0.046$; Fig. 3). We performed nonparametric "trim-and-fill" test through ran-

dom-effects model for sensitivity analysis. Additionally, the conclusion in our analysis was robust (data not shown).

Association between PPI and Re-bleeding-Related Mortality

There were 6 researches that revealed the association between PPI and re-bleeding-related short-term mortality. We defined the short-term mortality as deceased of <90 days after index hospitalization, and long-term mortality was >90 days or estimated as overall death rate. We found PPI use cannot improve patients' short-term sur-

Fig. 3. Funnel plot of plausible publication bias.

vival rate after EGVB (the pooled OR 0.93, 95% CI 0.23–3.85, $Z = 0.1$, $p = 0.92$; Fig. 4a). Furthermore, PPI use was not related with long-term mortality in cirrhotics with history of variceal bleeding neither. The pooled OR was 1.67 (95% CI 0.44–6.31, $Z = 0.75$, $p = 0.45$; Fig. 4b). However, there were only 3 articles involved which should be concerned with caution.

Association between PPI and Patients' Uncomfortable Complaints

Patients might feel chest pain, abdominal pain, chest tightness or dysphagia because of O-ring band trusses or ischemia. Among them, chest pain and dysphagia were most common in our experience. There were only 4 articles mentioned patients' complaints after endoscopic procedure. One RCT [9] documented a significant decrease of the adverse events incidence in patient with PPI and vasoconstrictor group (6%) rather than group with vasoconstrictor only (55%). Moreover, PPI use was associated with decreasing the incidence of chest pain (OR 0.05, 95% CI 0.00–0.96, $p < 0.05$) in their study [9]. Unfortunately, no other data displayed in their publications implied PPI use will improve patients' uncomfortable complaints. Details showed in Table 2.

Discussion

To our knowledge, PPI is widely used in peptic ulcer, gastroesophageal reflux disease and dyspepsia. However, its robust and rapid antacid efficacy with minor side ef-

fects has led to inappropriate use and abuse these days. Overuse of PPI may induce *Clostridium difficile* infection [24], pneumonia and menopausal fracture [25]. Furthermore, our previous research has confirmed that PPI use in cirrhotic patients with ascites will increase the risk of spontaneous bacterial peritonitis (not published yet). Although there are no consensuses about PPI use in EGVB, lots of physicians administrate PPI in the circumstance of upper gastrointestinal hemorrhage in cirrhotics empirically. The role of PPI in EGVB has been taken into consideration over decades. A review in 2008 addressed PPI overuse in cirrhosis might be empirical rather than evidence-based practice [13]. However, they also stated that the evidence for roles of PPI in varices bleeding was scarce at that time. Since then, although many number of relevant researches have been published, there was only one meta-analysis published to assess the role of PPI in cirrhotic patients with EGVB [14]. However, they found out PPI was only effective in cirrhotic patients who performed EVL for prophylaxis of variceal bleeding, rather than in urgent treatment or in other endoscopic managements.

This is the most comprehensive meta-analysis to evaluate the association between PPI and EGVB in liver cirrhosis patients. In the current meta-analysis, a total of 1,818 cirrhotic patients from 11 studies were involved. And 9 of them provided the information about PPI use and re-bleeding rate. Six articles investigated the association between PPI and bleeding-related mortality.

The overall estimate in this meta-analysis explored that PPI has a protective effect to prevent secondary bleeding after EVL or GVO. It may decrease post-procedure re-bleeding rate by almost 50% (pooled OR 0.52, 95% CI 0.35–0.77, $p = 0.001$). The conclusion is consistent with 3 previous studies [8, 9, 19] while contrary to the others [6, 7, 11, 21–23]. Furthermore, a controlled trial of 118 patients with acute bleeding from esophageal varices demonstrated PPI administration post-EVL may possess similar hemostasis efficacy with less side effects when compared to vasoconstrictor medication [9]. But the result should be further investigated. Although gastric varices hemorrhage (GVH) is less common than esophageal varices hemorrhage, it tends to be more deleterious with a higher re-bleeding rate and greatly challenging management [26–30]. We sub-analyzed the studies regarding esophageal varices hemorrhage and GVH with respect to different hemorrhage sites. It turns out that PPI plays a protective role despite of bleeding locations.

Fig. 4. Forest plots about related mortality of PPI administration after endoscopic therapy in cirrhotics with gastroesophageal variceal bleeding. **a** There were 6 studies that unveiled the association between PPI and re-bleeding-related short-term mortality (≤ 90

days). **b** Three studies involved have investigated the association between PPI and related long-term mortality (> 90 days or overall death rate). Weights are from random effects analysis.

We analyzed the plausible mechanism of PPI usage in cirrhotic patients with variceal bleeding. The esophageal varices originate from left gastric vein. EVL is a technique that prevents bleeding by using O-rings band to block the blood flow. Early recurrent bleeding often occurs between 24 h and 14 days after EVL [31]. The presumed reasons about post-EVL re-bleeding are as follows: incomplete obliteration during the first time manipulation; ulceration developed due to ischemia post-EVL, portal hypertension still exist, which may break through the vulnerable ulceration; the O-rings detached too early that tissue fibrosis from ulceration was not robust enough [10]. As MacDougall and Williams [32] documented, gastric acid reflux was not a significant factor in the pathogenesis of variceal hemorrhage. Variceal hemorrhage is associated with hepatic venous pressure gradient, Child-Pugh classification and so on. However, it is assumed that PPI administration may contribute to the early healing of the post-EVL ulceration by reducing the acid reflux in these patients [33]. In contrast, N-butyl-2 cyanoacrylate injection to criminal varices was the main hemostasis therapy for GVH. Foreign material induces inflammation and aseptic necrosis

which may explain the occurrence of gastric ulceration [34, 35]. Moreover, exposure to gastric acid fluid may accelerate the ulceration progress [21]. That may be the underlying mechanism by which acid suppression can reduce or delay re-bleeding in GVH. A randomized control study from Japan revealed that compared with H_2 receptor, PPI could improve the mean value of esophageal pH after sclerotherapy and maintain the overall pH > 4.0 [36]. They also demonstrated a significant reduction in the time required for post-sclerotherapy ulcer healing in PPI administrated group ($p < 0.05$). The conclusion is consistent with the hypothesis mentioned above.

As mentioned above, PPI overuse is always a big problem around the world. In the light of safety and cost-effectiveness, standardizing the use of PPI is imperative. In literature, short-term (10 days) administration of PPI after EVL may reduce ulcer size [12, 21]. However, Young et al. [37] highlighted that post-EVL ulceration would be resolved in 14.4 ± 1.4 days. Similarly, we speculated that short-term use of PPI might be insufficient to heal the endoscopic hemostasis-related ulceration. Our analysis found that only using PPI

Table 2. PPI use after endoscopic hemostasis was not associated with improvement of patients' uncomfortable complaints and ulcer incidence, but may decrease the size of ulceration in some extent

Author, year	Endoscopic therapy	Ulcer incidence			Ulcer size			Ulcer healing time			Chest pain			Dysphagia		
		PPI group	non-PPI group	<i>p</i> value	PPI group	non-PPI group	<i>p</i> value	PPI group	non-PPI group	<i>p</i> value	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Garg et al. [23], 1995	Sclerotherapy	16/21	18/23	0.70	–	–	–	–	–	–	0.38	0.07–2.21	0.42	0.58	0.17–2.01	0.58
Lo et al. [9], 2013	EVL	14/22	18/21	0.09	1/22 [†]	6/21 [†]	0.04	–	–	–	0.05	0.00–0.96	0.003	NA	NA	NA
Shaheen et al. [21], 2005	EVL	2.18 (0.2) [‡]	2.25 (0.31) [‡]	0.85	82 (22) [§]	37 (9) [§]	0.01	–	–	–	2.86	0.11–74.37	1.0	3.16	0.30–33.09	0.61
Hidaka et al. [6], 2012	EVL	–	–	–	–	–	–	–	–	–	NA	NA	NA	0.80	0.18–3.5	1.0

[†] The number of ulcer size which was >1.5 cm, showed by n/N.

[‡] The incidence of ulceration which was adjusted for number of bands placed, showed by mm², mean (SE).

[§] The ulcer size which performed the endoscopic procedure in day 10 after EVL, showed by mm², mean (SE).

EVL, esophageal variceal ligation; NA, not available; PPI, proton pump inhibitor.

>4 weeks may decrease re-bleeding rate. The effect of PPI use between 10 days and 4 weeks still remains uncertain. Further researches should be conducted to determine the optimal duration of PPI usage after endoscopic therapy.

Unlike previous meta-analysis [14], our study has overturned the conclusion that acid suppression therapy was only effective in patients who underwent EVL for prophylaxis of variceal bleeding. We found PPI use can decrease the re-bleeding rate after EVL or GVO on both prophylaxis and urgent treatment purpose. In conclusion, PPI administration (at least of 4 weeks) is recommended in EGVB irrespective of bleeding locations or treatment purposes.

In order to explain the possible moderate heterogeneity in our results, we subsequently analyzed the studies through design methods. There were 4 RCTs, 4 retrospective cohort studies, and 1 case-control study in our re-bleeding rate analysis. We categorized the group into RCTs and observational studies, to eliminate the potential bias. Both of them stated the evidence that PPI is beneficial for preventing secondary bleeding after endoscopic procedure. As expected, observational studies have a moderate heterogeneity (47.8%), which is higher than RCTs (0%). The heterogeneity might be associated with selection bias and recall bias.

We also analyzed 6 articles which provided the data about PPI use, short-term re-bleeding-related mortality and long-term mortality. Neither of them was associated with PPI use. A small size case-control study found that

PPI use increased the short-term and long-term bleeding-related mortality [38]. However, the remaining researches failed to find that PPI was associated with bleeding-related mortality. The mortality of liver cirrhosis may result from prophylactic administration of antibiotics [38], bacterial infection [39], Child-Pugh classification, β blocker use, and the severity of hemorrhage [8]. Interestingly, Kim et al. [8] supported our opinion that prophylactic use of PPI could reduce re-bleeding, but not associated with bleeding-related death. But their conclusion was only limited to patients undergoing GVO.

Although PPI can decrease the re-bleeding rate, it is not associated with re-bleeding-related mortality; we suppose that PPI should not be used as the unique rescue therapy during re-bleeding episode. Endoscopic hemostasis or transjugular intrahepatic portosystemic shunt is still the first-line therapy, if necessary.

Limitation

There are several limitations to our present research:

1. Almost all population involved in our study were Orientals, and we didn't search literature in other language because of our language limitation. Selection bias might be existed. The conclusion should be taken with caution when applied to general population.
2. The data relative to post-procedure induced ulceration, ulcer healing time and patients' uncomfortable complaints (like chest pain and dysphasia) were

scarce. It interfered with our analysis when investigating the relationship between PPI and ulcer sizes, ulceration healing time or adverse events. Some literature have documented that PPI could reduce ulcer sizes [9, 21]. Meanwhile, Lo et al. [9] concluded PPI would improve the complaints like chest pain and abdominal pain. However, within the limited data, we thought PPI use might not decrease the incidence of ulceration, and it was not robust to consider that PPI could significantly improve patients' uncomfortable complaints, such as chest pain [21, 23] or dysphagia [6, 23]. Since repeated endoscopy procedures after hemostasis may cause secondary trauma to patients, and most adverse events were transient, further researches may not be necessary in this issue. However, it is still necessary to explore the underlying mechanism about PPI and their role in ulceration.

3. The dosage and therapy duration of PPI differs among these researches. The efficacy of different dosage of PPI in hemostasis is undetermined. Long-term use of PPI may lead to other complications in cirrhotic patients. Thus, more researches concerning about dosage of PPI are warranted in the future.
4. Given that all 3 researches assessing the long-term mortality were observational studies, selection biases, recall bias and other confounding factors may exist. As abovementioned, long-term use of PPI increases the incidence of *Clostridium difficile* infection, pneumonia, menopausal fracture, spontaneous bacterial peritonitis and hepatic encephalopathy in liver cirrhosis. Therefore, the conclusion that PPI use is not associated with long-term mortality in EGVB patients should be extrapolated with caution. More precise and head-to-head researches should be taken into consideration.

Conclusion

In conclusion, PPI is widely used in our clinical practice, and its abuse and inappropriate use problem have arisen. Although, there are no related guidelines recommending routine PPI usage during the process of EGVB, we believe PPI use (at least 1 month) in the course of EGVB would decrease the re-bleeding rate by acid suppression and promotion of ulcer healing. Moreover, PPI use is both effective in prophylaxis and emergency treatment procedures. However, PPI use, no matter how long it takes, is not associated with bleeding-related mortality so far. Endoscopic hemostasis or transjugular intrahepatic portosystemic shunt is still the first-line therapy if necessary.

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Disclosure Statement

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Author Contributions

L.L. and B.C. screened the literature from database. The quality of enrolling studies and statistical analysis was assessed independently by Y.D. and X.J. Thesis writing and modification were completed by L.L., W.L., and C.S. Proofreading was performed by C.S.

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