

Comparison between portosystemic shunts and endoscopic therapy for prevention of variceal re-bleeding: a systematic review and meta-analysis

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Abstract

Background: Portosystemic shunts, including surgical portosystemic shunts and transjugular intra-hepatic portosystemic shunt (TIPS), may have benefit over endoscopic therapy (ET) for treatment of variceal bleeding in patients with cirrhotic portal hypertension; however, whether there being a survival benefit among them remains unclear. This study was to compare the effect of three above-mentioned therapies on the short-term and long-term survival in patient with cirrhosis.

Methods: Using the terms “variceal hemorrhage or variceal bleeding or variceal re-bleeding” OR “esophageal and gastric varices” OR “portal hypertension” and “liver cirrhosis,” the Cochrane Central Register of Controlled Trials, PubMed, Embase, and the references of identified trials were searched for human randomized controlled trials (RCTs) published in any language with full texts or abstracts (last search June 2017). Risk ratio (RR) estimates with 95% confidence interval (CI) were calculated using random effects model by Review Manager. The quality of the included studies was evaluated using the Cochrane Collaboration’s tool for the assessment of the risk of bias.

Results: Twenty-six publications comprising 28 RCTs were included in this analysis. These studies included a total of 2845 patients: 496 (4 RCTs) underwent either surgical portosystemic shunts or TIPS, 1244 (9 RCTs) underwent either surgical portosystemic shunts or ET, and 1105 (15 RCTs) underwent either TIPS or ET. There was no significant difference in overall mortality and 30-day or 6-week survival among three interventions. Compared with TIPS and ET, separately, surgical portosystemic shunts were both associated with a lower bleeding-related mortality (RR = 0.07, 95% CI = 0.01–0.32; $P < 0.001$; RR = 0.17, 95% CI = 0.06–0.51, $P < 0.005$) and rate of variceal re-bleeding (RR = 0.23, 95% CI = 0.10–0.51, $P < 0.001$; RR = 0.10, 95% CI = 0.04–0.24, $P < 0.001$), without a significant difference in the rate of postoperative hepatic encephalopathy (RR = 0.52, 95% CI = 0.25–1.00, $P = 0.14$; RR = 1.09, 95% CI = 0.59–2.01, $P = 0.78$). TIPS showed a trend toward lower variceal re-bleeding (RR = 0.46, 95% CI = 0.36–0.58, $P < 0.001$), but a higher incidence of hepatic encephalopathy than ET (RR = 1.78, 95% CI = 1.34–2.36, $P < 0.001$).

Conclusions: The overall analysis revealed that there seem to be no short-term and long-term survival advantage, but surgical portosystemic shunts are with the lowest bleeding-related mortality among the three therapies. Surgical portosystemic shunts may be the most effective without an increased risk of hepatic encephalopathy and TIPS is superior to ET but at the cost of a higher incidence of hepatic encephalopathy. However, some of findings should be interpreted with caution due to the lower level of evidence and the existence of significant heterogeneity.

Keywords: Portosystemic shunts; Endoscopic therapy; Variceal rebleeding; Cirrhosis; Meta-analysis

Introduction

Esophageal and gastric varices are one of the most serious complications of cirrhotic portal hypertension, which may result in massive gastrointestinal hemorrhage. Studies have

shown that gastroesophageal varices develop in approximately 50% of patients with cirrhosis.^[1] About one-third of patients with cirrhosis and varices develop hemorrhage,^[2] which is a significant cause of early mortality, reaching 30% to 50% for the first variceal bleed.^[3,4]

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Patients who survive the first episode of variceal bleeding are at increased risk of re-bleeding (>60% at 1 year), with a mortality rate of approximately 20%,^[5,6] for whom the secondary prophylaxis to prevent recurrence of variceal bleeding should be mandatory.

Surgical portosystemic shunts have played an important role in the treatment of variceal hemorrhage for more than half a century by total, partial, selective, or super-selective decompression of the portal, splenic, mesenteric, and gastroesophageal variceal venous systems, respectively; however, since their peak popularity from the 1960s through the 1980s, surgical portosystemic shunts have been gradually used with less frequency^[7] with the introduction of and improvements in the non-surgical therapeutic modalities (such as transjugular intra-hepatic portosystemic shunt (TIPS) and endoscopic therapy [ET]) and the development of liver transplantation over the past few decades. TIPS is a minimally invasive fluoroscopic-guided procedure, which is performed to create a shunt sustained by a metal stent between a hepatic vein and the intra-hepatic portal vein.^[8,9]

Because of its lower operative morbidity and mortality, TIPS began to replace surgical shunting as the definitive therapy for cirrhotic portal hypertension complicated by variceal hemorrhage which is refractory or recurs after pharmacologic therapies and ET.^[10,11] Furthermore, with the introduction and development of polytetrafluoroethylene (PTFE)-covered stents,^[12] it has largely replaced bare stents in many medical institutions owing to the improved patency and a decreased risk of occurrence of postoperative hepatic encephalopathy.^[13,14] Some researchers had even concluded that primary unassisted patency rates of PTFE-covered stents are similar to those of surgical shunting.^[14] ET (mainly endoscopic injection sclerotherapy [EIS] and endoscopic variceal ligation [EVL]) involves repetitive sessions of intra-variceal injection sclerotherapy, variceal band ligation, or both modalities with the goal of obliterating varices. EIS has been shown to effectively control acute variceal bleeding and reduce the risk of re-bleeding and mortality.^[15]

Actually, several randomized controlled trials (RCTs) and meta-analysis have reported the differences in efficacy for treatment of variceal bleeding in patients with cirrhotic portal hypertension between above-mentioned three interventions, separately. And prevention of variceal re-bleeding is clearly the key to improved outcomes^[16]; however, most of these studies were not powered to determine whether these therapies resulted in a survival benefit,^[17] and few previous reviews have compared surgical portosystemic shunts, TIPS and ET, respectively, to assess the survival advantage. To comprehensively address the question, we performed this meta-analysis of RCTs to compare the outcomes of surgical portosystemic shunts *vs.* TIPS, surgical portosystemic shunts *vs.* ET, and TIPS *vs.* ET in the long-term management of variceal hemorrhage by assessment of overall mortality, 30-day or 6-week survival, bleeding-related mortality, the rate of variceal re-bleeding, as well as the incidence of postoperative hepatic encephalopathy.

Methods

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^[18,19] and the Cochrane Collaboration's systematic review framework.^[20] Because this was a meta-analysis, ethics committee or institutional board approval was not required.

Literature search strategy

We used PubMed, Embase, and the Cochrane Central Register of Controlled Trials in the Cochrane Library to perform a literature search of articles published until June 2017. The following key terms were used: "variceal hemorrhage or variceal bleeding or variceal re-bleeding" OR "esophageal and gastric varices" OR "portal hypertension" and "liver cirrhosis." The search was limited from the inception up to June 2017 and had no language restrictions. We also searched the reference lists of the retrieved studies (last search performed in June 2017).

Inclusion and exclusion criteria

The study participants were patients with cirrhosis and portal hypertension, with no limitation on nationality or ethnicity. The criteria for inclusion of clinical trials were as follows: (1) RCTs published with full texts or abstract comparing surgical portosystemic shunts with TIPS, surgical portosystemic shunts with ET, or TIPS with ET (ET with or without concomitant long-term drug therapy, such as administration of beta-blockers) were included; (2) study participants aged >16 years with no other liver disorders except cirrhosis (preferably proven by biopsy) and at least one previous episode of gastroesophageal variceal bleeding that had subsequently stabilized, either spontaneously or by the use of non-surgical therapies such as vasoactive drugs and/or balloon tamponade and/or ET; (3) measurement of at least one of the following outcomes as the endpoint: primary study outcomes of overall mortality (death of any cause) and 30-day or 6-week survival, and secondary outcomes of bleeding-related mortality, the rate of variceal re-bleeding as well as the incidence of postoperative hepatic encephalopathy.

The exclusion criteria were as follows: (1) duplicate publication or provision of insufficient data; (2) studies that did not provide details on mortality and studies that involved patients with non-cirrhotic portal hypertension.

Publication selection and data extraction

Two independent reviewers (Zhou and Jiang) selected the publications by screening the titles and abstracts to determine whether they met the inclusion criteria. If necessary, an attempt was made to contact the original investigator for further data. Discrepancies between the two reviewers were resolved by discussion and consensus.

Data were extracted directly from the selected studies and collected to allow intention-to-treat analysis where possible. The relevant information included the first author's last name, publication year, study design, patient characteristics (age, sex, cause of liver disease, and Child-Pugh class), interventions, follow-up, and the following five outcomes: overall mortality, 30-day or 6-week survival, bleeding-related mortality, variceal re-bleeding, and post-operative hepatic encephalopathy.

Quality assessment

Two investigators (Zhou and Jiang) independently evaluated the quality of the included studies using the Cochrane collaboration's tool for assessing the risk of bias of RCTs.^[21] The following aspects were included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other types of bias specific to the study. Each factor was rated "low risk of bias," "high risk of bias," or "unclear risk of bias." Disagreements between the two investigators were resolved by discussion and consensus. Finally, the overall quality of the included studies was categorized into good, fair, or weak, if ≥ 4 , 3, or < 3 domains were rated as low risk of bias, respectively. A summary of the risk of bias assessment is also provided in Supplementary Figure 1, <http://links.lww.com/CM9/A31>.

Statistical analysis

Statistical analysis was performed with Review Manager Software (RevMan 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark). Analysis were performed according to the intention-to-treat method whenever possible, with all randomized patients included in the analysis within the group into which they were randomized. Dichotomous outcomes are expressed as risk ratios (RRs) with 95% confidence intervals (CIs).^[22] We assumed that heterogeneity was present even when data were not significant. A random-effects model with the Mantel-Haenszel method was used to ensure that the most conservative estimate was reported. Heterogeneity between studies was assessed with the I^2 statistic as calculated by the Chi-squared test; this value indicates the percentage of total variation across studies not attributable to random error.^[22] No heterogeneity is present when $I^2 = 0\%$. An I^2 value of $> 50\%$ was considered to indicate statistically significant heterogeneity.

When significant heterogeneity was identified ($I^2 > 50\%$), we performed subgroup analyses and sensitivity analyses to explore the possible causes of the heterogeneity. Subgroup analyses were used to assess the influence of variables on efficacy of the three interventions in the long-term management of variceal re-bleeding in patients with

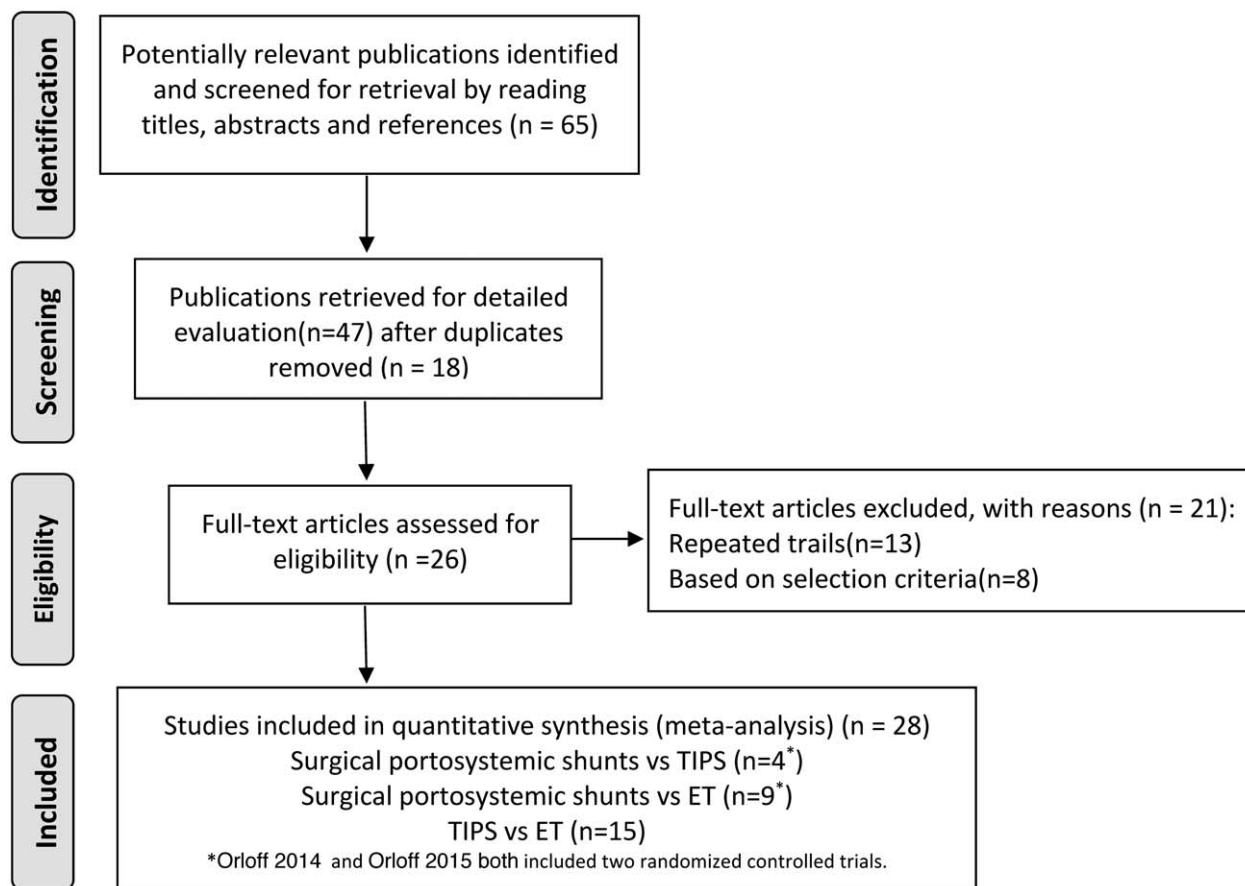


Figure 1: Flow diagram of study selection.

cirrhosis, as well as to explore the possible causes of heterogeneity. The following important factors were noted, including operation situations (emergent or elective), types of varices (esophageal, gastric, or gastroesophageal varices) and types of surgical shunts (non-selective or selective shunts). Chi-squared test was performed, which was set at a $P = 0.05$, to identify any subgroup differences. The sensitivity analysis was performed by using the leave-one-out approach, in which the meta-analysis was performed by removing each study in each turn, which was not performed if the number of included trials was small. A P value of <0.05 was considered to indicate statistical significance.

If possible, when the group included more than 10 studies, potential publication bias was qualitatively assessed by the visual symmetry of the funnel plots of the primary outcome. Asymmetry in the funnel plot indicated potential publication bias.

Results

Study selection

We identified 65 publications from the electronic databases by reading the title and abstract. Of these 65 publications, 18 were excluded as duplicates. Eight were excluded based on the selection criteria, and 13 were excluded because of repeated trials. Finally, 26 studies^[23-48] involving 28 RCTs (Orloff *et al.*^[25,26] included 2 RCTs) and 2845 patients (surgical portosystemic shunts *vs.* TIPS, $n = 496$; surgical portosystemic shunts *vs.* ET, $n = 1244$; and TIPS *vs.* ET, $n = 1105$) were included in our meta-analysis [Figure 1].

Characteristics of individual studies

The results from two studies were only reported in abstracts.^[34,42] Seven trials employed band ligation in the ET arm.^[26,34,37,38,42,44,46,47] In two trials, propranolol was used in addition to sclerotherapy, but only in the ET arm^[34,40]; in one trial, propranolol was used in addition to band ligation, but again only in the ET arm.^[47] Only two trials performed either sclerotherapy or band ligation),^[26,38] and one of these two trials added propranolol in the ET arm.^[38] In all other trials, sclerotherapy was used alone in the ET arm. As for the types of surgical shunts, there were two major kinds (portacaval shunts or distal splenorenal shunts). Portacaval shunts were used in five publications (Orloff 2014, Orloff 2015, Rosemurgy 2012, Cello 1987, and Planas 1991)^[24-27,30] and distal splenorenal shunts were employed in five trials.^[23,28,29,31,33] Furthermore, patients with cirrhosis developed gastric variceal bleeding in three trials (two trials in Orloff *et al.*^[26] one trial in Lo *et al.*^[48]). The characteristics of each individual study are presented in Table 1.

Study quality

The risk of bias in the included studies was strictly evaluated and the results are summarized in Table 2. Among 26 publications included in the systematic review, 23 were categorized as good quality, one was fair

quality,^[30] and two were weak quality.^[34,42] All trials had at least one problem with their methodological approach, which could account for systematic error (bias). Two trials were published as an abstract and the data were not available^[34,42]; the risk of bias in these two trials is unclear. No trial used double blinding. Only two trials employed blinded assessment of outcomes.^[23,48] Intention-to-treat analysis was used by most researchers, although this was not mentioned in seven trials.^[24,27,31,32,34,42,48]

Outcomes measurements

Overall mortality

Firstly, we evaluated the effect of therapy on overall mortality [Figure 2A]. Surgical portosystemic shunts did not significantly differ from TIPS, with significant heterogeneity (52% *vs.* 75%, RR = 0.64, 95% CI = 0.36–1.13, $I^2 = 94%$, $P = 0.12$). Comparing surgical portosystemic shunts *vs.* ET also had no significant difference in overall mortality, with significant heterogeneity (46% *vs.* 66%; RR = 0.82, 95% CI = 0.64–1.05, $I^2 = 80%$, $P = 0.11$). Similarly, TIPS *vs.* ET did not show a statistically significant difference, without heterogeneity (27% *vs.* 24%, RR = 1.13, 95% CI = 0.93–1.38, $I^2 = 0%$, $P = 0.22$).

30-day or 6-week survival

Then, we assessed the effect of therapy on 30-day or 6-week survival [Figure 2B]. Surgical portosystemic shunts compared with TIPS were not associated with a significant effect, with significant heterogeneity (84% *vs.* 82%; RR = 1.02, 95% CI = 0.88–1.19, $I^2 = 73%$, $P = 0.77$). We also found no significant difference between surgical portosystemic shunts and ET, with significant heterogeneity (88% *vs.* 81%, RR = 1.03, 95% CI = 0.94–1.13, $I^2 = 81%$, $P = 0.49$). Similarly, TIPS *vs.* ET showed no statistically significant difference, without heterogeneity (80% *vs.* 87%, RR = 0.92, 95% CI = 0.78–1.09, $I^2 = 0%$, $P = 0.34$).

Bleeding-related mortality

We also assessed the effect of therapy on bleeding-related mortality [Figure 3A]. Surgical portosystemic shunts were associated with significantly lower mortality caused by variceal bleeding than TIPS, without significant heterogeneity (1% *vs.* 32%, RR = 0.07, 95% CI = 0.01–0.32, $I^2 = 16%$, $P = 0.0007$). Surgical portosystemic shunts were also associated with significantly lower bleeding-related mortality than ET, without significant heterogeneity (2% *vs.* 23%, RR = 0.17, 95% CI = 0.06–0.51, $I^2 = 42%$, $P = 0.002$). However, pooling of all 13 studies comparing TIPS *vs.* ET resulted in a clear, although not significant, trend toward an advantage of TIPS over ET in terms of bleeding-related death, without significant heterogeneity (4% *vs.* 9%, RR = 0.53, 95% CI = 0.29–0.99, $I^2 = 10%$, $P = 0.05$).

Variceal re-bleeding

Next, we assessed the effect of therapy on variceal re-bleeding [Figure 3B]. Surgical portosystemic shunts were

Table 1: Characteristics of each included studies.

Studies	Year	Country	Group	Patients (n)	Male/female	Age (years)	Alcoholic cirrhosis (n)	Child-Pugh class			Follow-up time Median or mean (range or SD)
								A	B	C	
Surgical shunts vs. TIPS Henderson <i>et al</i> ^[2,3]	2006	USA	TIPS	67	44/23	52 ± 1	37	39	28	0	48 ± 26 months
			Distal splenorenal shunts	73	42/31	53 ± 10	43	41	32	0	44 ± 27 months
Rosemurgy <i>et al</i> ^[24]	2012	USA	TIPS	66	46/20	55 ± 12	40	12	25	29	median 15.5 years
Orloff <i>et al</i> ^[25]	2014	USA	Portacaval shunts	66	46/20	54 ± 14	44	9	24	33	median 6.4 years
			TIPS	78	56/22	49.0	73	16	39	23	NA
Orloff <i>et al</i> ^[26]	2015	USA	Portacaval shunts	76	60/16	49.1	61	15	37	24	NA
			TIPS	36	25/11	NA	32	0	22	14	NA
Surgical shunts vs. ET Cello <i>et al</i> ^[27]	1987	USA	Portacaval shunts	34	24/10		31	0	20	14	
			Sclerotherapy	32	29/3	44 ± 2	27	0	0	32	530 (21–1830) days
Teres <i>et al</i> ^[28]	1987	Spain	Portacaval shunts	32	26/6	44 ± 2	32	0	0	32	
			Sclerotherapy	55	44/11	54.1 ± 10.7	43	NA	NA	0	26.6 ± 16.9 months
Henderson <i>et al</i> ^[29]	1990	USA	Distal splenorenal shunts	57	41/16	53.9 ± 11.0	29			0	27.5 ± 15.6 months
			Sclerotherapy	37	NA	NA	23	21	16	61(30–84) months	
Planas <i>et al</i> ^[30]	1991	Spain	Distal splenorenal shunts	35			20	20	15		
			Sclerotherapy	41	29/12	52.2 ± 12.5	30	14	27	0	20.8 ± 15.0 months
Rikkers <i>et al</i> ^[31]	1993	USA	Portacaval shunts	41	26/16	56.1 ± 11.2	25	16	25	0	20.9 ± 13.9 months
			Sclerotherapy	30	NA	NA	27	20	10	87(48–118) months	
Isaksson <i>et al</i> ^[32]	1995	Sweden	Distal splenorenal shunts	30			25	20	10		
			Sclerotherapy	21	13/8	53.6 ± 10.5	14	4	11	6	mean 60.2 months
Santambrogio <i>et al</i> ^[33]	2006	Italy	Mesocaval shunts	24	19/5	51.6 ± 9.2	20	3	14	7	mean 69.5 months
			Sclerotherapy	40	33/7	53.8 ± 8.4	26	11	29	0	87 ± 61 months
Orloff <i>et al</i> ^[25]	2014	USA	Distal splenorenal shunts	40	27/13	49.4 ± 9.9	14	19	21	0	109 ± 58 months
			Sclerotherapy	106	81/25	47.8	88	32	46	28	NA
Orloff <i>et al</i> ^[26]	2015	USA	Portacaval shunts	105	81/24	49.8	87	26	49	30	NA
			Sclerotherapy/ Band ligation	259	168/91	49	68	26	160	73	NA
TIPS vs. ET Gdeath ^[34]	1995	France	Portacaval shunts	259	169/90	50	80	25	155	69	
			Sclerotherapy + Propranolol	33	46/19	51.4	61	0	0	65	NA
Cabrera <i>et al</i> ^[35]	1996	Spain	TIPS	32							

(continued)

Table 1
(continued).

Studies	Year	Country	Group	Patients (n)	Male/female	Age (years)	Alcoholic cirrhosis (n)	Child-Pugh class			Follow-up time Median or mean (range or SD)
								A	B	C	
Cello <i>et al</i> ^[36]	1997	USA	Sclerotherapy	32	23/9	55.9 ± 12.5	23	14	16	2	455 ± 298 days
			TIPS	31	20/11	55.7 ± 9.1	20	14	13	4	452 ± 298 days
Jalan <i>et al</i> ^[37]	1997	Scotland	Sclerotherapy	25	17/8	46.4 ± 1.6	17	NA	NA	NA	567 ± 104 days
			TIPS	24	19/5	48.8 ± 2.0	16	5	9	13	575 ± 109 days
Rossle <i>et al</i> ^[38]	1997	Germany	Band ligation	27	16/11	59.9 ± 8.6	21	2	14	15	16.8 ± 10.9 months
			TIPS	31	21/10	55.2 ± 9.5	26	2	14	15	15.7 ± 10.2 months
Sanyal <i>et al</i> ^[39]	1997	USA	Sclerotherapy/ Band ligation + Propranolol	65	44/21	56.6 ± 12.4	46	22	31	12	13 (8–25) months
			TIPS	61	40/21	54.3 ± 11.9	45	17	33	11	14 (8–23) months
Sauer <i>et al</i> ^[40]	1997	Germany	Sclerotherapy	39	27/12	52 ± 6	17	6	15	18	median 990 days
			TIPS	41	27/14	48 ± 8	16	7	13	21	median 956 days
Merli <i>et al</i> ^[41]	1998	Italy	Sclerotherapy + Propranolol	41	21/20	60.2 ± 12.6	26	12	18	11	median 1.45 years
			TIPS	42	27/15	52.8 ± 9.5	25	15	18	9	median 1.6 years
Sauer <i>et al</i> ^[42]	1998	Germany	Sclerotherapy	43	31/12	58.2 ± 10.7	17	13	25	5	77.7 ± 7.1 weeks
			TIPS	38	27/11	60.5 ± 8.5	9	13	20	5	73.9 ± 7.3 weeks
Garcia-Villarreal <i>et al</i> ^[43]	1999	Spain	Band ligation	42	NA	NA	NA	NA	NA	NA	median 1.25 years
			TIPS	43	NA	NA	NA	NA	NA	NA	median 1.35 years
Pomier-Layrargues <i>et al</i> ^[44]	2001	Canada	Sclerotherapy	24	22/2	55.5 ± 9.0	18	3	14	7	503 ± 463 days
			TIPS	22	15/7	58.2 ± 8.9	15	5	10	7	760 ± 390 days
Narahara <i>et al</i> ^[45]	2001	Japan	Band ligation	39	27/12	54.3 ± 10.9	24	NA	NA	NA	mean 581 days
			TIPS	41	29/12	52.9 ± 13.3	25	NA	NA	NA	mean 678 days
Gulberg <i>et al</i> ^[46]	2002	Germany	Sclerotherapy	40	30/10	54.5 ± 1.6	17	10	12	4	1047 ± 102 days
			TIPS	38	32/6	51.3 ± 1.6	9	10	12	4	1116 ± 92 days
Sauer <i>et al</i> ^[47]	2002	Germany	Band ligation	26	19/7	56 ± 2	23	11	15	2	median 2.0 years
			TIPS	28	20/8	57 ± 2	22	11	15	2	median 1.8 years
Lo <i>et al</i> ^[48]	2007	China	Band ligation + Propranolol	42	23/19	55.1 ± 12.5	24	10	19	13	3.6 ± 0.3 years
			TIPS	43	27/16	53.5 ± 11.8	29	15	16	12	4.1 ± 0.3 years
Lo <i>et al</i> ^[48]	2007	China	Sclerotherapy	37	28/9	52 ± 2	8	12	19	6	32 (1–50) months
			TIPS	35	25/10	55 ± 11	4	9	20	6	33 (3–46) months

ET: Endoscopic therapy; NA: Not available; SD: Standard deviation; TIPS: Transjugular intra-hepatic portosystemic shunt.

Table 2: Study quality and risk of bias assessment using the Cochrane Collaboration's tool.

Studies	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other types of bias	Score	Quality
Henderson <i>et al</i> (2006) ^[23]	+	+	-	+	+	+	+	6	Good
Rosemurgy <i>et al</i> (2012) ^[24]	+	+	-	-	+	+	+	5	Good
Orloff <i>et al</i> (2014) ^[25]	+	+	-	-	+	+	+	5	Good
Orloff <i>et al</i> (2015) ^[26]	+	+	-	-	+	+	+	5	Good
Cello <i>et al</i> (1987) ^[27]	+	+	-	-	+	+	+	5	Good
Teres <i>et al</i> (1987) ^[28]	+	+	-	-	+	+	+	5	Good
Henderson <i>et al</i> (1990) ^[29]	+	+	-	-	+	+	+	5	Good
Planas <i>et al</i> (1991) ^[30]	?	?	-	-	+	+	+	3	Fair
Rikkers <i>et al</i> (1993) ^[31]	+	+	-	-	+	+	+	5	Good
Isaksson <i>et al</i> (1995) ^[32]	+	+	-	-	+	+	+	5	Good
Santambrogio <i>et al</i> (2006) ^[33]	+	?	-	-	+	+	+	4	Good
Gdeaih (1995) ^[34]	?	?	?	?	?	?	?	0	Weak
Cabrera <i>et al</i> (1996) ^[35]	+	+	-	-	+	+	+	5	Good
Cello <i>et al</i> (1997) ^[36]	+	+	-	-	+	+	+	5	Good
Jalan <i>et al</i> (1997) ^[37]	?	+	-	-	+	+	+	4	Good
Rossle <i>et al</i> (1997) ^[38]	+	+	-	-	+	+	+	5	Good
Sanyal <i>et al</i> (1997) ^[39]	+	+	-	-	+	+	+	5	Good
Sauer <i>et al</i> (1997) ^[40]	+	+	-	-	+	+	+	5	Good
Merli <i>et al</i> (1998) ^[41]	+	+	-	-	+	+	+	5	Good
Sauer <i>et al</i> (1998) ^[42]	?	?	?	?	?	?	?	0	Weak
Garcia-Villarreal <i>et al</i> (1999) ^[43]	+	+	-	-	+	+	+	5	Good
Pomier-Layrargues <i>et al</i> (2001) ^[44]	+	+	-	-	+	+	+	5	Good
Narahara <i>et al</i> (2001) ^[45]	+	+	-	-	+	+	+	5	Good
Gulberg <i>et al</i> (2002) ^[46]	+	+	-	-	+	+	+	5	Good
Sauer <i>et al</i> (2002) ^[47]	+	+	-	-	+	+	+	5	Good
Lo <i>et al</i> (2007) ^[48]	+	+	-	+	+	+	+	6	Good

+ : Low risk of bias; - : High risk of bias; ? : Unclear risk of bias.

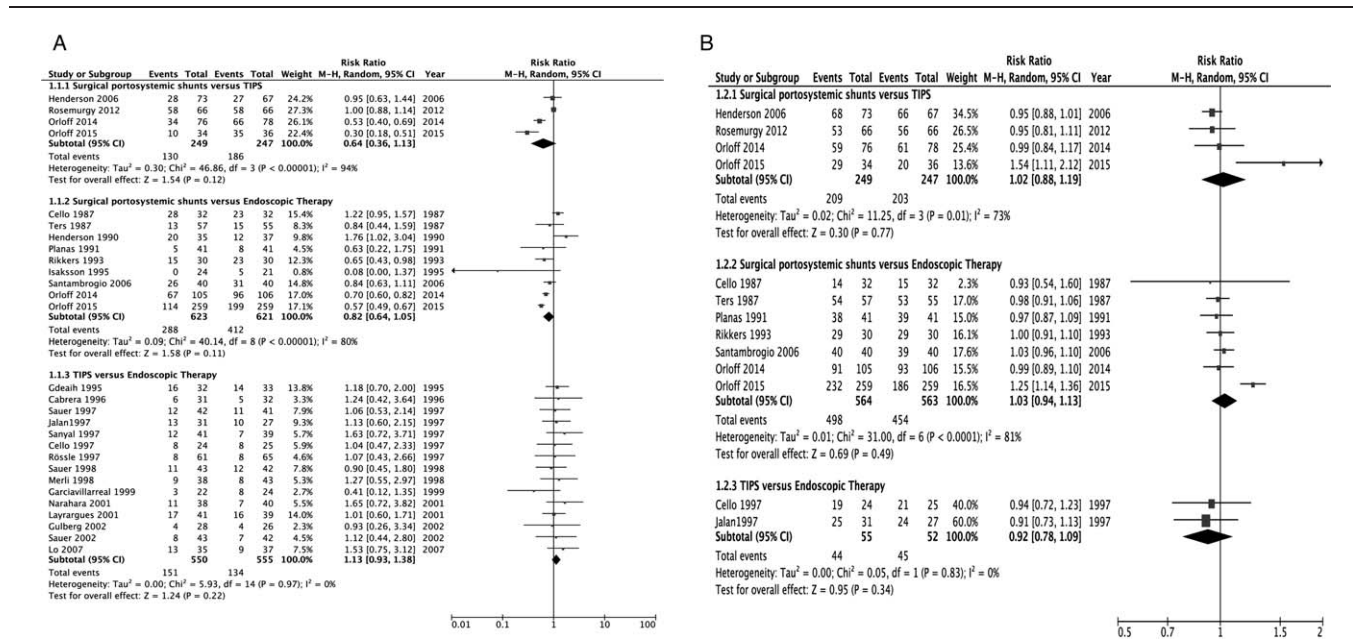


Figure 2: (A) Forest plot showing overall mortality. (B) Forest plot showing 30-day or 6-week survival.

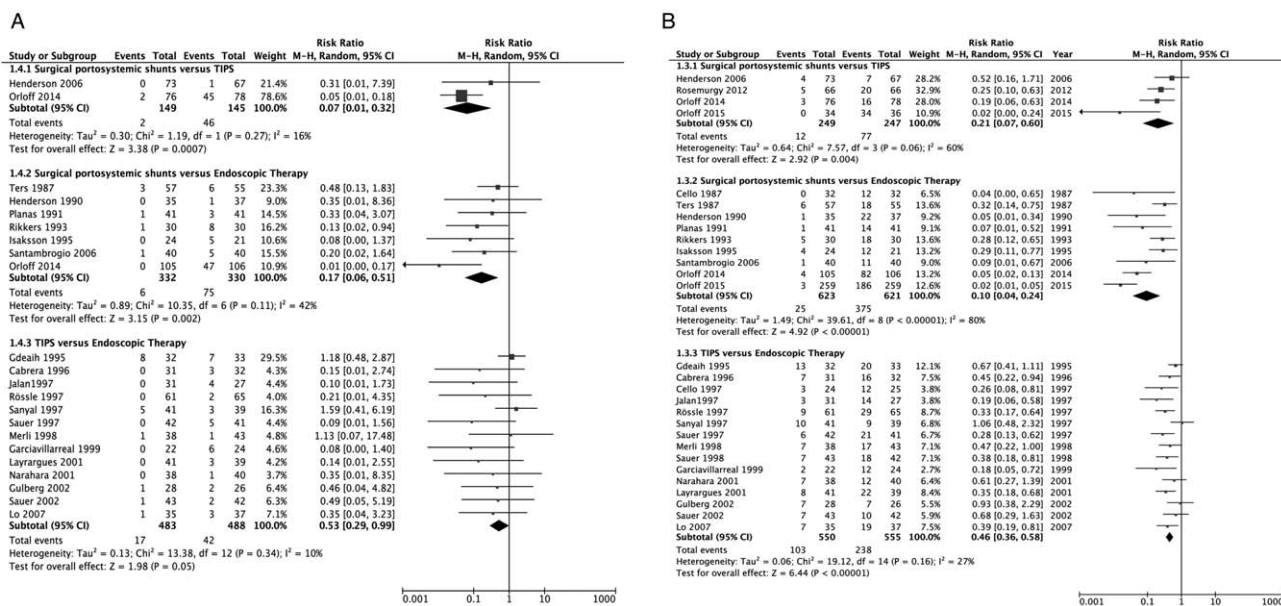


Figure 3: (A) Forest plot showing bleeding-related mortality. (B) Forest plot showing variceal re-bleeding.

associated with a significantly lower rate of re-bleeding caused by gastroesophageal varices than TIPS, without significant heterogeneity (5% vs. 31%, RR = 0.21, 95% CI = 0.07–0.60, $I^2 = 60%$, $P = 0.004$). Surgical portosystemic shunts were also associated with a significantly lower rate of variceal re-bleeding than ET, with significant heterogeneity (4% vs. 60%, RR = 0.10, 95% CI = 0.04–0.24, $I^2 = 80%$, $P < 0.00001$). Finally, the rate of variceal re-bleeding was significantly lower with TIPS than ET, but without significant heterogeneity (19% vs. 43%, RR = 0.46, 95% CI = 0.36–0.58, $I^2 = 27%$, $P < 0.00001$).

Postoperative hepatic encephalopathy

Finally, we evaluated the effect of therapy on postoperative hepatic encephalopathy [Figure 4]. Surgical portosystemic shunts resulted in a clearly, although not significantly, lower rate of hepatic encephalopathy than TIPS with significant heterogeneity (30% vs. 50%; RR = 0.52, 95% CI = 0.22–1.24, $I^2 = 86%$, $P = 0.14$). Comparing surgical portosystemic shunts vs. ET also had no significant difference in the rate of hepatic encephalopathy, with significant heterogeneity (15% vs. 17%; RR = 1.09, 95% CI = 0.59–2.01, $I^2 = 75%$, $P = 0.78$). However, TIPS was associated with a significantly higher rate of hepatic encephalopathy than ET, without significant heterogeneity (33% vs. 18%; RR = 1.78, 95% CI = 1.34–2.36, $I^2 = 33%$, $P < 0.0001$).

Additional analysis and publication bias

Subgroup analysis

Owing to the number of included studies in the comparison between surgical portosystemic shunts vs. TIPS is just four, so it is not fit for subgroup analysis. In the comparison

between surgical portosystemic shunts and ET, no significant improvement on heterogeneity was observed in the subgroup of overall mortality. The subgroup analysis of 30-day or 6-week survival and variceal re-bleeding both showed that regarding types of varices, operation situations and types of surgical shunts, most of the 95% CI between the subgroups were overlapped and partially address the heterogeneity, suggesting that there was no significant difference between the most subgroups. Moreover, the subgroup analysis of postoperative hepatic encephalopathy based on operation situations (emergent situation, elective situation, emergent, and elective situation) eliminated the heterogeneity. The other subgroup analysis could not address the heterogeneity of the meta-analysis. The results are presented in Supplementary Table 1, <http://links.lww.com/CM9/A31>.

Sensitivity analysis

For 30-day or 6-week survival and variceal re-bleeding with surgical portosystemic shunts vs. TIPS, the heterogeneity disappeared after removal of Orloff *et al*^[26] ($I^2 = 0$). For postoperative hepatic encephalopathy, the heterogeneity disappeared when we removed Henderson *et al*^[23] ($I^2 = 0$). Comparing surgical portosystemic shunts with ET, for 30-day or 6-week survival, the heterogeneity disappeared after removal of Orloff *et al*^[26] ($I^2 = 0$). The sensitivity analyses did not reveal possible explanations for the other outcomes with significant heterogeneity; that is, the heterogeneity for these outcomes was still significant after removing each study. The results are presented in Supplementary Table 2, <http://links.lww.com/CM9/A31>.

Publication bias

Supplementary Figure 2, <http://links.lww.com/CM9/A31> shows that in the funnel plots, there was no obviously

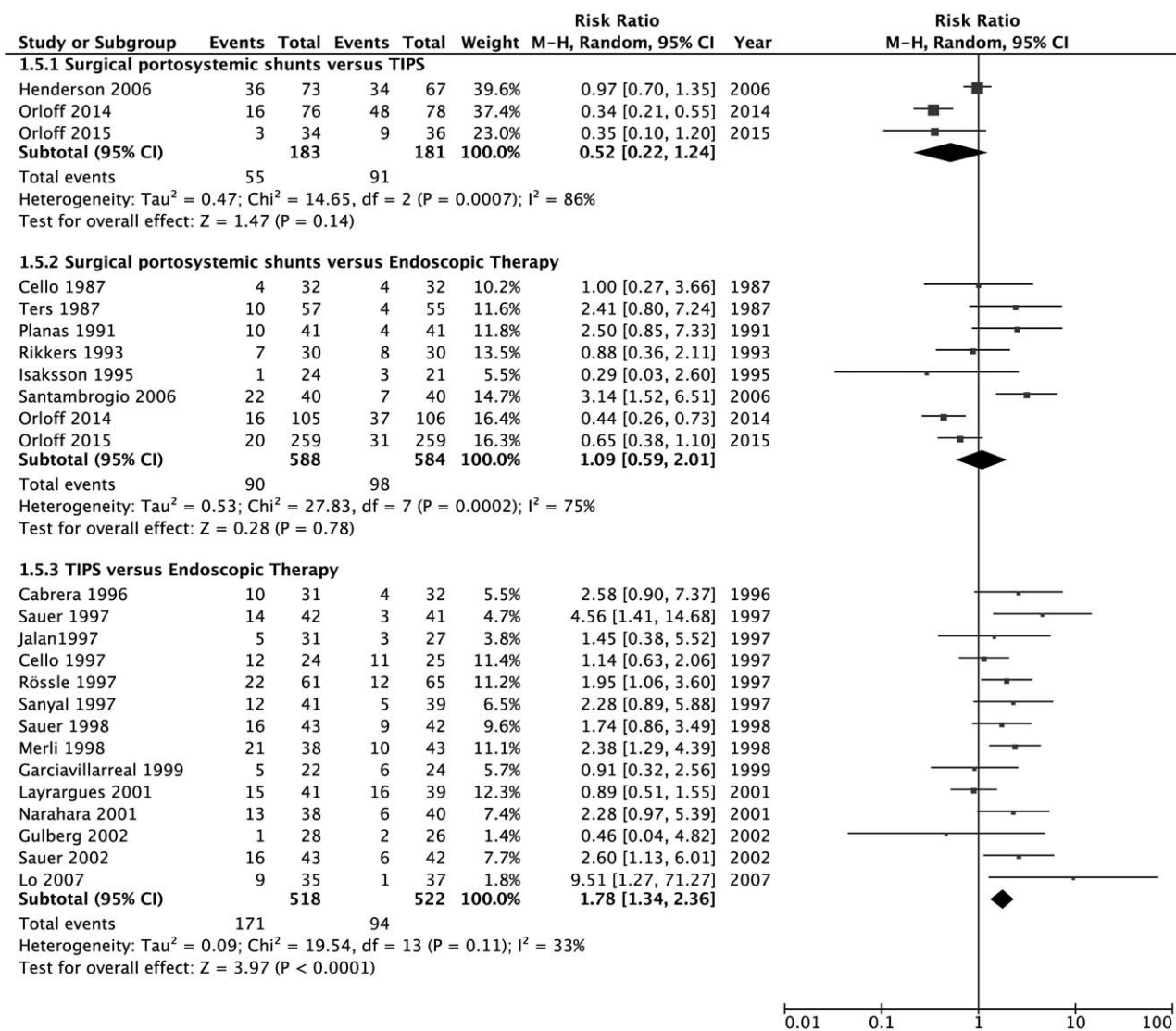


Figure 4: Forest plot showing postoperative hepatic encephalopathy.

visual indication of bias favoring TIPS or ET with respect to overall mortality, bleeding-related mortality, variceal re-bleeding, and postoperative hepatic encephalopathy.

Discussion

Esophageal and gastric varices are present in about 30% to 40% of patients with compensated cirrhosis and in 80% of those with decompensated cirrhosis.^[8,49] Additionally, variceal bleeding is the cause of about one-third of deaths in patients diagnosed with cirrhosis; even for patients who recover from the first episode of variceal hemorrhage, the re-bleeding risk and mortality rate are high.^[5-7,30] Therefore, therapy to prevent re-bleeding should be mandatory for these patients. Four main armamentariums are currently used to prevent re-bleeding. Since surgical portosystemic shunts were introduced into clinical practice in the mid-20th century, which have been a well-established therapy for variceal hemorrhage associated with end-stage liver disease. With the development and widespread utilization of ET and TIPS, variceal bleeding caused by cirrhosis is now almost exclusively treated by

gastroenterologists and radiologists who consider ET and TIPS minimally invasive. In addition, with the advent of liver transplantation as the definitive treatment for end-stage liver disease, increasingly more non-surgeons have come to firmly believe that the role of shunts is currently limited to that of a “bridge to transplantation” and that TIPS is able to fulfill this role.^[51,52] It seems that surgical shunts are becoming less important in clinical practice. Rosemurgy *et al*^[53] even considered that portal hypertension has disappeared from the purview of surgery and has migrated toward the world of non-surgical therapies, probably never to return. In contrast, Gur *et al*^[54] believed that removing surgical shunts from the surgical armamentarium is premature, and surgical shunts may offer satisfactory control of symptoms and positive long-term prognosis for patients with compensated liver cirrhosis in whom liver transplantation is either premature or not indicated. Thus, the role of surgical shunts remains controversial.

Our study reveals that there was no marked difference in the overall deaths or 30-day or 6-week survival rate among

the three therapies. Surgical portosystemic shunts were the most effective at preventing recurrent variceal hemorrhage, and TIPS were superior to ET. With respect to bleeding-related mortality, surgical portosystemic shunts were associated with a lower rate than TIPS which in turn was lower than ET without significant difference. These outcomes clearly indicate that surgical portosystemic shunts are actually the most effective at preventing variceal re-bleeding. In addition, we found that the difference of postoperative hepatic encephalopathy between surgical portosystemic shunts and ET was not notable. However, TIPS were associated with an increased incidence of hepatic encephalopathy, a major disadvantage of shunting that was more obvious following TIPS. Similar findings were also reported by Zheng *et al*,^[55] who concluded that TIPS is related to a lower variceal re-bleeding rate, fewer re-bleeding-related death but at the price of a higher rate of hepatic encephalopathy with no improvement in overall survival. These outcomes are also consistent with the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines which concluded that TIPS will effectively prevent variceal re-bleeding but will increase the incidence of portosystemic encephalopathy and will not improve survival of any of these patients.^[56] We found that overall mortality and 30-day or 6-week survival rates were similar between the two forms of portosystemic shunts (surgical shunts and TIPS), and surgical portosystemic shunts are even with lower mortality in patients with variceal bleeding, indicating that surgical portosystemic shunts are at least as safe as TIPS, although the number of included studies were small and the heterogeneity were significant. The outcomes of our study call into the question the widespread practice of using surgical portosystemic shunts only as a salvage treatment for failure of TIPS and other therapies. From an objective point of view, compared with surgical shunts, TIPS is a minimally invasive and relatively uncomplicated procedure, which can be performed in an emergency in awake, mildly sedated patients with compromised liver function under local anesthesia, who are generally considered unsuitable for surgical portosystemic shunts.^[57] Hepatic encephalopathy and TIPS dysfunction (occlusion or stenosis) may be the two major complications that have most significantly limited the effectiveness of TIPS. In the present study, we did not evaluate shunt dysfunction, which may necessitate more frequent re-interventions in patients who have undergone TIPS. Surgical portosystemic shunts showed a clear but not significant trend toward an advantage over TIPS with respect to hepatic encephalopathy. Moreover, the development of covered TIPS stents has not only reduced the frequency of shunt dysfunction but has also improved overall survival without increasing the risk of hepatic encephalopathy.^[58] Gur *et al*^[54] acknowledged the fact that despite certain shortcomings, TIPS will continue to be considered as a first-line therapy in patients with advanced cirrhosis and variceal bleeding after failed conventional medical therapies and ET. Nevertheless, surgical portosystemic shunts remain an important option in certain circumstances. The AASLD Practice Guidelines state that TIPS is preferred to surgical portosystemic shunts when patients with poor liver function are unresponsive to conventional medical therapies and ET; in patients with

good liver function and recurrent variceal bleeding after failed initial medical therapy and ET, both surgical portosystemic shunts and TIPS appear to be equivalent.^[56] In addition, surgical portosystemic shunts may offer unmatched long-term patency, the prevention of re-bleeding, and possibly improved survival in these patients, as well as low operative morbidity and mortality.^[54] A recent retrospective study also concluded that surgical portosystemic shunts achieved better results than TIPS with respect to shunt failure-free survival and overall survival in patients with complicated portal hypertension and well preserved hepatic function.^[59] Although in our study we are uncertain whether there is a difference in short- or long-term survival or the rate of variceal re-bleeding between surgical portosystemic shunts compared with TIPS owing to few included trials and small sample sizes of the individual included trials, our study indicate that surgical shunts may be at least as safe and efficient as TIPS.

ET plays a pivotal role in management of preventing first variceal bleeding, treatment of acute variceal bleeding, as well as prevention of variceal re-bleeding^[60]; however, ET is only effective for a short time because the portal pressure and blood flow remain unchanged and the varices frequently recur (about 50% at 2 years).^[5] Therefore, strict endoscopic follow-up and repeated courses of therapy are required. Considering the high success rate of TIPS in preventing uncontrolled variceal bleeding and the fact that high-risk patients with Child-Pugh class B or C disease may be better served by TIPS than repeated ET,^[16,61] TIPS is generally recommended as salvage therapy in patients who have failed endoscopic treatment among patients with acute variceal hemorrhage or initial combination of EVL plus non-selective beta-blockers for prevention of variceal re-bleeding.^[60,62] The precise timing of the procedure is not standardized, but it is usually considered after two occasions of failed endoscopy.^[63] Our meta-analysis showed that surgical portosystemic shunts were similar to ET in the outcomes of overall mortality, 30-day or 6-week survival, and the incidence of hepatic encephalopathy, but with a significantly lower rate of variceal re-bleeding. Although significantly heterogeneity was noticed in these results, based on operation situations, subgroup analysis of 30-day or 6-week survival, rate of variceal re-bleeding and hepatic encephalopathy showed the same effect in either emergent or elective situation without significant heterogeneity, indicating we could have certain certainty of the evidence for these results. But we still should be cautious about the conclusion of overall mortality.

Liver transplantation has been known as the ultimate therapy for patients with decompensated cirrhosis and may become the treatment of choice and provide patients with a normal life expectancy,^[7] which has also changed the landscape in managing cirrhotic portal hypertension.^[64] Hence, it would be highly beneficial to increase the survival of patients with portal hypertension and variceal bleeding while on the waiting list for liver transplantation.^[65] Specifically, the prevention of recurrent variceal hemorrhage might be expected to result in improved survival.^[66] Consequently, we should take appropriate

and personalized interventions for these patients to prevent variceal re-bleeding before liver transplantation is either premature or not indicated.

There is no significant heterogeneity for all five outcomes in the comparison between TIPS *vs.* ET. However, significant heterogeneity for the overall mortality still existed in both comparison of surgical portosystemic shunts *vs.* TIPS and ET despite the fact that it was performed with a random-effects model. A significant improvement was not observed in the subgroup analysis according to the operation situations (emergent or elective), types of varices (esophageal varices, gastric varices or gastroesophageal varices) and types of surgical shunts (non-selective or selective shunts). And the resource of heterogeneity was not observed after a sensitivity analysis when excluding any one of the included studies; however, the changes of statistical significance was noted when excluding any one of the studies by Rosemurgy *et al.*,^[24] Cello *et al.*,^[27] or Henderson *et al.*,^[29] which indicated the instability of this outcome in our meta-analysis. Considering the low certainty of this evidence, a conclusion about overall mortality from the present study should be carefully drawn.

Our comparison of surgical portosystemic shunts *vs.* TIPS for postoperative hepatic encephalopathy showed significant heterogeneity and the sensitivity analysis indicated that the cause of the heterogeneity appeared to be divergent results from the study by Henderson *et al.*^[23] In that study, patients with Child-Pugh class A or B liver disease underwent operations under elective situations at five different clinical centers, which was different from the other two trials. Heterogeneity in 30-day or 6-week survival appeared to result from the study by Orloff *et al.*,^[34] in which the patients' source of hemorrhage was gastric varices, which differed from other trials. Sarin *et al.*^[67] concluded that the risk of bleeding from gastric varices is approximately half that of esophageal varices but gastric variceal bleeding would result in a higher mortality rate. Additionally, these patients underwent operations in emergent situations, which may have increased the perioperative mortality rate.

Our meta-analysis has several limitations. Relatively few studies of surgical portosystemic shunts *vs.* TIPS were available for analysis; that is, the amount of pooled data was small. The results would have been more reliable with an increased amount of data. In addition, subgroup analysis was not performed for some outcomes because of the small number of trials. Moreover, due to the specificity of the interventions, double-blind assessment of methodological quality could not be performed in all included trials, which increases the risk of bias. Notably, the time of follow-up varied among the included studies, which may have thus confounded the conclusions. In addition, some clinical and methodological heterogeneity could not be well addressed by subgroup or sensitivity analysis. Therefore, all results presented in this review were the average effects of three interventions estimated by a random-effects model. Despite this, owing to the uneven methodological quality of the included studies, the results have some inevitable biases. Finally, we did not evaluate procedure-related complications, mortality caused by these complications, the length of hospital stay, or medical

expenses; and these factors may influence the patients' and clinicians' choice of treatments to various degrees.

In summary, the overall analysis revealed no survival advantage seem to exist among the three therapies, and surgical portosystemic shunts were associated with the lowest bleeding-related mortality. Surgical portosystemic shunts may be the most effective and TIPS is superior to ET but at the cost of a higher incidence of postoperative hepatic encephalopathy. However, some of results in this meta-analysis should be interpreted cautiously.

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Conflicts of interest

None.

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