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The effect of shortening vasoactive drug durations alongside endoscopic therapy in esophageal variceal bleeding: an updated systematic review and meta-analysis

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Abstract

Background The recommended duration of vasoactive drugs in esophageal variceal bleeding (EVB) spans 2-5 days. Prior meta-analyses of randomized trials include only a few studies that compared short vs. long vasoactive drug durations approximating this time range, including older management techniques, and only assessed variceal rebleeding at 5 days. We identified several additional randomized controlled trials (RCTs) assessing rebleeding at various durations, with updated management of EVB.

Methods We performed an updated systematic review and meta-analysis assessing the effect of shortening the vasoactive drug duration by 48-72 h. The primary outcome was rebleeding within 5 days. Secondary outcomes included rebleeding, mortality due to rebleeding, and all-cause mortality within 4-6 weeks (extended period) with subgroup analysis by vasoactive drug and type of endoscopic therapy. Length of stay, blood transfusion requirements and terlipressin-related adverse events were additional secondary outcomes.

Results Our comprehensive search strategy and screening process yielded 14 RCTs with 1060 patients (75.1% male): 7 trials used terlipressin, 4 octreotide, and 3 somatostatin. Shortened durations combined with band ligation led to similar rebleeding, with a trend towards less rebleeding when populations with more severe liver disease were excluded. There was greater rebleeding and mortality over an extended period when shorter durations were combined with sclerotherapy. Longer durations were associated with a longer hospital stay and, for terlipressin, more adverse events.

Conclusions Shorter vasoactive drug durations combined with band ligation in selected populations appear safe. Higher powered RCTs are needed, involving patients with different degrees of severity of EVB and liver disease.

Keywords Vasoactive, duration, esophageal variceal bleeding

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Conflict of Interest: None

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Introduction

The recommended duration of vasoactive drugs alongside endoscopic management in esophageal variceal bleeding (EVB) varies, with multiple societies recommending a broad range of 2-5 days [1-3]. Earlier studies [4,5] found a 5-day duration compared to placebo alongside endoscopic therapy effective in preventing EVB, but a subsequent study showed that a 2-day duration doubled treatment failures [6]. Since then, data from several randomized controlled trials (RCTs) [7-11] comparing shorter and longer durations of vasoactive drug durations have been pooled in systematic reviews and meta-analyses (SRMAs) [12,13]. These demonstrated similar rates of 5-day variceal rebleeding with shortened durations, approximating

the 2-day vasoactive drug duration, compared to longer durations, leading the European Association for the Study of the Liver to suggest that a shortened duration should be considered [2].

Neither of these SRMAs compared the outcomes of short vs. longer courses across a single vasoactive drug, and only 1 SRMA [12] included a single study on octreotide [8], the vasoactive drug of choice due efficacy and safety [14,15], relative to terlipressin. Terlipressin, however, has recently gained approval for hepatorenal syndrome in the United States [16], which may increase its popularity and, while several relevant RCTs [7,10,11] have been pooled for meta-analysis [12,13], newer published RCTs with updated management are available [17,18] in addition to published RCTs on somatostatin [19].

Our updated SRMA aimed to add data to variceal rebleeding at 5 days, but also to pool data from multiple studies on rebleeding and mortality at time points within approximately 6 weeks, as recommended by portal hypertension guidelines [1]. It was designed to assess each vasoactive drug individually, to determine any differences between drugs over shorter durations. Additionally, the study assessed whether the effect on EVB of shortening the duration of vasoactive drug therapy was influenced by the endoscopic technique of sclerotherapy vs. band ligation (BL), the standard of care. Finally, Child-Pugh Class C (CPCC) has been cited as a significant predictor of variceal rebleeding [3,8], with prior RCTs focusing on higher CPCC distributions [7,10,11]. We sought to add studies across various distributions of CPCC to explore the effect of shortening vasoactive drug durations in various severities of liver disease.

Materials and methods

Search strategy

A comprehensive search was constructed in Embase (Embase.com, Elsevier) by an experienced health sciences librarian (WLS) on 13 February 2024, using truncated keywords, phrases, proximity searching and subject headings. This strategy was translated to MEDLINE (OVID, National Library of Medicine), the Cochrane Central Register of Controlled Trials (CochraneLibrary.com, Wiley), the Web of Science Core Collection, the Korean Citation Index, and SciELO (Web of Science platform, Clarivate) and Global Index Medicus (World Health Organization) (see Supplementary Table 1 for detailed search strategies). No limits were applied to publication date or language. All results were exported to EndNote 20 citation management software (Clarivate, Philadelphia, PA, USA) (Supplementary Table 2) and duplicates were removed by successive iterations of EndNote's duplicate detection algorithms and manual inspection. Our systematic review process was conducted in accordance with the PRISMA guidelines (Supplementary Table 3) [20].

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Study selection criteria

Two study authors (SD and MA) reviewed records and excluded duplicated studies not removed by the software, articles on animals, articles on children, review articles, case reports and case studies/series, study protocols, studies not involving exclusively EVB, and studies not studying the vasoactive drug duration as the primary comparison. We chose to include abstracts to increase the data available and to decrease publication bias [21]. One full text manuscript was written in Farsi [22], so the entire text was preliminarily translated by ChatGPT 4.0 and afterwards by a native Farsi speaker (AS). From the review of full texts or abstracts, we excluded studies that: 1) did not perform initial endoscopic therapy; 2) did not administer any vasoactive drug in a comparison arm; and 3) where sample sizes or type of endoscopic therapy could not be determined after attempts to contact authors. Only RCTs were included, as durations in retrospective studies are confounded by the severity of bleeding [3,23]. In terms of shorter and longer vasoactive drug duration, we included all studies with durations that closely approximated or intersected with the 2- to 5-day range recommended, with only 1 study [24] having a slightly longer duration (6.5 days), and we excluded 2 studies that compared 5 vs. 10 days of terlipressin. While guidelines [1] recommend BL over sclerotherapy for endoscopic hemostasis, we included studies with any endoscopic techniques, planning to carry out a subgroup analysis. Inclusion of each study was agreed upon by 2 authors (SD and MA) and another (CL) resolved any disagreements regarding study inclusion.

Baseline characteristics

We gathered demographic data in addition to any factors reported in studies that would influence EVB, based on guidelines [1,3], including Child-Pugh Class % distribution, varix grade distribution, the presence of active bleeding on endoscopy, and success in achieving initial endoscopic hemostasis (Table 1). Not all studies reported a model for end-stage liver disease (MELD) or a Child-Pugh score between comparison arms. Therefore, we calculated the pre-2016 MELD scores, using an online calculator [25] with reported means and standard deviations of total bilirubin, creatinine, and prothrombin (PT) values, and used them to compare liver disease severity between comparison arms. PT was converted to the international normalized ratio, assuming an International Sensitivity Index (ISI) of 1.3, which is between reported lab ranges [26], and we reported whether the pre-2016 MELD

Table 1 Demographics and characteristics of studies included in the meta-analysis by vasoactive drug

Vasoactive Drug	Total N (Sh, Lg)	Mean Age (years)	Male (%)	Etiology of CLD (%)			Child–Pugh Distribution (%)			Child-Pugh Mean Total (Sh, Lg)	Difference in MELD Comparisons	Varix grade distribution %				Active Varix Bleed % Total (Sh, Lg)	Initial Hemostasis with Endoscopy (%)
Author *et al* [ref.], Year Location				Hepatitis	EtOH	Other	A	B	C			1	2	3	4		
Octreotide																	
Yucesoy *et al* [24], 2004 Kayseri, Turkey	51 (34, 27)	53.8	76.5	HBV (33) HCV (35)	18	14	43	38	15	8.7 (8.9, 8.4)	Higher in Longer	5	26	69	0	-	-
George *et al* [31], 2006 Salayang, Malaysia	37 (18, 19)	48.8	71.8	24	33	43	Majority >7			-	No	-	-	-	-	-	-
Hajiani *et al* [22], 2011 Ahvaz, Iran	71 (35, 36)	45.8	-	HBV (32) HCV (14)	0	53	-	-	-	8.0 (8.0, 8.0)	No	-	-	-	-	39	-
Rengasamy *et al* [8], 2015 Pudicherry, India	120 (62, 58)	47.9	70.0	-	-	-	28	55	20	-	Likely Higher in Longer	-	-	-	-	-	-
Terlipressin																	
Choudhary *et al* [30], 2011 Chandigarh, India	28 (14, 14)	44.2	85.7	-	67	32	-	-	-	-	Higher in Longer	-	-	-	-	-	-
Azam *et al* [7], 2012 Karachi, Pakistan	130 (65, 65)	49.8	74.6	HBV (12) HCV (58)	11	19	11	55	34	8.7 (8.9, 8.4)	No	0	11	39	50	24 (20, 25)	100
Solari *et al* [27], 2012 South America	51 (14, 37)	-	-	-	-	-	-	-	-	-	No	-	-	-	-	-	-
Salim *et al* [10], 2017 Lahore, Pakistan	90 (65, 25)	52.5	0.6	HCV (91)	-	9	0	54	46	9.0 (8.9, 9.3)	No	1	2	46	51	-	100
Zaman *et al* [11], 2019 Lahore, Pakistan	100 (50, 50)	55.2	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Poudel *et al* [17], 2022 Chandigarh, India	49 (25, 24)	48.1	83.7	-	-	-	-	-	-	-	Higher in Longer	-	-	-	-	-	100
Vaishnav *et al* [18], 2024 New Delhi, India	149 (74, 75)	42.0	87.2	HBV (13) HCV (9)	46	32	25	60	15	8.0 (8.0, 8.0)	No	0	37	63	0	7 (5, 8)	100
Somatostatin																	
Yaras *et al* [32], 2013 Mersin, Turkey	39 (20, 19)	82.1	59.0	HBV (21) HCV (33)	0	46	-	-	- 17	-	No	15	51	34	-	- 12	-
Chitapanux *et al* [9], 2015 Chiang Mai, Thailand	95 (50, 45)	47.3	91.6	HBV (23) HCV (9)	53	15	28	55	-	-	No	-	-	-	-	(14, 9)	100
Poudel *et al* [17], 2022 Minia, Egypt	50 (25, 25)	47.6	88.0	-	-	-	-	-		-	No	-	-	-	-	-	-

Sh, shorter course vasoactive drug therapy; Lg, longer course vasoactive drug therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; EtOH, liver disease due to alcohol; MELD, model for end-stage liver disease

scores were significantly different across treatment arms (Table 1). Unfortunately, the wide ranges in ISI did not allow us to compare MELD scores across studies [26].

Obtaining unpublished data

We noted studies that reported different measures for baseline characteristics, time periods of rebleeding, while 1 study [8] mixed sclerotherapy and BL without specifying how many were in the short- and long-duration groups. We emailed all corresponding authors listed in the study to obtain further data. We received responses from authors of 3 studies [8,17,18], with additional data on Child-Pugh Class distribution [18], mean blood products transfused [18], mean length of stay (LOS) [18], rebleeding at 5 days and 6 weeks [17], mortality due to rebleeding [17, 18] and all-cause mortality at 5 days and 6 weeks instead of 7 days and 8 weeks [17]. We also obtained a breakdown of patients who underwent sclerotherapy or BL in the 2-day and 5-day comparison, and which endoscopic treatment the patient who died received in the study [8] that mixed the treatments. All authors were notified of and consented to our plans to publish their unpublished data prior to providing it to us.

Extraction of primary and secondary outcome data

Our data were extracted into Microsoft Excel including previously unpublished data (Supplementary Table 4). We report variceal rebleeding within 5 days alongside BL, the endoscopic standard of care, as our primary outcome, despite guidelines [1] recommending 6-week mortality as the primary outcome in EVB studies. This is since neither rebleeding nor mortality was consistently reported at exactly 6 weeks, while of the studies that specified a primary outcome, most [7,10,11,18,27] chose 5-day rebleeding. Secondary outcomes were rebleeding at 5 days for sclerotherapy as well as rebleeding recorded at a duration between 4 to 6 weeks (henceforth to be referred to as the "extended period" [EP]), mortality due to rebleeding at the EP, all-cause mortality at the EP for both BL and sclerotherapy. This range accommodates the inclusion of 3 studies [7,8,18] that only measured rebleeding outcomes up to 1 month. It should be noted that rebleeding at 5 days was included in the number of rebleeds at the EP. Additionally, while the Baveno VII consensus [1] considers all mortality within 6 weeks as related to the initial variceal bleed, some included studies [7-9,22] and 1 study [18] author we asked made a distinction between death from variceal rebleeding directly and death from other causes, such as hepatic encephalopathy, so this was recorded as an additional outcome. Additional secondary outcomes were overall LOS, and blood transfusion requirements in units of packed red blood cells (pRBC), as well as adverse events specifically related to terlipressin, given concerns for its safety profile [15]. Note that the difference in short vs. longer vasoactive durations varied across studies from 2-3 days in BL, and given that LOS is partially dependent on the difference between short and long durations, we divided the LOS in each study by the difference in duration of vasoactive drugs in the study—henceforth known as corrected LOS (cLOS)—to allow the data to be pooled across studies. We also distinguished adverse events as total or severe, with the latter defined as those that had life-threatening consequences that required urgent intervention, that are potentially reversible with intensive treatment, or a death related to the drug as per classification of RCTs [28].

Meta-analysis

Outcome data were transferred from Microsoft Excel to Review Manager 5.4 software (Revman) for meta-analysis. Rebleeding, mortality, and adverse events were entered as dichotomous outcomes generating risk ratios and confidence intervals (CI). cLOS (days) and blood transfusion requirements (pRBC transfused) were continuous outcomes entered as mean and standard deviations, generating mean differences and confidence intervals. The random effects model was used, and a P-value of <0.05 was considered statistically significant. Statistical heterogeneity was assessed using Higgins I^2 index, calculated in Revman. For our primary outcome, several studies had zero rebleeding events in both comparison groups, resulting in fewer than 10 studies where an effect size (risk ratio) that could be calculated. Since at least 10 effect sizes are recommended for generating a funnel plot to assess publication bias, we did not generate one. The Risk of Bias (RoB) 2.0 Cochrane Tool for individually randomized parallel controlled trials [29] was used to assess study bias and to make an overall judgment as whether there was a high risk of bias, some concerns, or a low risk of bias (Supplementary Table 5). Subgroup analysis was performed to assess the effects between individual drugs and between endoscopic therapies of BL and sclerotherapy. Sensitivity analysis was performed on studies where there was a high risk of bias, and/or concerns about less-than-optimal randomization, as there were more factors influencing variceal rebleeding in 1 comparison arm (Table 1). Subsequently, a second layer of sensitivity analysis was performed by excluding studies that were likely to have a wider CPCC distribution. This was determined by assessing the CPCC distribution across all studies and noting 2 studies [7,10] reporting CPCC distributions >30%, whereas the rest were <20%. Additionally, 1 study [11] was conducted 6 months after another [10] at the same hospital, with similar protocols, so it was assumed CPCC distributions were similar. We performed a final separate sensitivity analysis by pooling only studies with high CPCC distributions or high-risk varices. Stratification of variceal severity was carried out in a similar way as for CPCC distribution, by identifying 2 studies [7,22] with 24% and 39% active variceal bleed on endoscopy, compared to other studies [9,18] that reported 12% and 7%.

Results

Our comprehensive search strategy and screening process (Fig. 1) yielded 14 RCTs [7-11,17-19,22,24,27,30-32] that were published from 2004-2024 and included 1060 patients, with a mean age of 49 years, of whom 75.1% were male. There were no differences in age, sex distribution, etiology of liver disease, or distribution of Child-Pugh scores across comparison arms, but baseline characteristics related to rebleeding [1] were statistically higher in 4 studies in the longer vasoactive drug duration comparison arm, including higher PT [8], calculated pre-2016 MELD [17,24] and reported MELD [30]. In terms of data quality, our risk of bias analysis revealed that 11 of 14 RCTs had at least some risk (see supplementary table 5), with only 2 non-open label studies [7,9], some concerns about randomization bias [8,17,24,30], and limited methods [11,27,30-32].

Our primary outcome was rebleeding within 5 days in the short vs. long vasoactive drug duration arms, alongside BL only, involving 12 studies. There was no significant difference between short vs. long durations, with an overall risk ratio of 0.79 (95%CI 0.37-1.65; P=0.67; I^2=0%; Fig. 2A). There was also no difference between individual drugs on subgroup analysis (Fig 2A).

In terms of secondary outcomes, at the EP, there was no significant difference in rebleeding, mortality due to rebleeding,

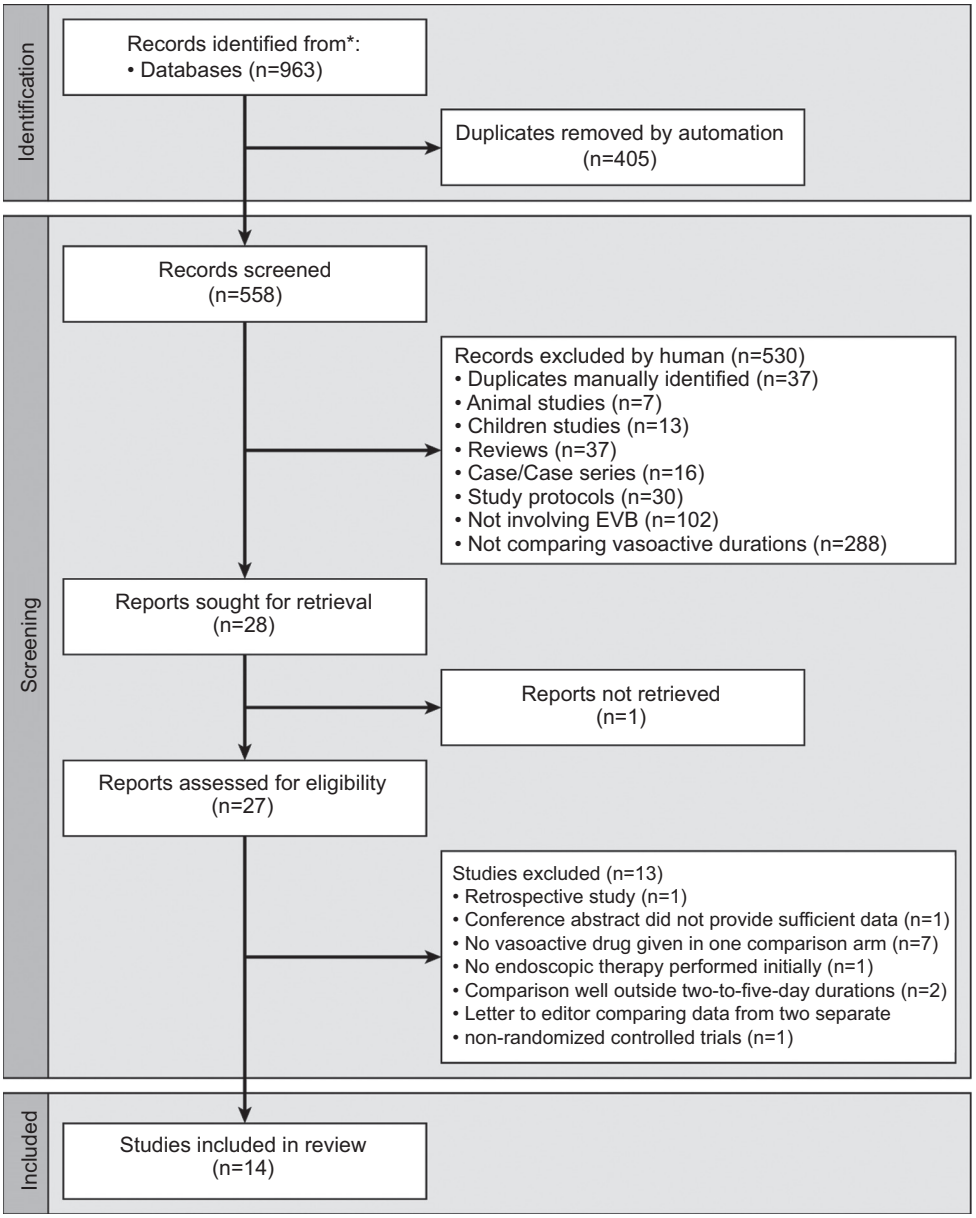

Figure 1 PRISMA flow chart for study selection
EVB, esophageal variceal bleeding

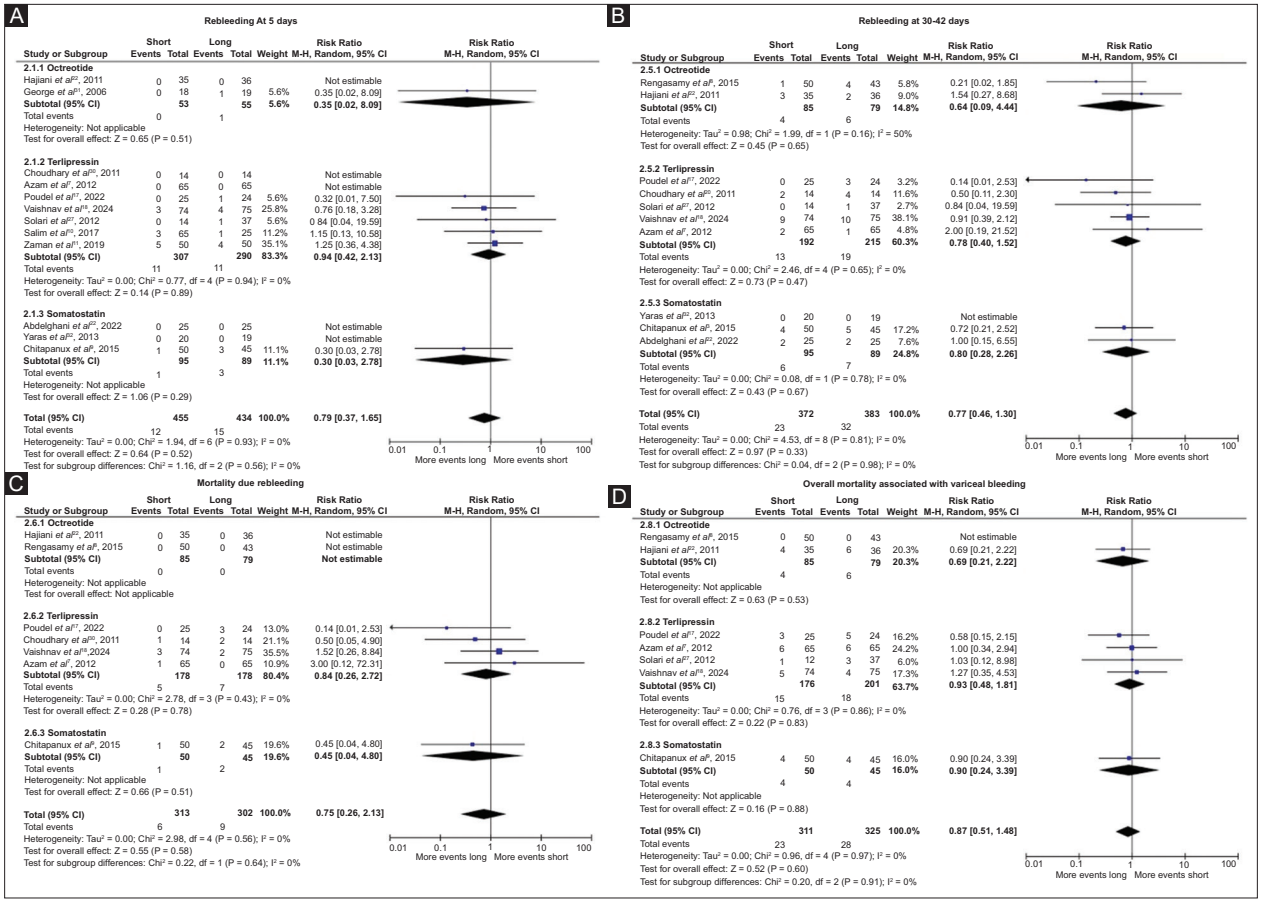

Figure 2 Forest plots comparing variceal rebleeding and associated mortality in short vs. long durations in esophageal variceal band ligation for vasoactive drugs. (A) Rebleeding within 5 days. (B) Rebleeding within the extended period (30-42 days). (C) Mortality due to rebleeding within the extended period (30-42 days). (D) Overall mortality associated with variceal bleeding
M-H, Mantel-Haenszel; CI, confidence interval

or all-cause mortality between short and long vasoactive drug duration all alongside BL, with risk ratios of 0.77 (95%CI 0.46-1.30; P=0.33; I^2=0%; Fig. 2B), 0.75 (95%CI 0.26-2.13; P=0.58; I^2=0%; Fig. 2C), and 0.87 (95%CI 0.51-1.48; P=0.52; I^2=0%; Fig. 2D), respectively.

2 studies [8,24] assessed patients who underwent sclerotherapy. In this group shortened durations led to more rebleeding at 5 days, with a risk ratio of 2.40 (95%CI 0.10-56.67; P=0.59; Fig. 3A), and at the EP, with a risk ratio of 4.24 (95%CI 0.96-18.78; P=0.06; I^2=0%; Fig. 3B), though these differences were not statistically significant. Shortened durations in sclerotherapy did lead to a statistically significant increase in mortality due to rebleeding, and to all-cause mortality at the EP (all mortality in sclerotherapy was due to rebleeding), both with a risk ratios of 5.68 (95%CI 1.06-30.49; P=0.04; I^2=0%; Fig. 3C, D). Finally, subgroup analysis comparing shortened durations in BL vs. sclerotherapy found that the latter led to significantly increased mortality (Fig. 3C, D).

There was a significantly greater number of total adverse events related to terlipressin in the long duration group, with a risk ratio of 1.66 (95%CI 1.23-2.26; P=0.001, I^2=0%; Fig. 4A), but no statistically significant difference in severe adverse events, resulting in a risk ratio of 1.01 (95%CI 0.19-5.40; P=0.99; I^2=0%; Fig. 4B). cLOS was significantly longer for the longer vasoactive drug duration in the BL subgroup, with a mean difference of 1.12 days (95%CI 0.71-1.53; P=0.003; I^2=89%; Fig. 4C). Finally, there was no significant difference between blood transfusion requirements with a mean difference of 0.15 more pRBCs transfused (95%CI -0.10-0.41; P=0.24; I^2=0%) in the longer duration group amongst patients who underwent BL; however, there was a difference between the BL and sclerotherapy groups in the blood transfusions required (Fig. 4D).

In terms of trends, prior to the sensitivity analysis there were statistically insignificant trends towards increased rebleeding, mortality due to rebleeding, and all-cause mortality in the longer vasoactive duration group who underwent BL. Octreotide and somatostatin both had similar trends of increased rebleeding within 5 days associated with the longer treatment durations (Fig. 2A), with only 1 study pooled on each, whereas shortening terlipressin had no notable trend and more studies were pooled. Study quality was assessed with the Risk of Bias 2.0 tool for all 14 studies (Supplementary Table 5), which revealed that 11 studies had some risk of bias. The sensitivity analysis, excluding studies with high CPCC distributions, revealed a trend towards more 5-day rebleeding with longer durations in patients who underwent BL (Supplementary Fig. 1A). Conversely, including

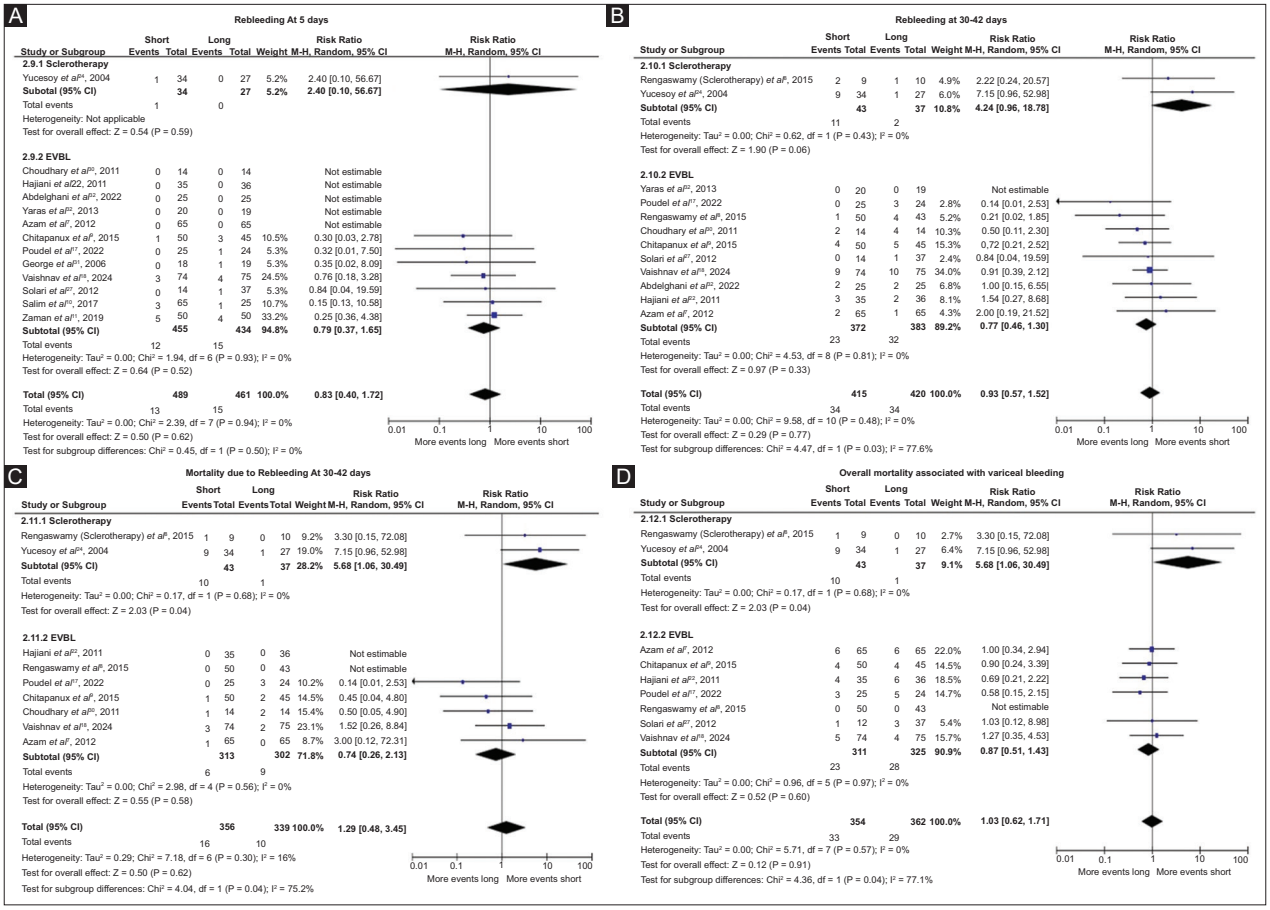

Figure 3 Forest plots comparing variceal rebleeding and associated mortality in short vs. long durations by endoscopic therapy. (A) Rebleeding within 5 days. (B) Rebleeding within the extended period (30-42 days). (C) Mortality due to rebleeding with the extended period (30-42 days). (D) Overall mortality associated with variceal bleeding
M-H, Mantel-Haenszel; CI, confidence interval

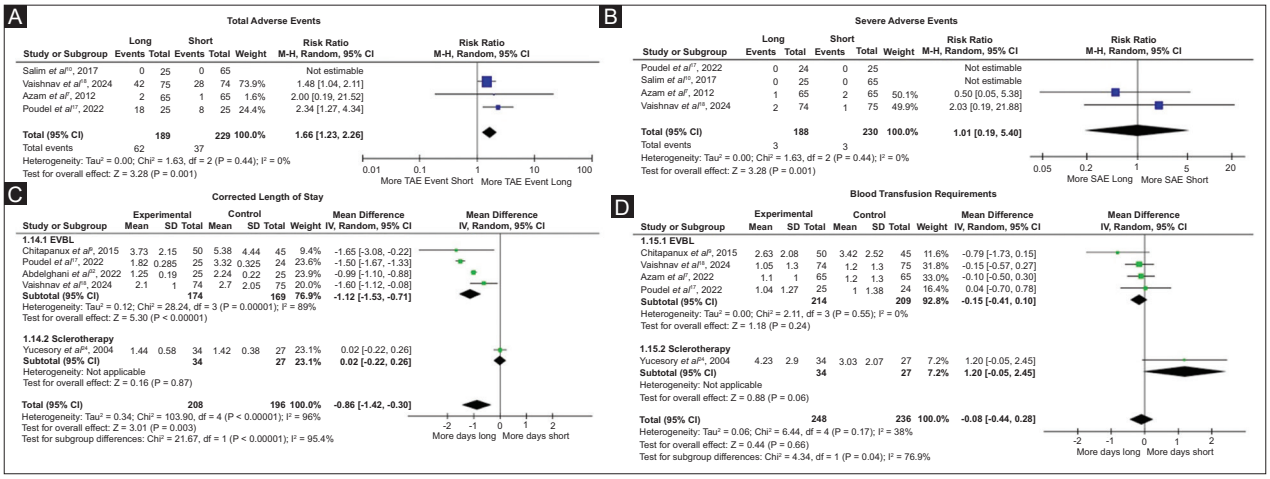

Figure 4 Forest plots comparing adverse events, corrected length of stay, and blood transfusion requirements in short vs. long durations for vasoactive drugs. (A) Total adverse events related to terlipressin. (B) Severe adverse events related to terlipressin. (C) Corrected length of stay. (D) Blood transfusion requirements
M-H, Mantel-Haenszel; CI, confidence interval

only studies with high-risk variceal features or high CPCC distribution [7,10-,22] revealed a trend towards more 5-day rebleeding (Supplementary Fig. 1B) and a trend towards greater mortality due to rebleeding at the EP (Supplementary Fig. 1C).

Discussion

The conclusion of our SRMA aligns with those of prior studies [16,17] in that shortening vasoactive durations by 48-72 h in combination with BL does not lead to increased rebleeding in EVB. Our results, however, add more precision by analyzing new outcomes, including variceal rebleeding, mortality due to rebleeding, and overall all-cause mortality at an extended time duration of 4-6 weeks (EP) for rebleeding and mortality, and demonstrating the observation across 3 different vasoactive drugs. Our study also resulted in 3 original observations related to vasoactive drug durations.

First, longer durations led to a longer LOS and more total terlipressin-related adverse effects, but blood transfusions and severe adverse effects related to terlipressin remained similar. This is in agreement with another study where 5-day vasoactive drug vs. 5-day pantoprazole infusions in EVB were compared, showing longer stays for the vasoactive group, though without statistical significance, suggesting a potential trend towards a greater LOS related to the longer administration duration of a vasoactive drug, rather than the duration of the intravenous infusion. Regarding blood transfusions, 2 studies [8,22] in our review, which were not pooled because they reported dichotomous data, reported no significant differences, with 1 [8] noting slightly more transfusions in the longer duration group. This trend may be driven by a confounder, such as increased intensive care monitoring leading to more transfusions [33], or it might support the trend of more 5-day rebleeding due to a more vasoactive drug: it is difficult to determine which without more granular data. Our finding that shortening terlipressin courses decreased total adverse events, but not severe ones, is supported by 2 studies [34,35] excluded from our analysis, which found significantly more total adverse events in the longer duration group, also with no differences in severe adverse events, and only 1 severe adverse event in the shorter terlipressin duration arm across all 3 studies. Overall, this finding suggests that shortening vasoactive drug duration would mainly reduce LOS and total adverse effects related to terlipressin.

Second, our subgroup analysis revealed that a shorter duration of vasoactive therapy combined with sclerotherapy was associated with more rebleeding and greater mortality in the extended period (EP). This makes intuitive sense, as sclerotherapy has been associated with acute rises in portal pressures lasting for 5 days [36,37], which may increase rebleeding risk; thus, longer vasoactive durations for up to 5 days to potentially counteract that effect should remain the standard of care whenever sclerotherapy is performed [38].

Finally, our sensitivity analysis by liver disease and variceal bleeding severity showed a trend for more 5-day rebleeding with longer vasoactive durations in cases with less severity, and a trend for less 5-day rebleeding and lower mortality at the EP associated with longer durations in cases with higher severity. The trend that shortening durations alongside BL decreases rebleeding in patients with less severe bleeding, particularly with octreotide and somatostatin, but increases rebleeding in severe liver disease or variceal bleeding cases, warrants a cautious approach to shortening vasoactive durations in severe EVB, pending further investigation. It should be noted that the lower levels of rebleeding in shorter durations were more prevalent in the octreotide and somatostatin subgroups, which share similar mechanisms of action [39]. Data suggest that longer durations of octreotide lead to tachyphylaxis and less sustained drops in portal pressures compared to terlipressin [39,40], although how this relates back to greater rebleeding is unclear. Additionally, the trend for more 5-day rebleeding with longer durations of octreotide/somatostatin, but not terlipressin, could just be due to the limited sample size for the former drugs.

Our SRMA summarizes the highest level of data available (RCTs) on short vs. long vasoactive drug durations, incorporating subgroup analysis by vasoactive drug and endoscopic technique, with sensitivity analyses to account for the severity of liver disease and variceal bleed, but our analysis does have limitations. First, 4 of 14 studies were conference abstracts with limited methodology and peer review, although all 3 vasoactive drugs were represented in abstracts. While we reached out to all authors systematically for additional data points and clarification regarding methods, we received responses from authors of more recent studies [8,17,18], which introduces a reporting bias favoring recent data. Several forms of clinical heterogeneity existed in the methodologies per study (Table 2). These included exact durations of short vs. long courses of vasoactive drugs, and the vasoactive drug administration's timing with respect to endoscopy, with 2 studies stopping vasoactive drugs after endoscopy [10,24], limiting exact day recommendations. Additionally, the time point for rebleeding and mortality after 5 days varied, and only 3 studies [8,18,22] mention β-blockers used for secondary prophylaxis to reduce portal pressures in EVB [1,41]. Our sample size was also limited, despite including 14 RCTs in our meta-analysis, as inconsistent methods of recording data such as transfusion requirements across studies resulted in several underpowered outcomes. Additionally, zero-events (no bleeds) in both arms limited our ability to detect differences in effect size, though they still suggest non-inferiority between short and long durations. In terms of publication bias, 11 of 14 studies showed some risk due to randomization and blinding issues. Our subgroup and sensitivity analyses faced limitations: previous meta-analyses [14,15,42] indicated minimal differences in vasoactive drug efficacies, making our study underpowered to detect any such differences. Furthermore, only 2 studies [8,24] were available for sclerotherapy subgroup analysis. While the sensitivity analysis improved data quality, it was limited by incomplete methodologies. Finally, the generalizability of our findings is limited, since 12 of 14 RCTs were conducted in Asia, with none from Europe, Canada or the United States, bringing into question their applicability to western healthcare settings.

More high quality RCTs with uniform methodology across different severities of liver disease and variceal risk profiles are required to determine whether shortening vasoactive drug duration is safe across all populations. In terms of outlook, high hepatic vein pressure gradient (HVPG) measures have been shown to be associated with early rebleeding [43], so

Table 2 Summary of methodologies of studies included in the meta-analysis by vasoactive drug

Vasoactive Drug Author *et al* [ref.], Year	Dose and Route Duration (h) (Sh, Lg)	Endoscopy Within (h)	Vasoactive Rx after endoscopy for Sh	Endoscopic Treatment	Antibiotic Prophylaxis	β-Blocker Initiation	Exclusion Criteria
Octreotide							
Yucesoy *et al* [24], 2004 Manuscript	50 μg IV bolus for 36 h. In standard, SQ 100μg/q8hafter sclerotherapy (36, 156)	36	No	All Sclerotherapy	-	-	Cardiovascular: CAD. Other Systemic Conditions: CKD, hypersensitivity to drugs. Treatments Received: Ongoing treatment for bronchial asthma.
George *et al* [31], 2006 Abstract	(48, 120)	24	Yes	EVBL	PRN	Propranolol on discharge	-
Hajiani *et al* [22], 2011 Manuscript	50 μg bolus then 50 μg/h infusion (48, 120)	8	Yes	EVBL	Ceftriaxone BID, unspecified dosage	-	Cardiovascular: CAD. Liver-Related Conditions: PAD, HCC, HE, or metastatic malignancy. Other Systemic Conditions: Asthma, octreotide hypersensitivity. Treatments Received: Endoscopic treatment of varices within 4 weeks. Additional Notes: Excluded bleeding from non-variceal sources.
Rengasamy *et al* [8], 2015 Manuscript	50 μg bolus then 50 μg/h infusion for 2d vs. 5 d (48, 120)	48	Yes	EVBL (multiband), Sclerotherapy	Ceftriaxone 1g BID, duration unspecified	β-blockers on discharge	Cardiovascular: Severe ischemic heart disease. Liver-Related Conditions: HCC or other malignancy. Other Systemic Conditions: Debilitating illnesses such as cerebrovascular accidents. Treatments Received: Use of vasoactive medicines, endoscopic therapy before referral. Additional Notes: Excluded concomitant gastric varices or other UGI sources of bleed.
Terlipressin							
Choudhary *et al* [30], 2011 Abstract	(48, 120)	24	Yes	EVBL	-	-	Liver Related Conditions: HCC, Gastric Varices.
Azam *et al* [7], 2012 Manuscript	2 mg bolus and 1 mg q6h (24, 72)	12	Yes	EVBL (multiband)	Ceftriaxone for 3d, unspecified dosage	Propranolol on discharge	Liver-Related Conditions: Child Pugh Score > 12, gastric varices, hepatoma, PVT. Additional Notes: Hemostasis failure on endoscopy.

(*Contd...*)

Table 2 (*Continued*)

Vasoactive Drug / Author *et al* [ref.], Year	Dose and Route / Duration (h) (Sh, Lg)	Endoscopy Within (h)	Vasoactive Rx after endoscopy for Sh	Endoscopic Treatment	Antibiotic Prophylaxis	β-Blocker Initiation	Exclusion Criteria
Solari *et al* [27], 2012 Abstract	(48, 120)	24	Yes	EVBL	-	-	Liver-Related Conditions: HCC outside Milan criteria. Additional Notes: Excluded massive bleeding and gastric bleeding from sources other than varices Cardiovascular: CAD.
Salim *et al* [10], 2017 Manuscript	2 mg then 1 mg q6h for 12h vs. 72h (12, 72)	12	No	EVBL	-	-	Liver-Related Conditions: Non-Cirrhotic.
Zaman *et al* [11], 2019 Manuscript	2 mg then 1 mg q6h for 24h vs. 72h (24, 72)	12	Yes	EVBL	Ceftriaxone 2g SID for 3d	-	-
Poudel *et al* [17], 2022 Manuscript	2 mg q4h for 48 h vs. 120 h (48, 120)	24	Yes	EVBL	Unspecified antibiotic administered for unspecified duration	-	Other Systemic Conditions: CKD, Pregnancy. Treatments Received: EVL, receiving pre-EVL terlipressin therapy, EVL done > 24h of admission. Additional Notes: Excluded UGI bleed for > 24h. Cardiovascular: CAD.
Vaishnav *et al* [18], 2024 Manuscript	2 mg q4h until endoscopy, then 1 mg q6h (24, 72)	12	Yes	EVBL (multiband)	Ceftriaxone 1g SID for 5d	Carvedilol on Cessation of Vasoactive Drug	Liver-Related Conditions: Acute on Chronic Liver Failure, HE, HCC, Metastases to Liver, Extrahepatic Portal Venous Obstruction. Other Systemic Conditions: Spontaneous Bacterial Peritonitis, Sepsis, Mechanical ventilation. Treatments Received: Patients on antiplatelets. Additional Notes: Excluded gastric variceal bleed.
Somatostatin							
Yaras *et al* [32], 2013 Abstract	250 μg bolus then 250 μg/h infusion (48, 120)	-	Yes	EVBL (multiband)	-	-	-
Chitapanux *et al* [9], 2015 Manuscript	250 μg bolus then 250 μg/h infusion for 3d vs. 5d (72, 120)	24	Yes	EVBL (multiband)	Ceftriaxone 2g SID for 3d	-	Liver-Related Conditions: Non-Cirrhotic Portal Hypertension associated with Portal Hypertension or Malignancy. Other Systemic Conditions: Stroke, Uremia, Sepsis, Bedridden. Treatments Received: Previously treated Gastric Variceal Bleeding.
Abdelghani *et al* [19], 2022 Manuscript	250 μg bolus then 500 μg/h infusion (48, 120)	24	Yes	EVBL	Unspecified antibiotic administered for unspecified duration	-	Other Systemic Conditions: CKD, Pregnancy. Treatments Received: EVL, patients not receiving pre-EVL terlipressin therapy, EVL done > 24h of admission. Additional Notes: Excluded UGI bleed > 24h.

Sh, short course vasoactive drug therapy; Lg, longer course vasoactive drug therapy; CAD, coronary artery disease; CKD, chronic kidney disease; EVBL, esophageal variceal band ligation; PRN, as needed; PAD, periphery artery disease; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; SID, once daily; BID, twice daily; UGI, upper gastrointestinal

measurements of portal pressures via HVPG that were made in the most recent RCT [18] may increase our understanding of how shortening each vasoactive drug reduces portal pressures, and how that affects variceal rebleeding.

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Summary Box

What is already known:

- Vasoactive drug regimens of 2-5-day durations are recommended, in combination with endoscopic band ligation, to reduce variceal rebleeding
- There are data to suggest that decreasing vasoactive drug duration from 3-5 days to 1-3 days does not increase the risk of variceal rebleeding within 5 days

What the new findings are:

- Decreasing vasoactive drug durations from 3-5 to 1-3 days alongside band ligation does not increase the risk of variceal rebleeding, all-cause mortality, nor mortality due to rebleeding at 1 month to 6 weeks across all vasoactive drugs
- Longer vasoactive drug durations led to a statistically significant longer hospital stay, and trended towards more units of blood transfused, and possibly even greater variceal rebleeding in populations with low liver disease severity
- Shorter vasoactive drug durations were associated with more rebleeding after sclerotherapy, and there was a trend towards slightly more rebleeding from shortened durations in populations with high-risk varices and/or high Child-Pugh C distributions

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Supplementary material

Supplementary Table 1 Comprehensive search constructed in EMBASE

No.	Query	Results
#1	'octreotide'/syn OR 'octreotide' OR 'bynfezia' OR 'cam 2029' OR 'cam2029' OR 'compound 201995' OR 'drg 0115' OR 'drg0115' OR 'longastatin' OR 'longastatina' OR 'mtd 201' OR 'mtd201' OR 'mycapssa' OR 'ocphyl' OR 'octrayne' OR 'octreoanne' OR 'octreolin' OR 'octreoteva' OR 'okrodin' OR 'okteva' OR 'olatuton' OR 'oncolar' OR 'pt 201' OR 'pt201' OR 'rg 3806' OR 'rg3806' OR 'samilstin' OR 'sandostatin' OR 'sandostatina' OR 'sandostatine' OR 'sandstatin' OR 'sdz 201995' OR 'sdz201995' OR 'siroctid' OR 'sms 201 995' OR 'sms 201-995' OR 'sms 201995' OR 'sms 995' OR 'sms 995aaa' OR 'sms201 995' OR 'sms201-995' OR 'sms201995' OR 'sms995' OR 'sms995 aaa' OR 'sms995aaa' OR 'somatuline la' OR 'treoject'	28497
#2	'somatostatin'/syn OR 'somatostatin' OR 'aminopan' OR 'ay 24910' OR 'ay24910' OR 'ghrih' OR 'growth hormone release inhibiting factor' OR 'modustatine' OR 'somatofalk' OR 'somatotropic hormone release inhibiting factor' OR 'somatotropin release inhibiting factor' OR 'somiaton' OR 'srih' OR 'srif' OR 'stilamin' OR 'stylamin' OR 'val 787' OR 'val787'	60018
#3	#1 OR #2	75880
#4	'terlipressin'/syn OR 'terlipressin' OR 'terlipresina' OR 'biv 201' OR 'biv201' OR 'glipressin' OR 'glipressina' OR 'glycylpressin' OR 'glycylpressine' OR 'glypressin' OR 'glypressine' OR 'lucassin' OR 'remestyp' OR 'stemflova' OR 'terlipresin' OR 'terlipressina' OR 'terlipressinacetat' OR 'terlipressini' OR 'terlivaz' OR 'triglycyl vasopressin' OR 'triglycyllypressin' OR 'triglycyllysine vasopressin' OR 'triglycyllysylvasopressin' OR 'triglycylvasopressin' OR 'val 283' OR 'val283' OR 'variquel' OR 'tglvp'	3892
#5	'vasopressin'/syn OR 'vasopressin' OR 'adh' OR 'anti diuretic hormone' OR 'antidiuretic hormone' OR 'beta hypophamine' OR 'pitressin' OR 'pressyn' OR 'tonephin' OR 'vasophysin' OR 'vasopin' OR 'vasopresin' OR 'vasopressine' OR 'vasostrict' OR 'vassopressin'	81592
#6	#4 OR #5	84067
#7	'esophageal and gastric varices*' OR 'esophageal varic*' OR 'esophageal varix*' OR 'esophagogastric varix*' OR 'esophagus varic*' OR 'esophagus varix*' OR 'oesophageal and gastric varic*' OR 'oesophageal varic*' OR 'oesophageal varix*' OR 'oesophagogastric varix*' OR 'oesophagus varic*' OR 'variceal bleed*' OR 'variceal hemorrhag*' OR 'bleeding varic*' OR 'early bleed*' OR 'esophagus varices'/syn OR 'esophagus varices bleeding'/syn	35346
#8	#3 AND #7	2016
#9	#6 AND #7	2031
#10	#8 OR #9	3063
#11	'treatment duration'/syn OR 'drug dose regimen'/syn OR 'dosage schedule comparison'/syn OR 'time factor'/syn OR 'short course*' OR 'shortened course*' OR duration* OR ((dose OR dosage OR dosing) NEAR/4 (schedule* OR regimen*))	1776989
#12	'5 day*' OR 'five day*' OR '5th day' OR 'fifth day' OR '120 hour*' OR 120h OR 120hr* OR '120 hr*' OR '4 day*' OR 'four day*' OR '4th day' OR 'fourth day' OR '96 hour*' OR 96h OR 96hr* OR '96 hr*' OR '3 day*' OR 'three day*' OR '3rd day' OR 'third day' OR '72 hour*' OR 72h OR 72hr* OR '72 hr*' OR '2 day*' OR 'two day*' OR '2nd day' OR 'second day' OR '48 hour*' OR 48h OR 48hr* OR '48 hr*' OR '1 day*' OR 'one day*' OR '1st day' OR 'first day' OR '24 hour*' OR 24h OR 24hr* OR '24 hr*'	1518534
#13	#11 OR #12	3114398
#14	#10 NOT ([animals]/lim NOT [humans]/lim) NOT ('conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR 'tombstone'/it OR 'case report'/de OR 'meta analysis'/de OR 'meta analysis topic'/de OR 'systematic review'/de OR 'systematic review topic'/de)	1465
#15	#13 AND #14	390

Supplementary Table 2 Results of comprehensive search

Database	Results	Platform
Embase	390	Embase.com (Elsevier)
MEDLINE	167	OVID
Cochrane Central Register of Controlled Trials	188	Cochrane Library (Wiley)
Web of Science Core Collection	181	Web of Science (Clarivate)
KCI - Korean Journal Index	3	Web of Science (Clarivate)
SciELO	3	Web of Science (Clarivate)
Global Index Medicus	31	World Health Organization
Total	963	
with duplicates removed	558	

Supplementary Table 3 The preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 checklist for our systematic review and meta-analysis

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	Page 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 4
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	Page 5
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6 & Supplementary Table 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6 & Supplementary Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8 and 9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 9-10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 10-11
Effect measures	12	Specify for each outcome the effect measure (s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 9-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8-9, 10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 10-11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	Page 10-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 11

(*Contd*...)

Supplementary Table 3 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 11
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 10-11
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 12 & 15
Study characteristics	17	Cite each included study and present its characteristics.	Page 12, Table 1 &2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 11 Supplementary Table 5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 12-13, Figures 2-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 12-13, Figures 2-4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 12-13, 17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 14, Supplementary Figure 1
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplementary Table 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 12-13
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 16-17
	23b	Discuss any limitations of the evidence included in the review.	Page 17-18
	23c	Discuss any limitations of the review processes used.	Page 17-18
	23d	Discuss implications of the results for practice, policy, and future research.	Page 18

Supplementary Table 4 Primary extracted data

Vasoactive Drug / Author, Year	Duration	All-Mortality at Extended Period (%)	Rebleeding at Extended Period (%)	Rebleeding Within 5 Days (%)	Mortality Due to Early Rebleeding (%)	All Documented Adverse Events (%)	Severe Adverse Events (%) (≥ Grade 4)	pRBC Received Mean±SD or No. requiring transfusion (%)	cLOS
Octreotide									
Yucesoy *et al* [24], 2004	Sh	9/34 (26)	9/34 (26)	1/34 (3)	9/34 (26)	-	-	4.2±2.9	1.4±0.6
	Lg	1/27 (4)	1/27 (4)	0/27 (0)	1/27 (4)	-	-	3.0±2.1	1.4±0.4
George *et al* [31], 2006	Sh	-	-	0/18 (0)	-	-	-	-	-
	Lg	-	-	1/19 (5)	-	-	-	-	-
Hajiani *et al* [22], 2011	Sh	4/35 (11)	3/35 (9)	0/35 (0)	0/35 (0)	-	-	N/A	-
	Lg	6/36 (17)	2/36 (6)	0/36 (0)	0/36 (0)	-	-	-	-
Rengasamy *et al* [8], 2015: EVBL	Sh	0/50 (0)	1/50 (2)	0/50 (0)	0/50 (0)	-	-	32/62 (51.6)	-
	Lg	0/43 (0)	4/43 (9)	0/43 (0)	0/43 (0)	-	-	32/58 (55.2)	-
Rengasamy *et al* [8], 2015:	Sh	1/9 (11)	2/9 (22)	0/9 (0)	1/9 (11)	-	-	-	-
Sclerotherapy	Lg	0/10 (0)	1/10 (10)	0/10 (0)	0/10 (0)	-	-	-	-
Terlipressin									
Choudhary *et al* [30], 2011	Sh	-	2/14 (14)	0/14 (0)	1/14 (7)	-	-	-	-
	Lg	-	4/14 (29)	0/14 (0)	2/14 (14)	-	-	-	-
Azam *et al* [7], 2012	Sh	6/65 (9)	2/65 (3)	0/65 (0)	1/65 (2)	1/65 (2)	1/65 (2)	1.1±1.0	-
	Lg	6/65 (9)	1/65 (2)	0/65 (0)	0/65 (0)	2/65 (3)	2/65 (3)	1.2±1.3	-
Solari *et al* [27], 2012	Sh	1/12 (8)	0/14 (0)	0/14 (0)	-	-	-	-	-
	Lg	3/37 (8)	1/37 (3)	1/37 (3)	-	-	-	-	-
Salim *et al* [10], 2017	Sh	-	-	3/65 (5)	-	0/65 (0)	0/65 (0)	-	-
	Lg	-	-	1/25 (4)	-	0/25 (0)	0/25 (0)	-	-
Zaman *et al* [11], 2019	Sh	-	-	5/50 (10)	-	-	-	-	-
	Lg	-	-	4/50 (8)	-	-	-	-	-
Poudel *et al* [17], 2022	Sh	4/25 (16)	3/25 (12)	0/25 (0)	0/25 (0)	8/25 (32)	-	1.0±1.3	1.8±0.3
	Lg	5/24 (21)	3/24 (13)	1/24 (4)	3/24 (13)	18/24 (4)	-	1.0±1.4	3.3±0.3
Vaishnav *et al* [18], 2024	Sh	5/74 (7)	9/74 (12)	3/74 (4)	3/74 (4)	28/74 (3)	1/74 (1)	1.1±1.3	2.1±1.0
	Lg	4/75 (5)	10/75 (1)	4/75 (5)	2/75 (3)	42/75 (5)	1/75 (1)	1.2±1.3	2.7±2.1
Somatostatin									
Yaras *et al* [32], 2013	Sh	-	-	0/20 (0)	-	-	-	-	-
	Lg	-	-	0/19 (0)	-	-	-	-	-
Chitapanux *et al* [9], 2015	Sh	4/50 (8)	4/50 (8)	1/50 (2)	1/50 (2)	-	-	2.6±2.1	3.7±2.2
	Lg	4/45 (9)	5/45 (11)	3/45 (7)	2/45 (4)	-	-	3.4±2.5	5.4±4.4
Abdelghani *et al* [19], 2015	Sh	-	2/25 (8)	0/25 (0)	-	8/25 (32)	3/25 (12)	-	1.3±0.2
	Lg	-	2/25 (8)	0/25 (0)	-	17/25 (4)	3/25 (12)	-	2.2±0.2

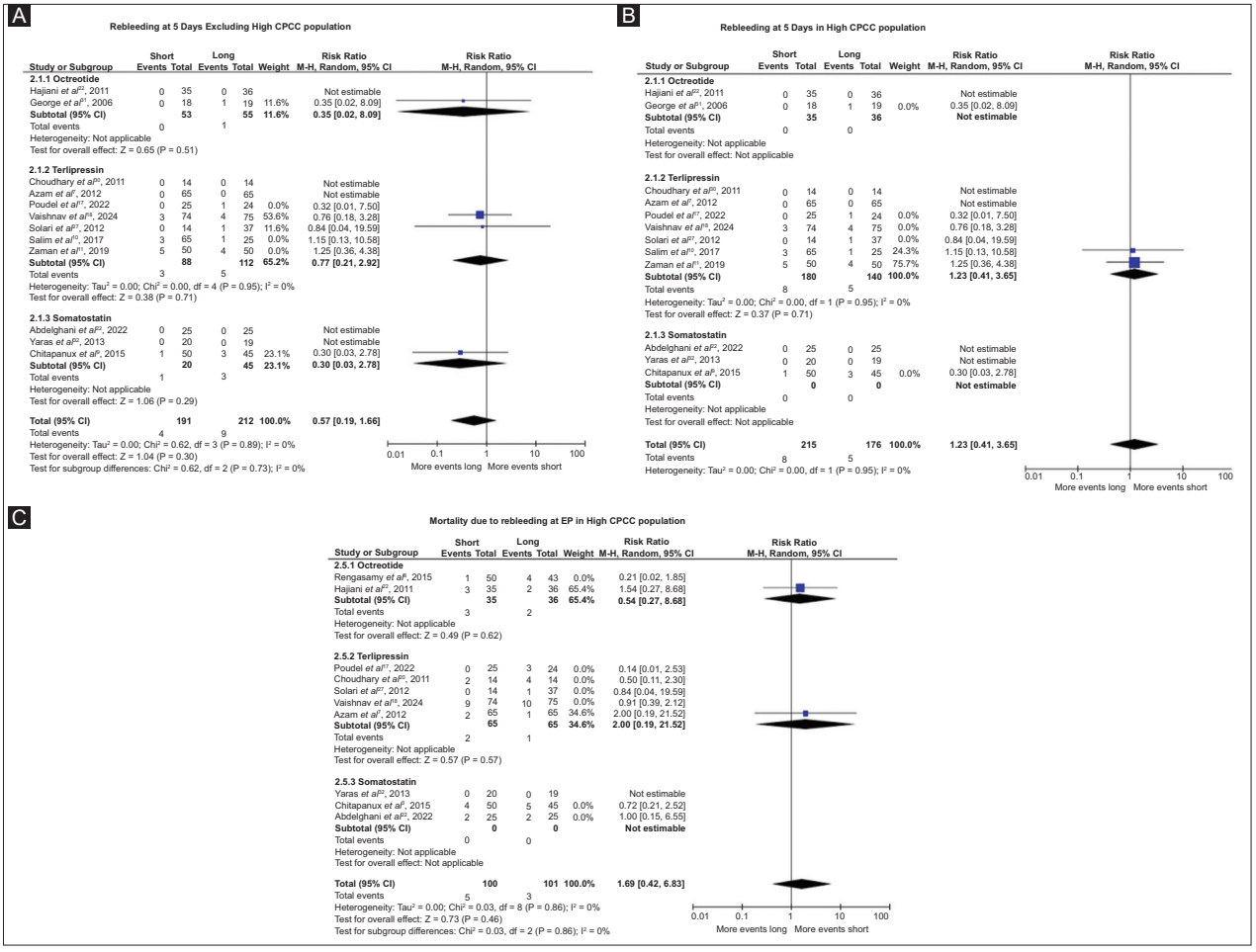
Sh, short course vasoactive drug therapy; Lg, longer course vasoactive drug therapy; cLOS, corrected length of stay

Data are calculated to correct for differences in length of stay and the number of days between the 2 therapy groups (Sh and Lg)

Supplementary Table 5 The Risk of Bias (RoB) 2.0 Cochrane tool for individually randomized parallel controlled trials for our studies

Vasoactive Drug Author [ref.], Year	Randomization Process	Intended Intervention	Outcome Data	Measurement of Outcomes	Reported Results	Overall	Comments
Octreotide							
Yucesoy *et al* [24], 2004	Some	Some	Low	Some	Some	Some Risk	Imbalance in variceal grades. No pre-specified outcomes. No method of randomization/blinding documented.
George *et al* [31], 2006	Low/Unclear	Unclear	Unclear	Unclear	Unclear	Some Risk	Child–Pugh scores similar. Abstract methods limited.
Hajiani *et al* [22], 2011	Low/Unclear	Some	Low	Some	Some	Some Risk	Similar baseline characteristics. No pre-study protocols. No method of randomization/blinding documented.
Rengasamy *et al* [8], 2015	Some	Low	Some	Some	Some	Some Risk	Computer-based randomization/allocation, but PT significantly higher in longer group with MELD/Child–Pugh reported. No documentation of results of dropouts. No blinding documented.
Terlipressin							
Choudhary *et al* [30], 2011	High	Unclear	Unclear	Unclear	Unclear	Some/High Risk	MELD scores reported higher in the longer group. Abstract methods limited.
Azam *et al* [7], 2012	Low	Low	Low	Low	Low	Low Risk	-
Solari *et al* [27], 2012	Low/Unclear	Unclear	Unclear	Unclear	Unclear	Some Risk	Child–Pugh scores similar. Abstract methods limited.
Salim *et al* [10], 2017	Low	Some	Low	Some	Some	Some Risk	No blinding documented or pre-study protocol.
Zaman *et al* [11], 2019	Low/Unclear	Some	Low	Some	Some	Some Risk	Lack of baseline characteristics, but likely similar protocol to Salim *et al*. No blinding or pre-study protocols.
Poudel *et al* [17], 2022	Some	Low	Low	Some	Some	Some Risk	Pre-2016 MELD is statistically higher. Open label.
Vaishnav *et al* [18], 2024	Low	Low	Low	Some	Some	Low Risk	Open label.
Somatostatin							
Yaras *et al* [32], 2013	Low/Unclear	Unclear	Unclear	Unclear	Unclear	Some Risk	No statistical differences in variceal grades. Abstract methods limited.
Chitapanux *et al* [9], 2015	Low	Low	Low	Low	Low	Low Risk	-
Abdelghani *et al* [19], 2015	Some	Some	Some	Some	Some	Some Risk	No statistical difference in baseline characteristics. No randomization method documented. No pre-study protocols. Open label.

PT, prothrombin time; MELD, model for end-stage liver disease



Supplementary Figure 1 Forest plots comparing variceal rebleeding and associated mortality in short vs. long durations in esophageal variceal band ligation for vasoactive drugs, including sensitivity analysis. (A) Rebleeding within 5 days but excluding studies with randomization bias and high Child-Pugh Class C (CPCC). (B) Rebleeding within 5 days and pooling high CPCC and/or high-risk varices. (C) Rebleeding within the extended period (30-42 days) including pooling high CPCC and/or high-risk varices

M-H, Mantel-Haenszel; CI, confidence interval