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Review Article

Endoscopic variceal ligation vs pharmacotherapy in the influencing of mortality and rebleeding rate on secondary prevention of esophageal variceal bleeding: a meta-analysis

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Abstract: To evaluate endoscopic variceal ligation (EVL) vs pharmacotherapy in the influencing of mortality and rebleeding rate on secondary prevention of esophageal variceal bleeding. Four electronic databases, including PubMed, EMBASE, the Cochrane Library, and Clinical Trails. gov, were searched to identify relevant randomized clinical trials up to 7 October 2016. Six studies, enrolling a total of 689 patients, were included in this meta-analysis. For all-cause mortality, a statistically significant difference (risk ratio (RR)=0.71, 95% CI [0.58, 0.88], I^2=0%, P=0.002) was observed between EVL and pharmacotherapy. The other overall meta-analysis results, included mortality caused by bleeding (RR=0.90, 95% CI [0.50, 1.61], I^2=27%, P=0.71), rebleeding (RR=1.12, 95% CI [0.49, 1.65], I^2=78%, P=0.55), and rebleeding from varices (RR=1.30, 95% CI [0.74, 2.25], I^2=82%, P=0.36), were not significantly different for mortality caused by bleeding for EVL versus pharmacotherapy. All results of the meta-regression analysis showed no significant differences, and the publication bias was not found by funnel plot. This study suggested that pharmacotherapy is superior to EVL for reducing mortality, whereas EVL is more effective in reducing rebleeding during the secondary prevention of esophageal variceal bleeding.

Keywords: Esophageal variceal bleeding, endoscopic variceal ligation, pharmacotherapy, mortality, rebleeding

Introduction

Bleeding from esophageal varices is a serious complication of portal hypertension [1, 2]. After an initial episode of acute variceal bleed, patients with cirrhosis have a 70% risk of rebleeding [3], and in those who show rebleeding, a mortality rate of 20% to 35% is observed [4]. Related studies suggested that the incidence of variceal bleeding in the United Kingdom is increasing, probably owing to the increased prevalence of cirrhosis because of alcohol consumption, viral hepatitis, and non-alcoholic fatty liver disease [5, 6]. These risk factors [6] contribute to the complexity of the disease, including extremely easy-to-cause secondary bleeding, and even death. Therefore, it is particularly important to the secondary prevention of esophageal variceal bleeding for the prognosis of disease [4, 5]. Many studies have suggested that are duction in the rebleeding rate occurs with endoscopic variceal ligation (EVL), pharmacotherapy with beta-blockers and/or isosorbide mononitrate (ISMN) [7-12]. Interestingly, more mortality and rebleeding benefits from pharmacotherapy compared with EVL alone were noted in the secondary prevention of esophageal variceal bleeding. In addition, many previous meta-analyses [13] had also reported on these issues, but the key confounding factors [4, 6], including alcohol, viral infection, and Child score, had not been evaluated in these analyses. The latest literature on these issues should also be included in this study owing to the fact that rebleeding after an initial esophageal variceal hemorrhage remains a significant problem despite therapy using EVL, non-selective β-blockers (NSBB), or a combination of these.

With an aim to improve the prognosis and life-expectancy of patients with esophageal varice-

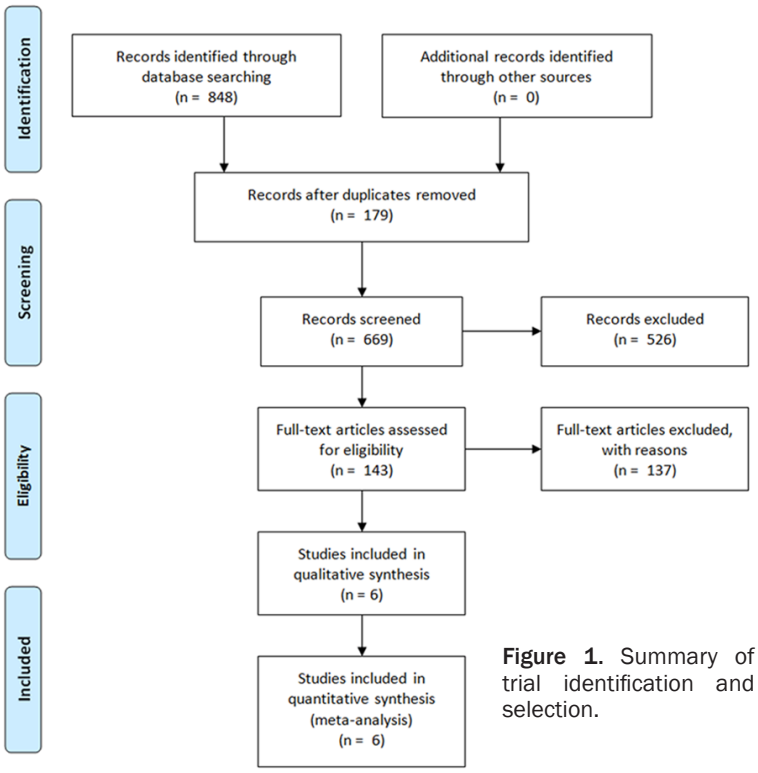

Figure 1. Summary of trial identification and selection.

al hemorrhage by secondary prevention of esophageal variceal bleeding using EVL or pharmacotherapy alone, we conducted a meta-analysis [14] to comprehensively assess the mortality and rebleeding rate after EVL or pharmacotherapy alone during the secondary prevention of esophageal variceal bleeding.

Materials and methods

Search strategy

We searched the medical literature using electronic databases, PubMed, EMBASE, the Cochrane Library and ClinicalTrails.gov, up to 7 October 2016 to identify eligible randomized clinical trials that investigated EVL versus pharmacotherapy for the secondary prevention of esophageal variceal bleeding. Both Medical Subject Headings (MeSH) and text words were used as follows: "endoscopic variceal bleeding", "gastrointestinal hemorrhage", "esophageal and gastric varices", "gastric varix", "esophageal varices", "portal hypertension", "endoscopic variceal ligation", and "ligation".

Literature selection and exclusion

All studies were selected in accordance with the following inclusion criteria: 1) Studies were randomized, clinical trials, 2) Patients older than 16 years with at least one previous episode of gastroesophageal bleeding, 3) Intervention was pharmacotherapy to control rebleeding, no restriction to type and dose of pharmacotherapy, 4) Use of EVL to prevent rebleeding in the control group; and 5) Included at least one of the following outcomes: all-cause mortality, mortality caused by bleeding, rebleeding, or rebleeding from varices during the treatment.

Studies were excluded in accordance with following criteria: 1) Studies including patients with gastroesophageal bleeding gastric varices alone, 2) Studies comparing these outcomes in the primary prevention of gastroesophageal bleeding alone, 3) Study's arm sample size less than 30. 4) Duplicates, and 5) Data were insufficient or could not be obtained by contacting the corresponding author.

Data extraction and quality assessment

The relevant information, including patients' characteristics, underlying illnesses, mean time on dialysis, interventions, controls, outcomes (all-cause mortality, mortality caused by bleeding, rebleeding, and rebleeding from varices), and follow-up time, were independently extracted and entered in a database by two investigators. For missing data, we contacted the correspondent authors of original studies to obtain it if possible. Intention-to-treat (ITT) datasets [14] were used to analyze all outcomes when available.

Two investigators independently evaluated the methodological quality of eligible trials by using the Cochrane Collaboration's tool for assessing risk of bias [14] (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias). Disagreements between the two authors on data extraction and quality assessment were

Table 1. Baseline information of the included studies

Study	Year	Region	Sample	Mean age ± SD (P/EVL)	Male/ Female	Alcohol (P/EVL)	Viral (P/EVL)	Child score (P/EVL) A; B; C			Pharmacotherapy	EVL	Mean time interval between sessions (days)	Outcomes
Villanueva [7]	2001	USA	144	60±12/58±14	90/54	33/30	24/26	19/11	39/43	14/18	Nadolol 20~80 mg/day; Isosorbide 20~80 mg/day	EVL	14-21	①; ②; ③; ④
Lo [8]	2002	Taiwan	121	51±13/52±12	28/93	22/16	36/39	13/13	35/35	13/12	Nadolol 10~40 mg/day; Isosorbide 20~40 mg/day	EVL	21-28	①; ②; ③; ④
Patch [9]	2002	Italy	102	50.7/52.4	70/32	32/36	NA	8/5	19/18	24/28	Propranolol 40 mg/day; Isosorbide 20~40 mg/day	EVL	14	①; ②; ④
Sarin [10]	2005	India	137	36.2±16/35.8±17.2	96/41	15/18	23/25	27/35	28/26	11/10	Propanolol 10~40 mg/day; Isosorbide 20~40 mg/day	EVL	14	①; ②; ③; ④
Lo [11]	2008	Taiwan	121	51±13/52±12	93/28	22/16	36/39	13/13	35/35	13/12	Nadolol 10~40 mg/day; Isosorbide 20~40 mg/day	EVL	21-28	①; ②; ③; ④
Stanley [12]	2014	UK	64	51.4±10.8/49.6±12.87	43/21	NA	0/0	11/11	28/28	25/25	Carvedilol 6.25~12.5 mg/days	EVL	7,14 6 months	①; ②; ③; ④

P: pharmacotherapy; EVL: endoscopic variceal ligation; NA: not obtainable; Outcome: ① mortality, ② mortality caused by bleeding, ③ rebleeding, ④ rebleeding from varices.

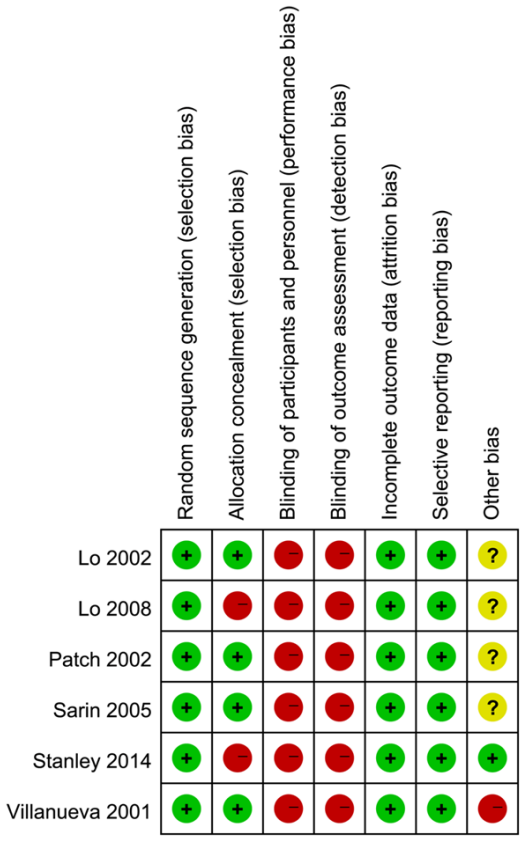

Figure 2. Risk of bias in included studies.

resolved by discussion or by consulting the lead investigator.

Statistical analysis

Review Manager (RevMan) 5.3 software (Cochrane collaboration, London, UK) was used to perform all data analyses. For dichotomous data [15, 16], we used relative risk (RR) with its 95% confidence interval (CI) as an effect estimator. We performed a statistical test for heterogeneity and adopted I^2 of greater than 40 as evidence for heterogeneity according to Cochrane handbook [17]. If heterogeneity were presented, we would use a random-effects model to synthesize effect size [18]. In addition, the baseline and possible confounding factors, including age, gender, region, sample, alcohol, viral, Child score, and publication year were detected using meta-regression analysis [14, 19]. Visual inspection of the funnel plot was used to potential publication bias as qualitative method [20]. In a funnel plot, studies with a larger sample size, which provide a more precise estimate of an intervention's effect, form the spout of the funnel, whereas studies with a smaller sample size and less precision form the cone end of the funnel. Asymmetry in the funnel plot indicates potential publication bias.

Results

Study selection and data collection

We initially identified 848 records obtained from four electronic databases (**Figure 1**). Based on the inclusion and exclusion criteria, the retrieved titles and abstracts were independently screened by two reviewers and full-text copies of eligible studies were downloaded for the meta-analyses. Finally, six eligible studies [7-12] were included in our research.

Study characteristics

We found six eligible studies [7-12], which enrolled a total of 4,412 patients. The all-cause mortality was reported in 217 of 689 patients from six studies [7-12], the mortality caused by bleeding was noted in 42 of 587 patients from five studies [7, 8, 10-12], the rebleeding occurred in 295 of 689 patients from six studies [7-12], and the rebleeding, and rebleeding from varices involved in 219 of 689 patients from six studies [7-12]. **Table 1** summarizes the clinical characteristics of all studies.

Quality of the included studies

The risk of bias in the included studies was strictly evaluated. The double-blind failed to been performed, this is mainly due to the nature of the EVL. Details of methodological approach are presented in **Figure 2**.

All-cause mortality

For all-cause mortality, six studies [7-12] were involved, and only one study [11] suggested that there were statistically significant differences between pharmacotherapy and EVL, and pharmacotherapy was superior. **Figure 3** shows a statistically significant difference (risk ratio (RR)=0.71, 95% CI [0.58, 0.88], I^2=0%, P=0.002) between pharmacotherapy and EVL, without evidence of heterogeneity, using a fixed-effects model.

Figure 3. Forest plot of all-cause mortality of EVL compared with pharmacotherapy.

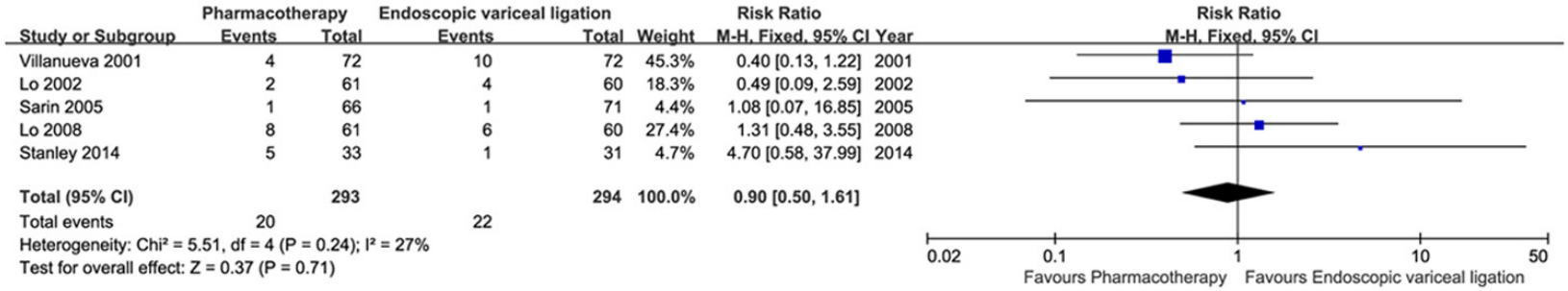

Figure 4. Forest plot of mortality caused by bleeding of EVL compared with pharmacotherapy.

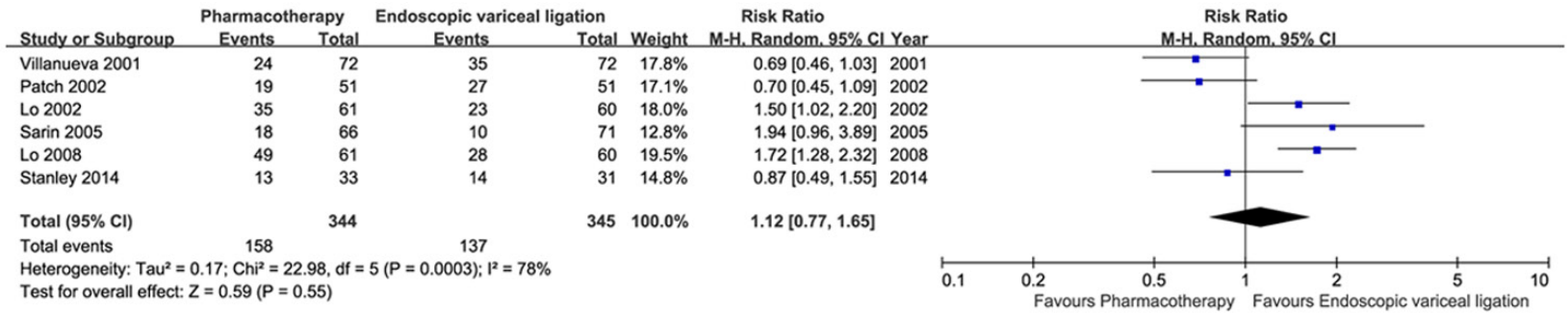

Figure 5. Forest plot of rebleeding of EVL compared with pharmacotherapy.

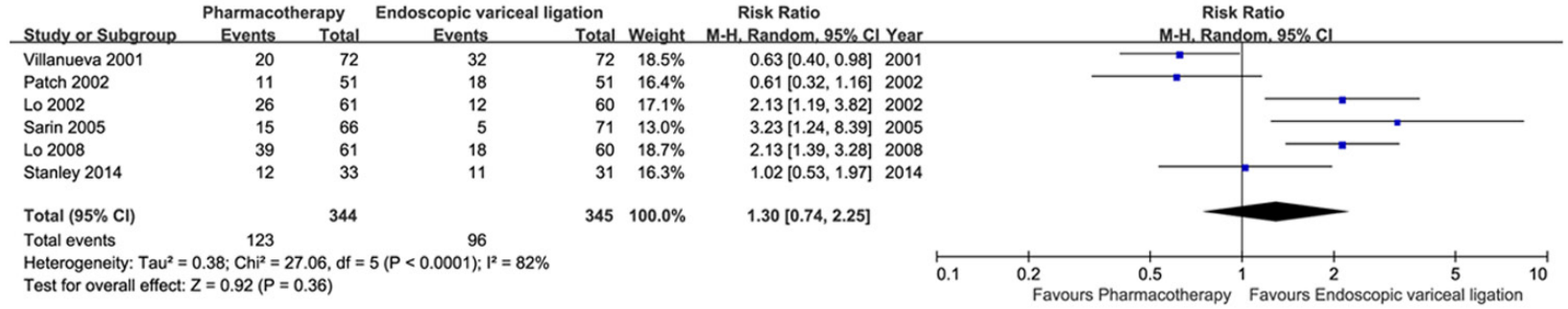

Figure 6. Forest plot of rebleeding from varices of EVL compared with pharmacotherapy.

Table 2. Meta-regression results for the all outcomes

Confounding factors	Mortality			Mortality caused by bleeding			Rebleeding			Rebleeding from varices		
	Number of study	Coef 95% *CI*	*P*	Number of study	Coef 95% *CI*	*P*	Number of study	Coef 95% *CI*	*P*	Number of study	Coef 95% *CI*	*P*
Age	6	0.004 (-0.064, 0.072)	0.885	5	-0.031 (-0.434, 0.372)	0.824	6	-0.051 (-0.135, 0.034)	0.170	6	-0.109 (-0.236, 0.017)	0.075
Gender	6	0.285 (-1.869, 2.437)	0.732	5	2.624 (-11.260, 16.508)	0.590	6	-0.184 (-3.980, 3.612)	0.899	6	-0.566 (-7.852, 6.720)	0.840
Region (Ref=USA/UK)	2	NA	NA	2	NA	NA	2	NA	NA	2	NA	NA
Asian	4	0.052 (-0.568, 0.672)	0.828	3	-1.317 (-6.625, 3.992)	0.488	4	0.673 (-0.447, 1.793)	0.171	4	1.168 (-1.009, 3.344)	0.211
Sample	6	0.001 (-0.012, 0.014)	0.809	5	-0.051 (0.099, -0.004)	0.053	6	0.006 (-0.019, 0.032)	0.523	6	0.012 (-0.034, 0.059)	0.502
Alcohol	6	0.854 (-1.552, 3.259)	0.380	5	17.432 (-41.465, 76.330)	0.416	6	-2.410 (-6.181, 1.360)	0.151	6	-4.697 (-11.571, 2.177)	0.131
Viral	6	0.033 (-1.453, 1.519)	0.954	5	-4.986 (-13.767, 3.796)	0.169	6	1.277 (-1.520, 4.074)	0.274	6	1.762 (-3.916, 7.440)	0.437
Child score												
A	6	-0.251 (-1.646, 1.144)	0.644	5	1.541 (-15.668, 18.751)	0.794	6	2.027 (-0.605, 4.659)	0.099	6	3.404 (-2.492, 9.300)	0.184
B	6	-0.208 (-1.555, 1.139)	0.690	5	4.053 (-6.666, 14.773)	0.315	6	-1.097 (-4.021, 1.827)	0.357	6	-1.585 (-7.353, 4.183)	0.488
C	6	0.004 (-1.542, 1.550)	0.995	5	6.580 (-0.28, 12.879)	0.054	6	-1.340 (-3.890, 1.209)	0.218	6	-2.336 (-7.105, 2.433)	0.246
Publish year	6	-0.019 (-0.089, 0.052)	0.501	5	0.269 (-0.015, 0.552)	0.057	6	0.014 (-0.138, 0.167)	0.809	6	0.016 (-0.270, 0.301)	0.887

Abbreviations: CI: confidence interval, Coef: coefficient, Ref: reference, NA: not available.

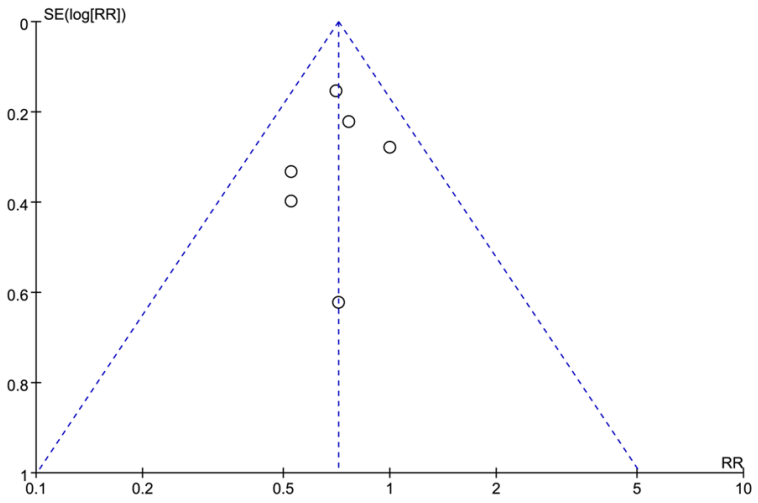

Figure 7. Funnel plot of all-cause mortality of EVL compared with pharmacotherapy.

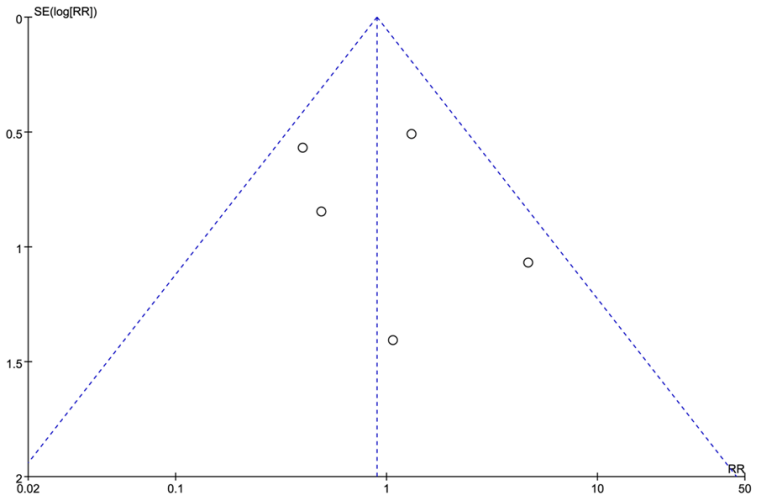

Figure 8. Funnel plot of mortality caused by bleeding of EVL compared with pharmacotherapy.

Mortality caused by bleeding

For the mortality caused by bleeding, each included study [7, 8, 10-12] suggested that there were no significant differences. **Figure 4** shows that there was no significant difference between the risk (RR=0.90, 95% CI [0.50, 1.61], I^2=27%, P=0.71) of pharmacotherapy and EVL, with mild evidence of hete rogeneity, using a fixed-effects model.

Rebleeding

For the rebleeding analysis, six studies [7-12] were included, and two of those [8, 11] suggested that there was a statistically significant difference between pharmacotherapy and EVL. **Figure 5** shows the difference between the pharmacotherapy versus the EVL (RR=1.12, 95% CI [0.49, 1.65], I^2=78%, P=0.55), which was not statistically significant, with large heterogeneity, using a random-effects model.

Rebleeding from varices

For the rebleeding from varices, six studies [7-12] were included, and five of those [7, 8, 10, 11] suggested that there was a statistically significant difference between pharmacotherapy and EVL. **Figure 6** shows that there was no significant difference between pharmacotherapy and EVL (RR=1.30, 95% CI [0.74, 2.25], I^2=82%, P=0.36), with large heterogeneity, using a random-effects model.

Meta-regression

All results from meta-regression analysis for all outcomes showed there were no significant difference between the EVL and pharmacotherapy groups after adjusting for differences in baseline and possible confounding factors (**Table 2**).

Publication bias

There was no potential publication bias based on symmetry from the funnel plot for all-cause mortality (**Figure 7**), mortality caused by bleeding (**Figure 8**), rebleeding (**Figure 9**), and rebleeding from varices (**Figure 10**).

Discussion

After an initial variceal hemorrhage, the frequency of recurrent bleeding ranges from 30% to 40% in the first 6 weeks [21, 22]. The risk of rebleeding depends on the severity of liver disease, variceal size, concomitant renal failure,

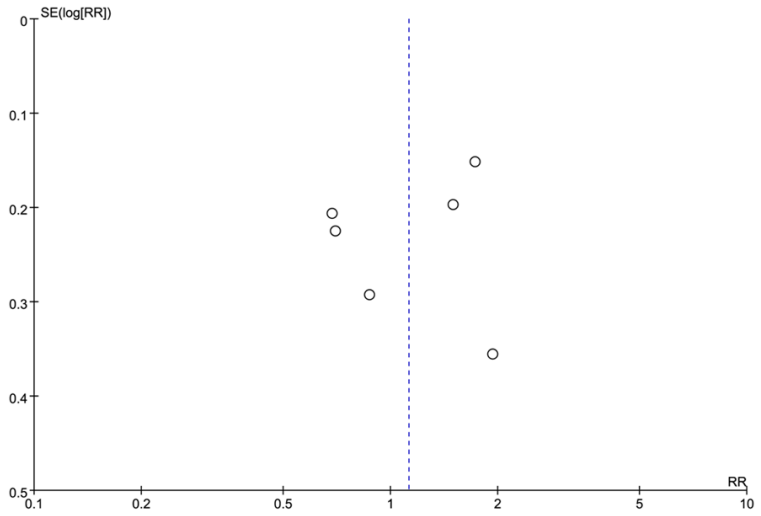

Figure 9. Funnel plot of rebleeding of EVL compared with pharmacotherapy.

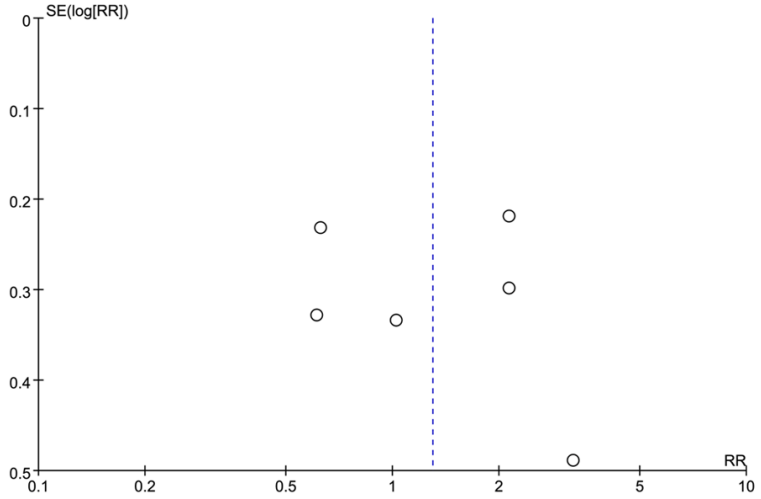

Figure 10. Funnel plot of rebleeding from varices of EVL compared with pharmacotherapy.

continued alcoholism, and the presence of hepatoma [23]. There is a close correlation between increased portal pressure and the risk of recurrent bleeding and survival rate [23, 24].

The current schemes including, pharmacotherapy, sclerotherapy, and ligation, are used to treat secondary prevention of variceal bleeding [23]. However, rebleeding rates are as high as 50% after repeat sclerotherapy [25], and sclerotherapy has been replaced almost universally by EVL. Although EVL rapidly results in variceal obliteration, studies have shown that rebleeding rates from esophageal varices range from 13% to 51% [26, 27]. In the past two decades, multiple treatment modalities have been introduced to prevent rebleeding and improve overall mortality after a variceal bleed [28]. These include pharmacological therapies [23, 24, 26, 28] such as NSBB, used either alone or in combination with ISMN. In 2009, Ravipati et al [28] reported that there were no relevant differences in the efficacy of the secondary prevention of esophageal variceal bleeding using both schemes including EVL and pharmacotherapy. However, Lo et al [11] in 2008 demonstrated that compared with EVL, pharmacotherapy had a worse effect on the mortality outcome, but better effects on rebleeding and rebleeding from varices. The risk and benefits of using both pharmacotherapy and EVL for the secondary prevention of esophageal variceal bleeding are still unclear and controversial.

This meta-analysis included six studies on the comparative efficacy of the secondary prevention of esophageal variceal bleeding using pharmacotherapy and EVL for esophageal variceal bleeding. The rates of mortality and rebleeding have been a concern for esophageal variceal bleeding. On the basis of all-cause mortality, this study showed the superior effect of pharmacotherapy in reducing the mortality rate, but both schemes had no obvious difference in reducing mortality caused by bleeding, rebleeding, and rebleeding from varices. According to the results of the retrospective meta-analysis, confounding factors did not appear to have significantly influenced the outcomes in five studies.

Portal hypertension results from an increased intra-hepatic resistance to portal blood flow, which is aggravated by splanchnic vasodilation and a hyperkinetic circulation leading to an increased portal inflow. NSBB and vasodilators

have been used to reduce portal inflow and intra-hepatic resistance, respectively. Use of NSBBs rather than selective β-1 blockers provides both a reduction in the cardiac output (β-1 effect) and an unopposed constriction of the splanchnic vessels (β-2 effect), leading to reduced variceal inflow. However, endoscopic treatments include local mechanical therapies such as EVL, which has an outstanding efficacy as a fast topical hemostatic treatment for esophageal variceal bleeding, but results in a poor control of bleeding.

A meta-analysis published in 2009 by Ravipati [13] with the results differing across included studies, especially for all-cause mortality, did not show any statistically significant differences between pharmacotherapy and EVL. The following differences between those three reviews were noted: First, our research had updated the systematic literature search to include recently published literatures including, such as Lo et al [11] and Stanley et al [12], whereas the previous one did not. Second, the first meta-analysis claimed that in their study, both schemes of pharmacotherapy and EVL were not significantly different in the secondary prevention of esophageal variceal bleeding based on the small sample size. However, our results showed a superior effect of pharmacotherapy on reducing the mortality rate as compared to EVL; our inclusion of larger sample studies may have led to greater accuracy. Third, we performed the meta-analysis to detect baseline and possible confounding factors, such as age, gender, region, sample, alcohol, viral infection, Child score, and publication year. In addition, in our study, the funnel plot was used as a qualitative method to detect potential publication bias, and the methodological quality of eligible trials was displayed to help us better understand the reliability of the evidence, whereas the previous study did not include this.

The advantage of this research was that all included studies were randomized controlled, clinical trials and with large sample sizes [29]. However, there were several limitations. First, few trials met our inclusion and exclusion criteria, and subgroup analysis was not performed to avoid low statistical power [16]. Second, the double blind methods of methodological quality of eligible trials could not be performed, owing to the specificity of EVL. Further clinical research is needed to confirm these results [18].

Conclusions

This study suggested that pharmacotherapy is superior to EVL for reducing mortality, whereas EVL is superior in reducing rebleeding during the secondary prevention of esophageal variceal bleeding.

Disclosure of conflict of interest

None.

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