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INTERVENTIONAL RADIOLOGY

Comparative outcome of transjugular intrahepatic portosystemic shunt with or without variceal obliteration: a systematic review and meta-analysis

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Abstract

Background Transjugular intrahepatic portosystemic shunt (TIPS) has been used for the secondary prevention of variceal bleeding. TIPS can be combined with variceal embolization (TIPS-VO), but its benefit remains controversial. The present systematic review and meta-analysis were conducted to compare the incidence of rebleeding, adverse events, and mortality among patients with TIPS alone and with TIPS-VO.

Methods A literature search from January 2000 to June 2022 was done for studies comparing the outcome of patients undergoing TIPS alone or TIPS-VO. A subgroup analysis was conducted for patients undergoing TIPS with covered stents.

Results A total of 11 studies with data from 1044 patients were included. The incidence of rebleeding was significantly higher in the TIPS alone group in both overall population OR 2.01 (1.42–2.83) and the subgroup (OR 1.92, 95% CI 1.21–3.04). There was no difference between the two groups concerning the risk of hepatic encephalopathy (OR 1.15, 95% CI 0.83–1.59), procedural adverse events (OR 0.86, 95% CI 0.54–1.39), shunt dysfunction (OR 1.20, 95% CI 0.82–1.75), overall mortality (OR 1.03, 95% CI 0.73–1.46), and mortality due to variceal rebleeding (OR 1.58, 95% CI 0.44–5.64). There was no significant heterogeneity or publication bias among the included studies. The certainty of evidence remains low for all the outcome expect for variceal rebleeding.

Conclusion The present meta-analysis provides a moderate-quality evidence for the benefit of TIPS-VO in reducing the incidence of rebleeding. However, the decision for combining variceal embolization with TIPS should be made on a case-to-case basis.

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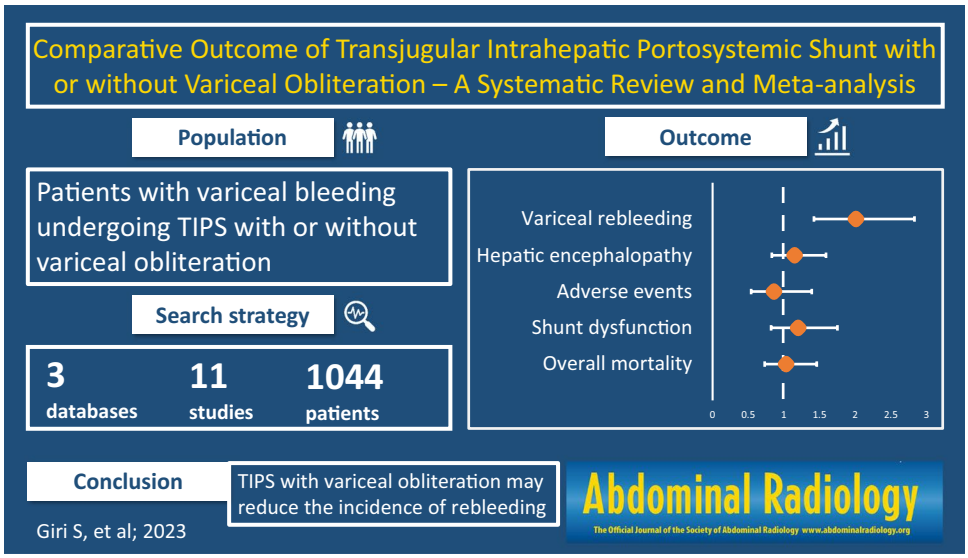
Graphical abstract



Keywords Transjugular intrahepatic portosystemic shunt · Variceal bleeding · Variceal embolization · Meta-analysis

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) plays a critical role in the prevention and treatment of the complications of portal hypertension [1, 2]. Current practice guidelines recommend that TIPS should be the preferred option in patients who fail endoscopic and pharmacological therapy for the prevention of variceal rebleeding [3] and those with refractory cirrhotic ascites [4]. Few studies have advocated the pre-emptive TIPS for treating acute variceal bleeding in high-risk patients [5, 6]. The pooled incidence of overall rebleeding after TIPS was shown to be 14.1% in a meta-analysis [7]. Another study reported a 23% risk of rebleeding at 1 year in patients who underwent TIPS for variceal bleeding [8].

There has been significant improvement in the devices and techniques of TIPS procedure, like the use of polytetrafluorethylene (PTFE)-covered stents to decrease the incidence of shunt dysfunction and rebleeding [9]. However, the risk of rebleeding is not entirely eliminated despite the use of covered stents. Thus, there is a need for adjunctive therapy, which can reduce the risk of rebleeding after TIPS. In the pre-TIPS era, the efficacy of variceal embolotherapy was studied for the management of gastroesophageal varices [10]. But percutaneous transhepatic embolotherapy does not improve portal hypertension, leading to recurrent bleeding in 35–65% of patients on follow-up [11]. Thus, Tesdal et al. studied the role of adjunctive embolotherapy of gastroesophageal collaterals with TIPS and reported a reduction in rebleeding compared to TIPS alone [12]. However, subsequent studies have shown conflicting results concerning the outcome of TIPS with or without embolotherapy. Hence, we conducted a meta-analysis to systematically compare the incidence of shunt malfunction, variceal rebleed, adverse events, and mortality between patients treated with TIPS alone and those treated with TIPS combined with variceal obliteration (TIPS-VO) by embolization.

Methods

Information sources and search strategy

A comprehensive search of all suitable studies was conducted using the databases of MEDLINE, EMBASE, and Science Direct from January 2000 to June 2022. The keywords used were (“transjugular intrahepatic portosystemic shunt” OR “TIPS”) AND (“embolization" OR "embolotherapy”). To ensure that no potentially relevant items were overlooked, manual searching of reference lists of the included studies was also undertaken. The study methodology was designed and executed to adhere to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines [13].

Study selection

The PICO criteria used for included comparative studies were (a) *Patients*—those with variceal bleeding; (b)

Intervention—TIPS alone; (c) *Comparison*—TIPS with variceal embolization; and (d) *Outcomes*—the incidence of shunt dysfunction, variceal rebleeding, encephalopathy, adverse events (AE), and mortality. Following the selection criteria above, the titles and abstracts of all studies were independently reviewed by two authors. Any disagreements were resolved by a third reviewer. The exclusion criteria used were non-comparative studies, case series, and studies involving persons < 18 years of age.

Data extraction

Two independent reviewers performed the data extraction, and a third reviewer resolved any disagreement. Data were collected under the following headings: study author and year, country of study, study design, number of patients, age and sex distribution, details of the procedure, and outcomes.

Risk of bias in individual studies

After data extraction, the same two reviewers performed quality assessments using validated tools. The Cochrane risk-of-bias tool was used for randomized controlled trials (RCTs) and the Cochrane Collaboration's risk of bias in non-randomized studies of interventions tool was used for non-randomized studies.

Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) were calculated for all the dichotomous outcomes. Regardless of heterogeneity, the Mantel–Haenszel test for random effects was used. A Cochran's Q test and I^2 statistics were used to determine the heterogeneity between the studies. A P value of Q test < 0.1 or the I^2 value > 50% was considered

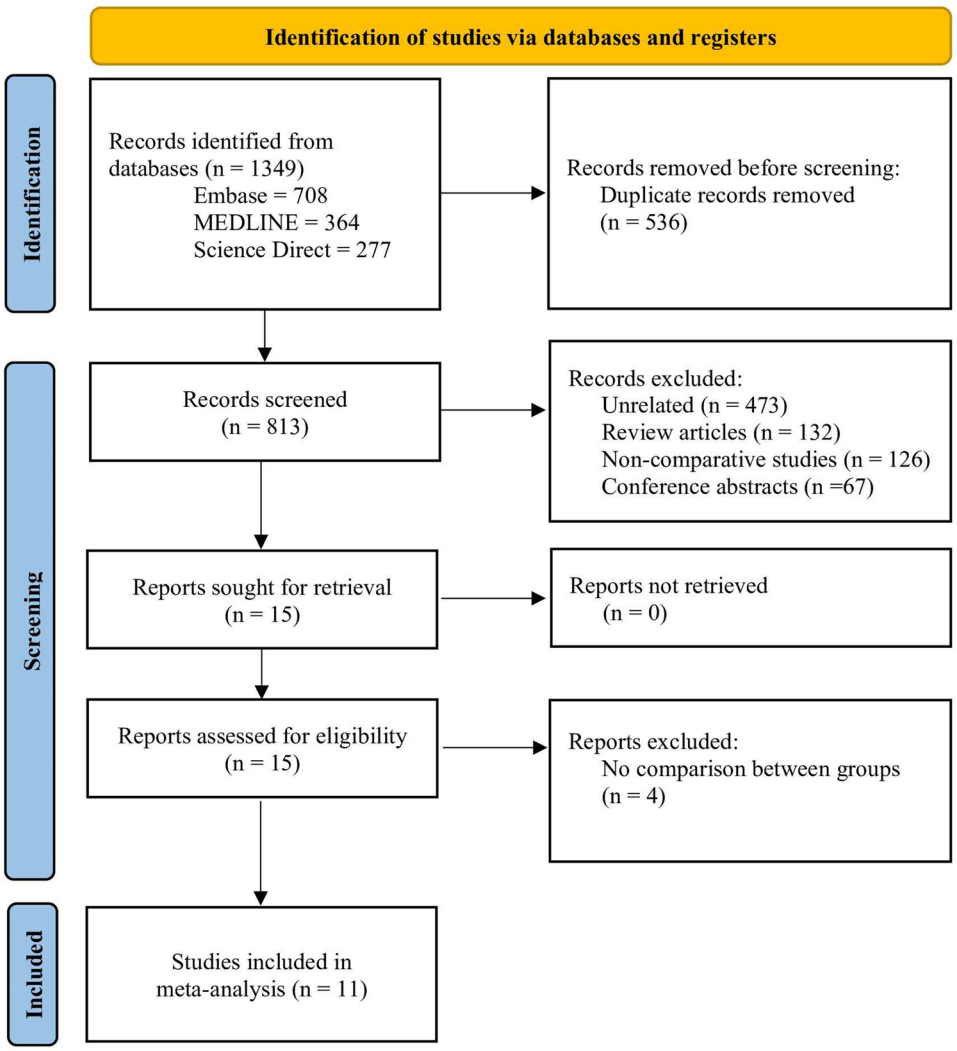


Fig. 1 PRISMA flowchart for study identification, selection, and inclusion process

Table 1 Baseline characteristics of included studies

Author	Country	Study design	No. of patients	Type of stent	Approach to embolization	Embolic agent
Tesdal et al. [12]	Germany	Prospective	95	Palmaz and Wallstent bare stents	After TIPS	Sclerosant and coils
Wu et al. [14]	China	Retrospective	358	–	After TIPS	Coils & gelatin sponge
Gaba et al. [15]	USA	Retrospective	52	Viatorr covered stents	After TIPS	Coils
Xiao et al. [16]	China	Retrospective	79	Bare Bard LUMINEXX 3 vascular stents	After TIPS	Coils and/or α-cyanoacrylate
Xue et al. [17]	China	Retrospective	80	Fluency covered stents ($n=37$), Bard Luminexx, Cordis Smart and Cook Zilver bare stents ($n=43$)		Steel coil or ethanol
Chen et al. [18]	China	RCT	106	Fluency covered stents	Before TIPS	Coils
Shi et al. [19]	China	Retrospective	101	Fluency partially covered stents	Before TIPS	Cyanoacrylate
Lakhoo et al. [20]	USA	Retrospective	26	10-mm VIATORR stent grafts	Before TIPS	Coil or vascular plug devices
Yu et al. [21]	China	Retrospective	82	8-/10-mm covered stent	After TIPS	Metallic coil in 36 (65.5%), α-cyanoacrylate + coil in 18 (32.7%), and vascular plug in 1 (1.8%) patient
Shah et al. [22]	USA	Retrospective	40	10-mm Viatorr stent grafts ($n=30$), Viatorr controlled expansion stent grafts ($n=10$)	After TIPS	Sclerosant
Lv et al. [23]	China	RCT	135	8-mm Fluency covered stents	Before TIPS	Coils

TIPS Transjugular intrahepatic portosystemic shunt

significant. Visual inspection of funnel plots was used for publication bias assessment. The sensitivity analysis was performed using a leave-one-out meta-analysis, in which one study is excluded at each analysis in order to analyze each study's influence on the overall effect size estimate and identify influential studies. RevMan software (version 5.4.1, Cochrane Collaboration) and STATA software (version 17, StataCorp., College Station, TX) were used for statistical analysis.

Results

Study characteristics and quality assessment

Of the 1349 records identified, 11 studies [12, 14–23] were included in the final analysis. Figure 1 shows the PRISMA flowchart for the study selection and inclusion process. Table 1 summarizes the baseline characteristics of the included studies with type of stent and methods of occlusion. Table 2 summarizes the baseline characteristics of included patients in both the groups. The majority of the studies were retrospective [14–17, 19–22] with only three prospective studies [12, 18, 23]. Most of the studies were conducted in China [14, 16–19, 21, 23]. Uncovered stents were used in two studies [12, 16], both covered and uncovered were used in one study [17], covered stents were used in seven studies [15, 18–23], and stent type was unknown in one study [14]. Study quality assessment showed moderate risk of bias for majority of the studies [15, 16, 18–23] with high risk of bias for three studies [12, 14, 17] (Supplementary Fig. 1).

Variceal rebleeding

All eleven studies reported comparative data on the incidence of variceal rebleeding. TIPS alone was associated with a higher risk of rebleeding than TIPS-VO with an OR 2.01 (95% CI 1.42–2.83; $I^2=1\%$) (Fig. 2). On subgroup analysis of patients with covered stents, the risk of rebleeding was still higher in the TIPS alone group (OR 1.92, 95% CI 1.21–3.04; $I^2=0\%$).

Hepatic encephalopathy

The data on the incidence of overt HE were reported in eight studies. There was no difference in the risk of HE between TIPS alone and TIPS-VO on overall analysis (OR 1.15, 95% CI 0.83–1.59; $I^2=0\%$) (Fig. 3A) or with covered stents (OR 1.36, 95% CI 0.91–2.03; $I^2=0\%$) (Supplementary Fig. 2).

Table 2 Baseline characteristics of the patients in the included studies

Author	Groups	No. of patients	Age, in years	Male/Female	Emergent indication	Etiology of cirrhosis (Viral/Alcohol/Others)	Child-PughA/B/C	Type of varices	Follow-up duration
Tesdal et al. [12]	TIPS	42	57.1 ± 12.2	27/15	2 (5%)	7/25/1	13/22/7	–	48.7 ± 37.8 months (1–127)
	TIPS + E	53	54.7 ± 10.3	34/19	10 (19%)	7/30/16	21/26/6	–	
Wu et al. [14]	TIPS	227	52 ± 26	196/67	–	–	40/121/102	–	68.7 ± 47.6 months
	TIPS + E	36	44 ± 16	78/17	–	–	26/54/15	–	56.87 ± 18.3 months
Gaba et al. [15]	TIPS	37	52 (26–76)	20/17	32 (86.5%)	Viral + alcoholic/others: 36/16	9.0 (5–15)	Esophageal/gastric varices: 24/13	199 (1–1669) days
	TIPS + E	15	52 (32–60)	9/6	14 (93.3%)		8.0 (6–14)	Esophageal/gastric varices: 7/8	252 (1–1763) days
Xiao et al. [16]	TIPS	36	45.4 ± 9.1	28/8	4 (11.1%)	26/10/0	14/18/4	Esophageal/fundal varices: 23/13	45.6 months (1–85.6)
	TIPS + E	43	43.2 ± 7.8	31/12	8 (18.6%)	28/15/0	15/20/8	Esophageal/fundal varices: 25/18	
Xue et al. [17]	TIPS	40	51.00 ± 12.83	52/28	2 (3%)	–	37/22/21	EV/GV: 29/11	–
	TIPS + E	27				–		EV/GV: 10/17	–
Chen et al. [18]	TIPS	52	51.6 ± 11.8	32/20	3 (5.5%)	Viral + alcoholic/others: 50/2	9/40/3	–	15 (1–49) months
	TIPS + E	54	53.2 ± 13.4	34/20	5 (9.2%)	Viral + alcoholic/others: 49/5	12/37/5	–	18 (3–45) months
Shi et al. [19]	TIPS	48	49.7 ± 9.0	30/18	–	34/13/1	11/28/9	–	35.4 ± 18.7 months
	TIPS + E	53	51.0 ± 11.0	38/15	–	37/12/4	16/29/8	–	36.2 ± 17.5 months
Lakhoo et al. [20]	TIPS	8	53.5 (26–81)	16/21	14 (54%)	10/7/9	–	GOV1/GOV2/IGV1/IGV2/U10/2/4/2/8	128.5 days (1–1295)
	TIPS + E	18					–		
Yu et al. [21]	TIPS	27	54.5 ± 12.3	19/8	0 (0%)	15/5/7	14/11/2	GOV2/IGV1:22/5	20.0 ± 11.5 months
	TIPS + E	55	53.6 ± 11.5	35/20	3 (5.4%)	34/5/16	21/24/10	GOV2/IGV1:34/21	23.2 ± 12.6 months
Shah et al. [22]	TIPS	22	56 ± 9	10/12	34 (63%)	Viral + alcoholic/others: 16/6	3/14/5	GOV1/GOV2/IGV1/IGV2 8/8/5/1	–
	TIPS + E	18	60 ± 12	9/9		Viral + alcoholic/others: 10/8	2/13/3	GOV1/GOV2/IGV1/IGV25/6/7/0	–
Lv et al. [23]	TIPS	65	50.8 ± 11.6	44/21	–	54/3/8	31/26/8	EV 21/GOV1 33/GOV2 11	2 years
	TIPS + E	69	49.0 ± 11.5	55/14	–	53/4/12	38/27/4	EV 23/GOV1 34/GOV2 12	

EV Esophageal varix, *GV* Gastric varix, *GOV/IGV/U* Gastroesophageal varix/Isolated gastric varix/Unspecified, *TIPS* Transjugular intrahepatic portosystemic shunt, *TIPS + E* TIPS + Embolization

Procedural adverse events

Four studies reported on the incidence of AEs with either of the procedures. The odds of AE were comparable between the TIPS alone group and TIPS-VO (OR 0.86, 95% CI 0.54–1.39; $I^2 = 0\%$) (Supplementary Fig. 3).

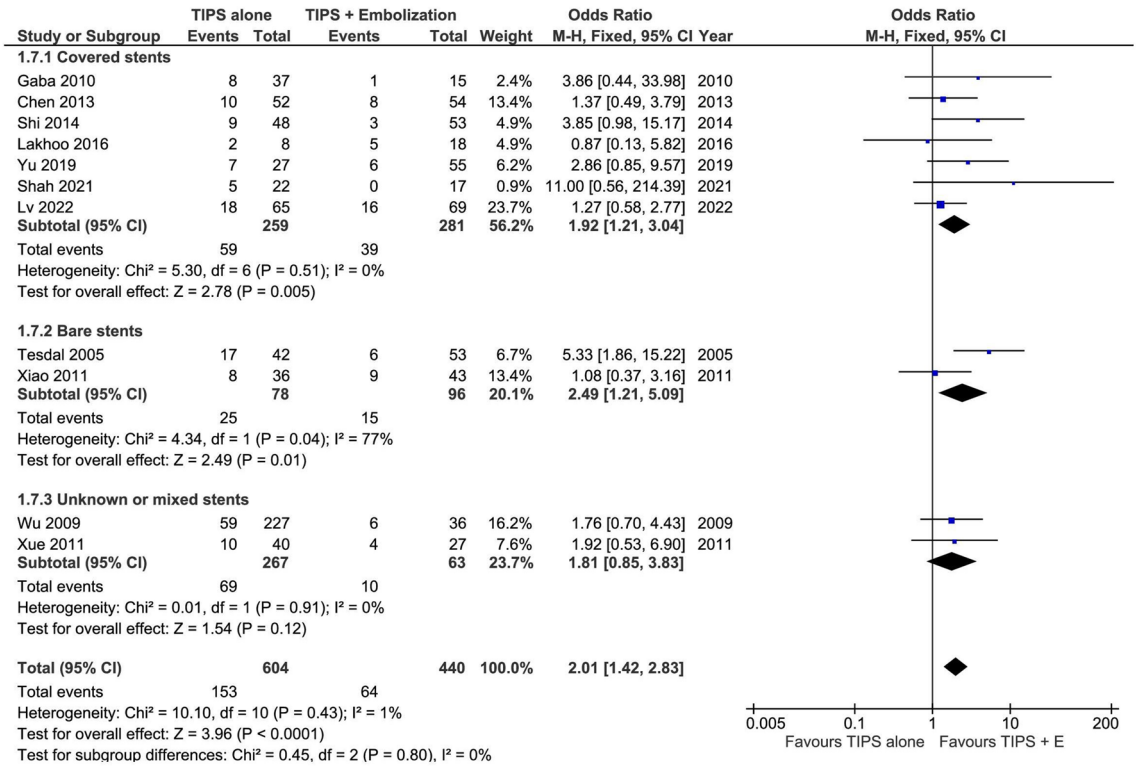


Fig. 2 Forest plot comparing the risk of variceal rebleeding in patients undergoing transjugular intrahepatic portosystemic shunting with or without variceal obliteration

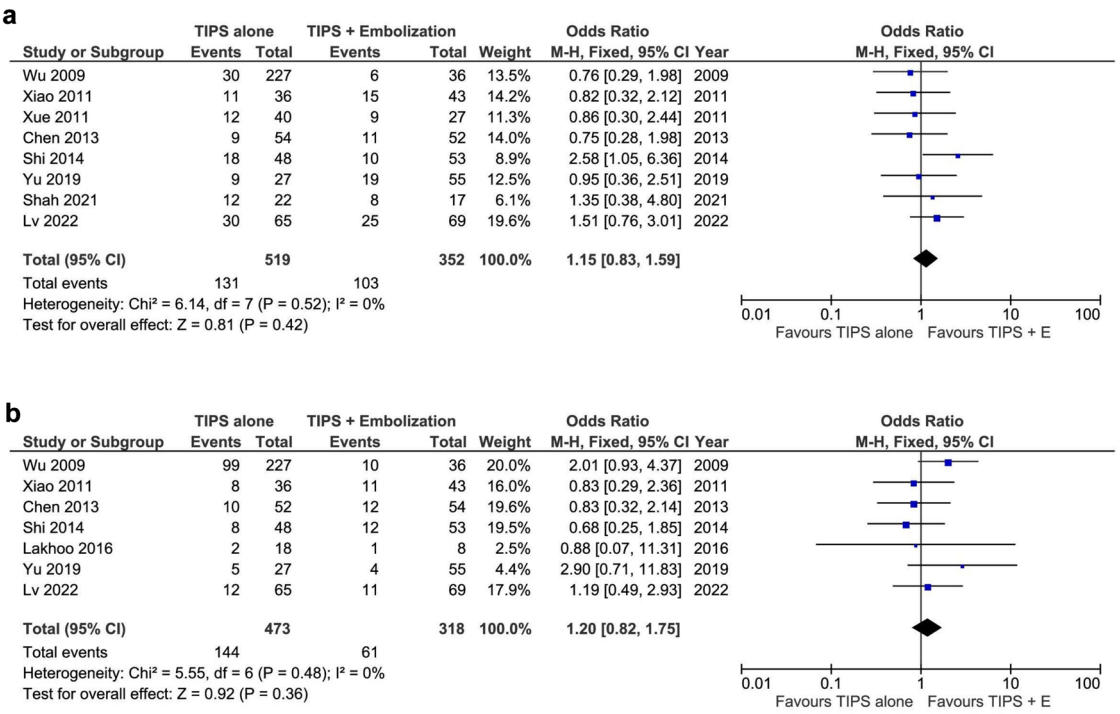


Fig. 3 Forest plot comparing the risk of **a** hepatic encephalopathy, and **b** shunt dysfunction in patients undergoing transjugular intrahepatic portosystemic shunting with or without variceal obliteration

Table 3 Summary of table with grade of evidence for various outcomes

Population—Patients with variceal bleeding									
Intervention—TIPS with variceal embolization									
Comparator—TIPS alone									
Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of patients (Studies)	Certainty assessment				Overall certainty of evidence
	With TIPS alone	With TIPS + E			Risk of bias	Inconsistency	Indirectness	Imprecision	
Variceal rebleeding	24.8% (21.4–28.2)	12.4% (7.7–17.1)	OR 2.01 (1.42–2.83)	11 studies ($n=1044$)	+	−	−	−	Moderate ●●●○
Hepatic encephalopathy	31.5% (20.6–42.4)	28.5% (21.8–35.3)	OR 1.15 (0.83–1.59)	8 studies ($n=871$)	+	+	−	−	Low ●●○○
Adverse events	23.3% (2.7–43.8)	25.4% (11.5–39.3)	OR 0.86 (0.54–1.39)	4 studies ($n=381$)	+	+	−	+	Very low ●○○○
Shunt dysfunction	21.9% (11.4–32.5)	18.4% (12.0–24.8)	OR 1.20 (0.82–1.75)	7 studies ($n=791$)	+	−	−	−	Low ●●○○
Overall mortality	26.8% (15.1–38.4)	25.8% (19.3–32.4)	OR 1.03 (0.73–1.46)	7 studies ($n=817$)	+	+	−	−	Low ●●○○

OR Odds ratio, *TIPS* Transjugular intrahepatic portosystemic shunt, *TIPS + E* TIPS + Embolization

Shunt dysfunction

The data on the the incidence of shunt dysfunction was reported in seven studies. There was no difference in the odds of shunt dysfunction between the two groups on overall analysis (OR 1.20, 95% CI 0.82–1.75; $I^2=0\%$) (Fig. 3B) or with covered stents (OR 1.03, 95% CI 0.63–1.69; $I^2=0\%$) (Supplementary Fig. 4).

Mortality

The data on the incidence of overall mortality were reported in seven studies. There was no difference in the odds of all-cause mortality between the two groups on overall analysis (OR 1.03, 95% CI 0.73–1.46; $I^2=0\%$) or with covered stents (OR 1.06, 95% CI 0.70–1.62; $I^2=0\%$) (Supplementary Fig. 5). Overall, three studies reported differences in mortality related to variceal bleeding. Mortality was comparable between the groups (OR 1.58, 95% CI 0.44–5.64; $I^2=9\%$) (Supplementary Fig. 6).

Publication bias, sensitivity analysis, and certainty of the evidence

There was no publication bias for any of the outcomes (Supplementary Fig. 7). On leave-one-out analysis, there was no difference in the odds of various outcomes between the two groups. Table 3 shows the summary of findings with the grade of evidence.

Discussion

TIPS plays a critical role in the management of the complications of portal hypertension [1, 2]. Current practice guidelines recommend that TIPS should be the preferred option in patients who fail endoscopic treatment for the prevention of variceal rebleeding [3]. Although literature generally favors a reduction in rebleeding rate following TIPS-VO, as demonstrated by Tesdal et al., there is lack of high level of evidence about the role of embolization in the management of varices. Moreover, the effect on shunt patency or mortality remains to be proven. In this meta-analysis on the above-said topic, we have included 11 studies with data from 1044 patients. The study results demonstrate that TIPS alone was associated with a higher pooled proportion of variceal rebleed (24.8% vs. 12.4%). In comparison, the incidence of hepatic encephalopathy (31.5% vs. 28.5%), adverse events (23.3% vs. 25.4%), shunt dysfunction (21.9% vs. 18.4%), and mortality (26.8% vs. 25.8%) remained comparable.

Similar observations were reported in a previous meta-analysis by Qi et al. [24]. The previous meta-analysis reported no difference in the odds of variceal bleeding between the two groups in the subgroup with covered stents. It is suggested that using covered stents will reduce shunt dysfunction, making competing shunt elimination and occlusion of varices much less important [25]. However, in the present analysis, the odds of variceal rebleeding were lower with TIPS-VO, even in patients with covered stents

(OR 1.92, 95% CI 1.21–3.04), suggesting the importance of adjunctive variceal embolization with TIPS.

In the RCT by Lv et al., the overall analysis reported similar rebleeding rates between TIPS alone and TIPS-VO. However, a subgroup of patients did not achieve sufficient reduction in portal pressure gradient (PPG) after TIPS. In this subgroup, the rebleeding rate within 2 years was lower with TIPS-VO compared to TIPS alone (25% vs. 50%) [23]. Furthermore, gastric varices have lower portal pressure than esophageal varices due to the presence of a gastrorenal portosystemic shunt and can bleed even with a low PPG of less than < 12 mm Hg. In the RCT by Lv et al., most of the included patients had type 1 gastroesophageal varices (GOV1) (continuation of esophageal varices and shunts are less common), and only 17% of the patients had GOV2, which might have led to a similar rate of rebleeding between both the groups. On the other hand, the study by Yu et al. included patients with GOV2 or type 1 isolated gastric varices, and the 2-year rebleeding rate was significantly lower in the TIPS-VO groups [21]. Thus, in patients with cardiofundal varices and those with an insufficient fall in PPG after TIPS, variceal embolization may confer a benefit over TIPS alone.

Shunt dysfunction or occlusion is the most important cause of variceal rebleeding. Pre-existent collateral vessels and shunt may compete with TIPS for antegrade blood flow, with a resultant reduction in blood flow within the shunt and liver detoxification, leading to shunt dysfunction and increased risk of HE. Large splenorenal shunts have been shown to be associated with a higher incidence of TIPS dysfunction [25]. Therefore, TIPS combined with the embolization of collaterals might theoretically reduce the incidence of shunt dysfunction and HE. Few retrospective studies have shown the advantage of concurrent variceal embolization in preventing shunt dysfunction [26, 27]. Studies by Wu et al. [14] and Shi et al. [19] have shown fewer incidences of HE with TIPS with variceal embolization. Despite this, the present meta-analysis did not find any significant differences in shunt dysfunction or encephalopathy incidence.

Higher incidences of adverse events were seen in the TIPS-VO group, primarily due to post-embolization syndrome (fever, abdominal pain, and nausea). Other AEs like sepsis, right heart failure, spontaneous bacterial peritonitis, and ulcer were reported in four studies [18, 19, 22, 23]. However, there was no statistically significant difference in the incidence of AEs between groups. So, despite the use of sclerosants and coils, TIPS-VO is not associated with an increased incidence of AEs. Mortality was reported in seven studies [14–16, 18, 19, 21, 23] and showed no difference between the groups in overall and subgroup analysis. Liver failure was the most common cause of mortality. Mortality due to variceal rebleeding was reported in three studies and was similar in both groups [15, 21, 23]. Thus, despite a reduction in variceal rebleeding, TIPS-VO does not confer mortality benefit.

The strength of the present analysis was the absence of heterogeneity among the studies concerning various outcomes. However, there were a few limitations that warrant further discussion. First, studies included in this metanalysis used a variety of agents for variceal obliteration using coils, gel foam, glue, or a combination. Zhou et al. reported that glue and coil have similar treatment efficacy and safety for variceal obliteration during TIPS with a significantly lower material cost of glue [28]. But whether a combination of agents confers a benefit over either remains a topic of future research. Second, there was heterogeneity in the type of stents used. Covered stents have been reported to have higher probabilities of overall survival and shunt patency than the bare stents [2]. Third, the types of varices in various studies were different, which could affect the outcome. Lastly, the included studies reported on all-cause mortality rather than mortality due to variceal bleeding. Also, the number of studies reporting mortality due to variceal rebleeding was small to draw a firm conclusion.

To conclude, increasing data support the concept that variceal embolization can reduce post-TIPS rebleeding rates without increasing AEs, even for those undergoing TIPS with covered stents. Patients with visualization of vessels during the post-TIPS portal venogram, those with gastric varices, and those without significant reduction in portosystemic gradient after TIPS are the candidates who may benefit from variceal embolization. Future prospective studies, studying patients with cardiofundal varices and a combination of embolic agents, are required to validate the present analysis findings and assess survival benefits of TIPS-VO.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not required for meta-analysis.

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