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TIPS *versus* Endoscopic Therapy for Variceal Rebleeding in Cirrhosis: A Meta-analysis Update*

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Summary: Endoscopic therapy (ET) is most common method for preventing variceal bleeding in cirrhosis, but the outcomes are not perfect. Recently, transjugular intrahepatic portosystemic shunt (TIPS) is introduced into clinical practice. However, the beneficial effects of TIPS compared to ET on cirrhotic patients is unknown. The aim of this study was to evaluate and compare the effects of TIPS with those of the most frequently used ET for prevention of variceal rebleeding (VRB) in liver cirrhosis. The PubMed, EMBASE, and Cochrane Library databases were searched from inception to February 2017. The primary study outcomes included the incidence of VRB, all-cause mortality, bleeding-related death, and the incidence of post-treatment hepatic encephalopathy (PTE). The odds ratios (ORs) with 95% confidence intervals (CI) were pooled for dichotomous variables. Subgroup analyses were performed. Twenty-four studies were eligible and they included 1120 subjects treated with TIPS and 1065 subjects treated with ET. Although there was no significant difference in survival and PTE, TIPS was superior to ET in decreasing the incidence of VRB (OR=0.27; 95% CI, 0.19–0.39, P<0.00001), and decreasing the incidence of bleeding-related death (OR=0.21; 95% CI, 0.13–0.32, P<0.00001). Subgroup analysis found a lower mortality (OR=0.48; 95% CI, 0.23–0.97; P=0.04) without any increased incidence of PTE (OR=1.37; 95% CI, 0.75–2.50; P=0.31) in the studies of a greater proportion (≥40%) of patients with Child-Pugh class C cirrhosis receiving TIPS, and TIPS with covered stent did not increase the risk of PTE compared to ET (OR=1.52, 95% CI =0.82–2.80, P=0.18). It was concluded that TIPS with covered stent might be considered the preferred choice of therapy in patients with severe liver disease for secondary prophylaxis.
Key words: transjugular intrahepatic portosystemic shunt; endoscopic therapy; variceal bleeding; cirrhosis; meta-analysis

Variceal bleeding is the most lethal form of gastrointestinal bleeding and the most severe complication of portal hypertension in cirrhosis. There is a general consensus that all previous bleeding from varices should have secondary prophylaxis to prevent variceal rebleeding (VRB). The significance of secondary therapy after variceal bleeding has been well known. However, the most optimal therapeutic strategies remain under debate[1]. Currently, endoscopic therapy (ET), including endoscopic banding ligation (EBL), endoscopic injection sclerotherapy (EIS) and cyanoacrylate injection with or without the addition of β-blockers, remains the prevalent method for the treatment and prevention of recurrent gastroesophageal variceal bleeding. However, VRB occurs in approximately 50% of cirrhosis and ET fundamentally acts directly on varices without a reduction of portal hypertension. Transjugular intrahepatic portosystemic shunt (TIPS) refers to the interventional creation of communication between the hepatic vein and an intrahepatic branch of the portal vein using an expandable stent, thereby decompressing the portosystemic pressure gradient. For nearly 25 years, TIPS has been widely used for the treatment of portal hypertension-related complications in liver cirrhosis[2]. The potential drawbacks of TIPS are that it cannot reduce the overall mortality and can increase the incidence of post-treatment hepatic encephalopathy (PTE)[3]. Thus, TIPS has always been regarded as the second line of therapy of choice for gastroesophageal variceal bleeding, which is not responsive to ET or medicines in liver cirrhosis[4]. Currently, more and more studies have evaluated the effect of TIPS and ET in management of gastroesophageal VRB, but results of these studies are inconsistent. Hence, a meta-analysis of the data derived from the published literature would be necessary. The aim of our meta-analysis is to provide an evidence-based guidance regarding the effect of TIPS and ET on VRB, PTE, and survival.

1 MATERIALS AND METHODS

1.1 Literature Search

The literature was searched in PubMed, EMBASE and Cochrane Central databases (from the database inception up to February 1, 2017) using the keywords "TIPS or transjugular intrahepatic portosystemic shunt", "endoscopy or endoscopic" and "variceal bleeding". We also performed a manual search of the reference lists of

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published articles.

1.2 Inclusion Criteria

Studies included in our meta-analysis met the following criteria: (1) they had a randomized and prospective design; (2) results were published in English as full reports; (3) the study population were composed of patients with at least one episode of gastroesophageal variceal bleeding; (4) they compared TIPS with ET (including EIS, EBL or cyanoacrylate injection), and (5) the following outcomes were assessed: VRB, PTE, and death.

1.3 Exclusion Criteria

Studies exclusion in our meta-analysis met the following criteria: (1) age of more than 75 years or pregnancy; (2) a history of hepatic or extrahepatic malignancy; (3) bleeding from ectopic varice, such as gastric, duodenal or rectal varices; (4) patients with portal-vein thrombosis; (5) severe organ dysfunction: heart failure, respiratory failure, and other factors.

1.4 Data Extraction

Three investigators (Zhang H, Zhang H and Li H) were independently assigned to extract the data from each primary paper. Discrepancies or disagreements were resolved by consensus. The extracted data included the first author, year of publication, country or region, number of patients, study design, style of ET, site of bleeding, type of TIPS stent, mean diameter of TIPS stent, successful TIPS placement, hepatic venous pressure gradient (HVPG) before and after TIPS (mmHg), baseline characteristics [mean age, sex, etiology of cirrhosis, blood transfusion, albumin (g/L), bilirubin (mg/dL), PT%, and Child-Pugh class and/or score], and follow-up periods.

1.5 Definitions

VRB was defined as the total number of patients who developed VRB after treatment, not including the bleeding of peptic ulcer during the follow-up period. All-cause deaths were defined as the total number of patients who died due to all causes after treatment during the follow-up period, including liver failure, sepsis or carcinoma, intra-abdominal hemorrhage, and other factors. Bleeding-related deaths were defined as the total number of patients who died due to rebleeding after treatment.

1.6 Assessment of Study Quality

The modified Jadad scale[5], in which the descriptions of randomization, allocation concealment, investigator blinding, and withdrawals and drop-outs were assessed, was used to score the quality of randomized studies. The quality scale ranged from 0 to 5 points, with a high-quality study score being at least 3 and a low-quality study score being 2 or less. The Newcastle Ottawa scale[6], in which the selection, comparability, and outcome were assessed, was used to score the quality of non-randomized studies. The maximum score that could be given was 9. High-quality studies were defined with scores of ≥5 points.

1.7 Data Synthesis and Statistical Analysis

The pooled odds ratio (OR) and 95% confidence intervals (CI) were calculated from each study using either a fixed-effects model (Mantel-Haenszel method) or random-effects model (Der Simonian and Laird method). When the heterogeneity was significant, the random-effects model was used in the pooled data, otherwise the fixed-effects model was used. Due to the lack of detection of significant heterogeneity clinically by heterogeneity testing in statistics, subgroup analyses were performed to identify the potential causes of heterogeneity for VRB, mortality, and PTE according to the following parameters: site of variceal bleeding (esophageal, gastric, or mixed), type of study design (randomized or non-randomized), type of ET (EIS or ELB or Glue), type of TIPS stents (covered or/and bare stents or unknown/bare stents), mean diameter of TIPS stents (>10 cm or ≤ 10 cm), and proportion of patients with Child-Pugh class C cirrhosis (≥40% or <40%), study quality (high or low quality), follow-up time (≤18 or >18 months). Heterogeneity among the studies was assessed using the I^2 statistic or the χ^2 test. I^2>50% or P<0.10 was considered to represent significant heterogeneity. In the subgroup analysis, P<0.05 for χ^2 test was considered to have a significant heterogeneity in statistics. All statistical analyses and plots were performed using the Review Manager statistical software version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).

Table 1 Characteristics of studies included in the meta-analysis

The first author	Year	Country/ region	Study design	*n* TIPS/ET	Mean age (years)*	Male*	Etiology of cirrhosis (%) Alcohol (%)*	Blood transfusion (U)*	Albumin (g/L)*	Bilirubin (mg/dL)*	PT (%)*	CP class (%) C (%)*	CP score*
Cabrera[7]	1996	Spain	RCT	31/32	55.8±9.1	20/23	65/72	3.9±4.0	30.1±3.6	1.8±1.4	65±13	13/6	7.1±1.6
					55.9±12.5			3.2±2.7	29.4±4.3	1.6±0.8	65±16		7.2±1.8
Cello[8]	1997	USA	RCT	24/25	48.8±2.0	19/17	79/88	5.3±0.5	26±1	1.8±0.2	NR	NR	9.0±0.4
					46.4±1.6			4.0±0.5	27±2	2.1±0.3			7.8±0.5
Jalan[9]	1997	Scotland	RCT	31/27	55.2±9.5	21/16	84/78	5.8±1.2	NR	NR	NR	48/48	9.2±2.3
					59.9±8.6			6.3±3.7					9.1±2.6
Rössle[10]	1997	Germany	RCT	61/65	54.3±11.9	40/44	69/65	NR	33±5	2.3±1.5	63±14	18/18	8.1±2.1
					56.6±12.4				35±5	2.0±1.6	66±18		7.6±2.0
Sanyal[11]	1997	USA	RCT	41/39	48±8	26/27	39/44	NR	NR	NR	NR	51/46	NR
					52±6								
Sauer[12]	1997	Germany	RCT	42/41	52.8±9.5	15/20	60/63	3.1±3.0	NR	NR	NR	21/27	7.8±2.3
					60.2±12.6			3.5±2.9					8.3±2.5
Merli[13]	1998	Italy	RCT	38/43	60.5±8.5	31/27	16/35	NR	32±4	1.5±1.0	66±14	13/12	NR
					58.2±10.7				33±6	1.8±1.5	66±18		
Garcia-Villarreal[14]	1999	Spain	RCT	22/24	58.2±8.9	15/22	68/75	4.2±3.6	29.2±4.2	2.6±1.4	57±17	32/29	8.6±2.2
					55.5±9.0			2.5±2.1	29.8±4.6	2.9±1.8	54±15		8.8±2.2

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Narahara[15]	2001	Japan	RCT	38/40	51.3±1.6 54.5±1.6	32/30	24/43	NR	31±1 29±1	1.7±0.3 1.9±0.3	62±5 66±3	NR	6.8±0.3 7.4±0.3
Pomier-Layrargues[16]	2001	Canada	RCT	41/39	52.9±13.3 54.3±10.9	29/27	61/62	3.4±2.9 3.1±2.5	24.9±4.5 25.0±5.3	2.9±2.2 5.2±5.4	NR	NR	9.6±1.6 9.8±1.6
Gülberg[17]	2002	Germany	RCT	28/26	57±2 56±2	20/19	79/88	NR	NR	NR	NR	7/15	NR
Sauer[18]	2002	Germany	RCT	43/42	53.5±11.8 55.1±12.5	27/23	67/57	2.9±2.4 2.2±2.7	NR	NR	NR	28/31	7.9±2.1 8.2±2.0
Lo[19]	2007	Taiwan	RCT	35/37	55±11 52±2	25/28	11/22	9.3±8.4 7.1±5.6	29±5 31±5	1.9±1.5 2.1±1.4	NR	17/16	7.8±1.8 7.6±5.6
Procaccini[20]	2009	USA	Not-RCT	44/61	52.0±14.1 54.5 ±14.1	26/43	39/39	NR	NR	NR	NR	NR	NR
García-Pagán[21]	2010	Spain	RCT	32/31	52±10 49±6	21/23	69/65	2.7±2 2.9±3	26±7 26±7	3.7±4.8 4.4±4.9	53±15 50±15	50/48	9.3±1.8 9.5±1.8
Popovic[22]	2010	Slovenia	Not-RCT	50/46	52.0 ± 13.2 55.8 ± 12.2	29/27	62/61	NR	NR	NR	NR	32/30	8.7±1.9 8.4±1.7
Xue[23]	2012	China	Not-RCT	64/62	51 ± 13 54 ± 12	42/42	3/11	NR	32.3±5.0 30.9±5.3	1.4±0.7 1.6±0.8	NR	17/26	7.0±2.0 8.0±2.0
García-Pagán[24]	2013	Spain	Not-RCT	45/30	56 ± 12 55 ± 9	34/18	56/60	3.8±2.8 5±3.6	25±6 26±5	3.4±3 4.2±4.6	48±15 43±18	60/67	9.8±1.5 10.4±1.7
Holster[25]	2016	Nether-lands	RCT	37/35	56 (37-75) 54 (30-71)	18/23	35/51	2.6±3.5 2.8±2.8	30.4±5.2 30.9±6.9	3.8±5.2 2.7±2.2	NR	14/11	7.5±2.0 7.3±1.9
Kochhar[26]	2015	USA	Not-RCT	140/29	56.2 ± 12.0 56.9 ± 12.0	90/15	38/52	NR	NR	NR	NR	17/24	7.8±2.0 8.0±2.6
Rudler[27]	2014	France	Not-RCT	31/31	53.2± 9.0 52.4±8.1	24/25	77/77	4.4±4.5 2.5±2.3	25±4 26±4	5.7±4.0 8.2±9.6	41±13 40±11	11/4	11.1±2 11.3±2
Monescillo[28]	2004	Spain	RCT	26/26	56±12 59±11	22/19	81/61	3.7±2.7 2.2±2.3	26±5 26±6	5.8±5.3 3.6±3.1	44±13 47±17	46/46	9.2±2.0 9.2±2.3
Sauerbruch[29]	2015	Germany	RCT	90/95	55.4±9.8 54.5±9.7	62/63	67/74	NR	NR	1.4±0.7 1.5±0.8	NR	8/8	6.9±1.5 7.0±1.7
Jalan[30]	2002	London	Not-RCT	86/139	58.7±1.4 52.9±1.2	52/94	NR	NR	29±0.8 32±0.6	5.8±0.6 3.9±0.6	NR	60/32	9.5±0.3 8.2±0.3

RCT: randomized controlled trial; TIPS: transjugular intrahepatic portosystemic shunt; ET: endoscopic therapy; NR: not reported; *n*: number; PT: prothrombin time; CP: Child-Pugh.

*All data were indicated as TIPS/ET.

Table 2 Technical parameters of the included studies in the Meta-analysis

The first author	Year	*n* TIPS/ET	Style of ET	Site	Style of stents	Mean diameter of stent (mm)	Successful TIPS placement (%)	HVPG Before/After ($\bar{x}$±*s*, mmHg)	Study quality	Follow-up (months)*
Cabrera[7]	1996	31/32	EIS	EVB	Bare	10	97	20.8±5.6 10.5±2.8	High	15
Cello[8]	1997	24/25	EIS	EVB	Bare	NR	100	23.9±1.9 7.7±0.5	High	19
Jalan[9]	1997	31/27	EBL	EVB	Bare	12	90	19.4±1.1 8.9±1.1	High	16
Rössle[10]	1997	61/65	EIS/ Glue	EVB+GVB	Bare	NR	100	22±5 8±4	Low	14
Sanyal[11]	1997	41/39	EIS	EVB	Bare	8–12	95	23±3 11±2.5	High	32
Sauer[12]	1997	42/41	EIS	EVB	bare	8–12	100	23.6±7.2 12.8±1.8	High	18
Merli[13]	1998	38/43	EIS	EVB	Bare	10	87	24±0.9 10±0.7	High	18
Garcia-Villa-rreal[14]	1999	22/24	EIS	EVB	NR	12	100	19.3±4.6 7.0±2.0	High	21
Narahara[15]	2001	38/40	EIS	EVB+GVB	Bare	8–10	100	22.4±0.7 9.4±0.6	High	36
Pomier-Layrargues[16]	2001	41/39	EBL	EVB	NR	10	98	NR	Low	21
Gülberg[17]	2002	28/26	EBL	EVB	NR	8–10	93	23±1 13±1	Low	18

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Sauer[18]	2002	43/42	EBL	EVB	Bare	8–12	100	24.4±8.2 12.1±2.1	High	46
Lo[19]	2007	35/37	Glue	GVB	Bare	10	100	21.4±7.5 7.5±3.5	High	32.5
Procaccini[20]	2009	44/61	Glue	GVB	Bare+Covered	NR	100	NR	Low	61
García-Pagán[21]	2010	32/31	EBL	EVB	Covered	8–10	100	20.2±7 6.2±3	High	16
Popovic[22]	2010	50/46	EIS	EVB+GVB	Bare	NR	96	23.9±4.4 14.2±2.8	Low	32
Xue[23]	2012	64/62	EBL/Glue	EVB+GVB	Bare+Covered	8–10	100	NR	Low	20
García-Pagán[24]	2013	45/30	EBL	EVB	Covered	8–10	100	18.6±5 6.4±3	High	14
Holster[25]	2016	37/35	EBL/Glue	EVB+GVB	Covered	8–10	100	13.4±3.3 4.4±2.1	High	23
Kochhar[26]	2015	140/29	Glue	GVB	Covered	NR	100	NR	High	<18
Rudler[27]	2014	31/31	EBL	EVB	Covered	8	100	18±4.8 7±3.7	Low	12
Monescillo[28]	2004	26/26	EIS	EVB+GVB	Bare	12	NR	24.0±2.7 NR	High	12
Sauerbruch[29]	2015	90/95	EBL	EVB	Covered	8	100	22±6 11±5	High	22.
Jalan[30]	2002	86/139	EBL	EVB+GVB	Bare	10–12	96.5	19.3±2.1 8.2±1.2	Low	<18

TIPS: transjugular intrahepatic portosystemic shunt; ET: endoscopic therapy; NR: not reported; *n*: number; EVB: esophageal variceal bleeding; GVB: gastric variceal bleeding; EBL: endoscopic banding ligation; EIS: endoscopic injection sclerotherapy; HVPG: hepatic venous pressure gradient.
*All data were considered as TIPS.

2 RESULTS

2.1 Study Selection

The literature search retrieved 1224 citations and a manual search was performed on 11 citations, 558 of which were excluded because they were duplicates. Of the 677 potentially eligible studies, 653 publications were excluded because they were reviews, meta-analysis (*n*=183), conference paper, comments, letters, short survey (*n*=265), or case reports (*n*=95), they included no TIPS as interventions (*n*=38) or no ET as comparators (*n*=59), and they had no data related to rebleeding (*n*=13). Finally, 24 studies that focused on comparing TIPS to ET and evaluated the effect of prevention of VRB were included (fig. 1).

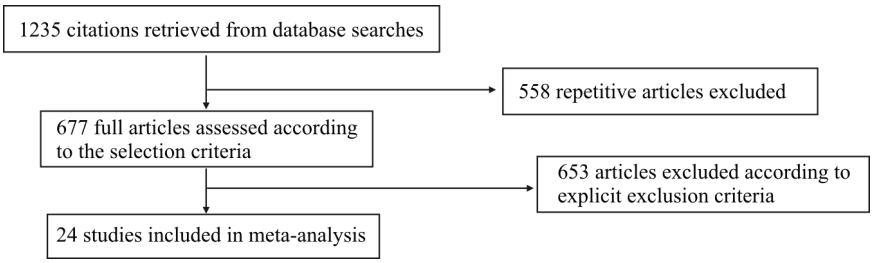

Fig. 1 Flow chart of the study selection

2.2 Study Characteristics

The 24 studies included 2185 cirrhotic patients with VRB, of whom 1120 and 1065 patients were assigned to the TIPS and ET groups, respectively (table 1). These studies were performed in 12 countries or regions (Spain, France, USA, UK, Germany, Italy, Japan, Canada, Taiwan, Slovenia, China, Netherlands). Most of the baseline characteristics were comparable between the groups (table 1). The detailed parameters of all of the included studies are described in table 2.

2.3 Study Quality

Except for three studies[10, 16, 17] with score <4 points, the rest of randomized studies were scored ≥4 points according to the modified Jadad scale, and they were considered to be of relatively high-quality. Notably, it was impractical to use a double-blinding method due to the nature of interventional modalities. According to the Newcastle Ottawa scale, five non-randomized studies[20, 22, 23, 27, 30] were considered to be of poor quality due to the score ≤4 points and the studies[24, 26] with the score ≥5 were considered to be of high-quality.

2.4 Overall Rebleeding

Twenty-four studies reported data on overall rebleeding, including 2185 patients (1120 treated with TIPS and 1065 patients treated with ET). The heterogeneity among the studies was significant (I^2=61%). Using

the random-effects model, the pooled OR was significant (OR=0.27; 95% CI, 0.19–0.39; P<0.00001), suggesting that TIPS could significantly decrease the incidence of VRB (fig. 2).

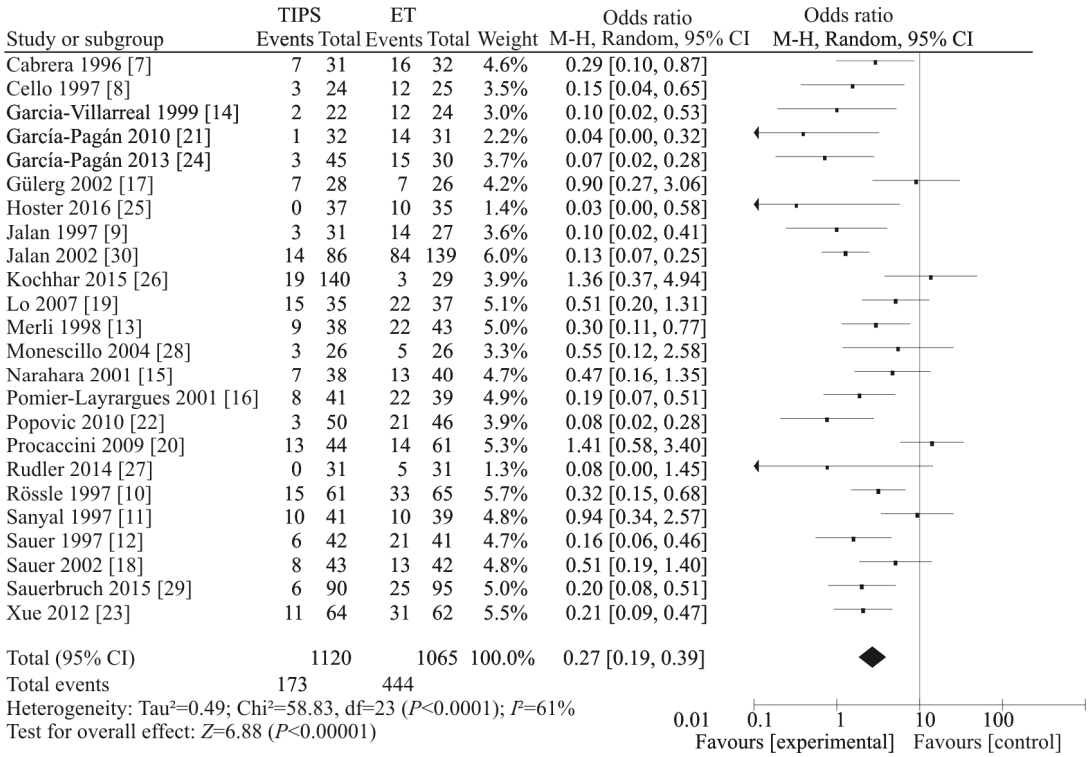

Fig. 2 Forest plots of meta-analyses comparing the rates of overall rebleeding between patients treated with TIPS and ET

2.5 All-cause Mortality

Twenty-four studies reported data on deaths due to all causes, including 1102 treated with TIPS and 1063 treated with ET. The heterogeneity among the studies was significant (I^2=48%). Using the random-effects model, the pooled OR was not significant (OR=0.84; 95% CI, 0.63–1.12; P=0.23), suggesting that TIPS did not reduce the overall mortality (fig. 3).

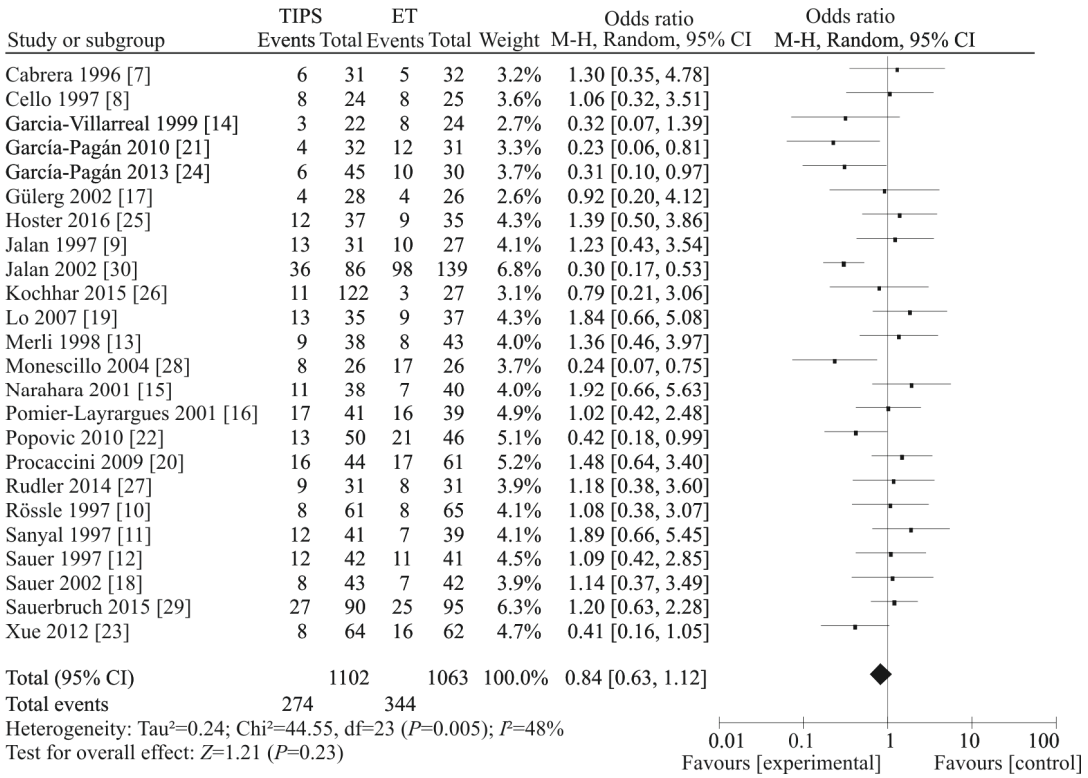

Fig. 3 Forest plots of meta-analyses comparing the rates of mortality due to all causes between patients treated with TIPS and ET

2.6 Bleeding-related Death

Twenty-one studies reported data on bleeding-related death, including 912 treated with TIPS and 950 treated with ET. The heterogeneity among the studies was not significant (I^2=4%). Using the fixed-effects model, the pooled OR was significant (OR=0.21; 95% CI, 0.13–0.32; P<0.00001), suggesting that TIPS significantly decreased the incidence of bleeding-related death (fig. 4).

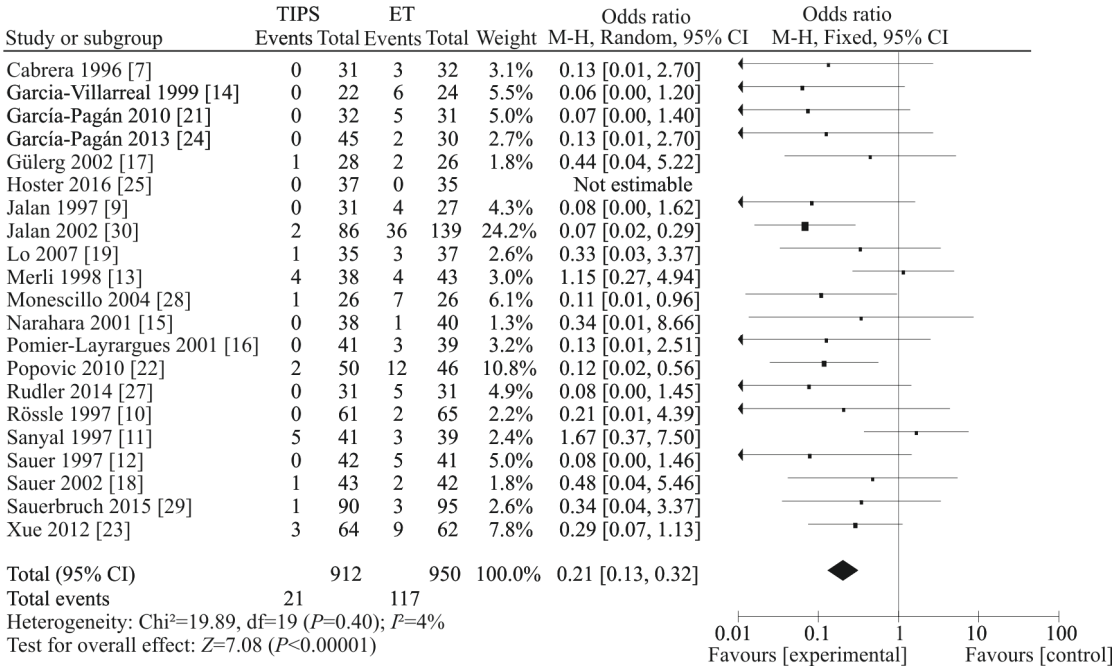

Fig. 4 Forest plots of meta-analyses comparing the rates of bleeding-related death between patients treated with TIPS and ET

2.7 Post-treatment Hepatic Encephalopathy

Twenty-four studies reported data on PTE, including 1112 treated with TIPS and 1065 treated with ET. The heterogeneity among the studies was significant (I^2=47%). Using the random-effects model, the pooled OR was significant (OR=1.82; 95% CI, 1.34–2.47; P=0.0001), suggesting that TIPS had a high risk of PTE (fig. 5).

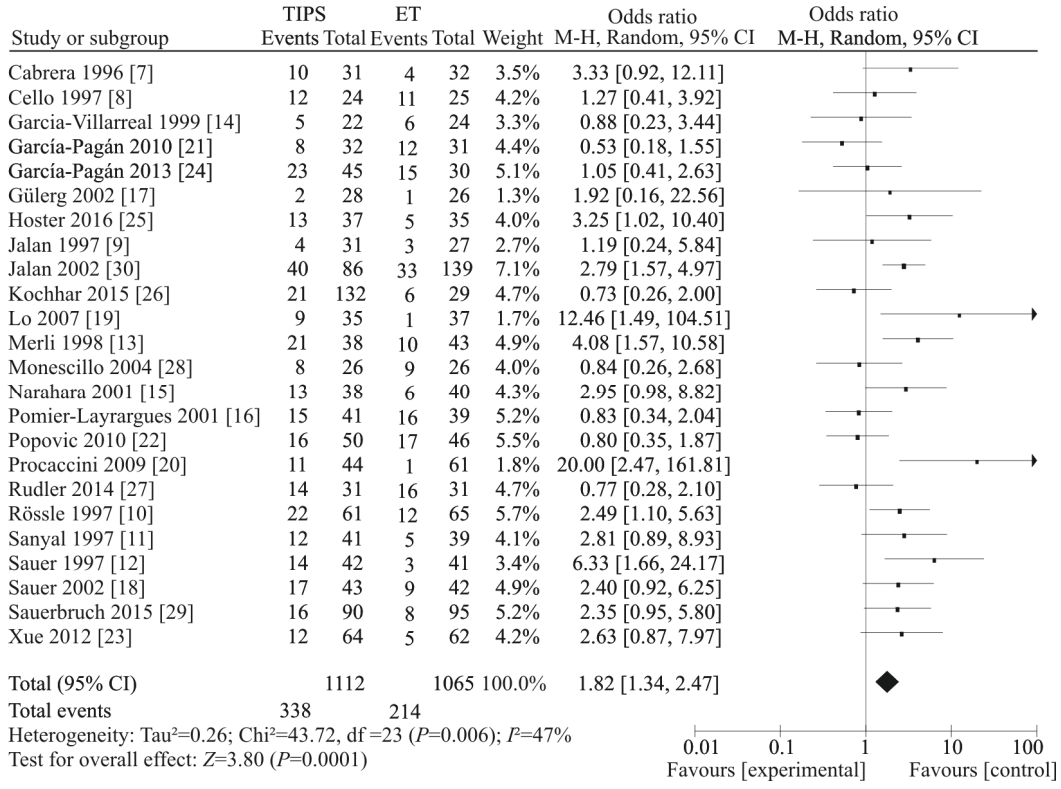

Fig. 5 Forest plots of meta-analyses comparing the rates of post-treatment hepatic encephalopathy between patients treated with TIPS and ET

2.8 Subgroup Analysis

The subgroup analyses were carried out in the respects of the site of bleeding, type of study design, type of ET, type of TIPS stents, mean diameter of TIPS stents, proportion of patients with Child-Pugh class C cirrhosis, study quality and follow-up time (table 3). Subgroup analysis found a lower mortality (OR=0.48; 95% CI, 0.23–0.97; *P*=0.04) without any increased incidence of PTE (OR=1.37; 95% CI, 0.75–2.50; *P*=0.31) in the studies of a greater proportion (≥40%) of patients with Child-Pugh class C cirrhosis receiving TIPS, and TIPS with covered stent did not increase the risk of PTE compared to ET (OR=1.52, 95% CI=0.82–2.80, *P*=0.18).

Table 3 Results of subgroups analyses on TIPS *vs.* ET

Subgroups	Studies (*n*)/ Patients (*n*)	OR (95% CI)	Heterogeneity	Test for subgroup difference
(A) Overall rebleeding	24/2185	0.27 [0.19, 0.39] (*P*<0.00001)*	I^2=61% (*P*<0.0001)	
Site of bleeding				I^2=86% (*P*=0.0007)
EVB	15/1289	0.22 [0.14, 0.33] (*P*<0.00001)*	I^2=49% (*P*=0.02)	
GVB	3/346	0.96 [0.55, 1.68] (*P*=0.88)	I^2=27% (*P*=0.25)	
EVB/GVB	6/550	0.23 [0.15, 0.35] (*P*<0.00001)	I^2=39% (*P*=0.14)	
Type of study design				I^2=62% (*P*=0.10)
Randomized studies	17/1327	0.28 [0.22, 0.37] (*P*<0.00001)	I^2=37% (*P*=0.06)	
Non-randomized studies	7/858	0.24 [0.09, 0.63] (*P*=0.004)*	I^2=82% (*P*<0.0001)	
Type of ET				I^2=84% (*P*=0.0004)
EIS or/and glue	10/754	0.28 [0.18, 0.44] (*P*<0.00001)	I^2=37% (*P*=0.06)	
ELB or/and glue	10/860	0.19 [0.11, 0.33] (*P*<0.00001)	I^2=46% (*P*=0.05)	
Glue	3/346	0.96 [0.49, 1.90] (*P*=0.91)	I^2=27% (*P*=0.25)	
EIS/EBL	1/225	0.13 [0.07, 0.25] (*P*<0.00001)	NR	
Type of TIPS stents				I^2=0% (*P*=0.83)
Covered or/and bare stents	8/857	0.22 [0.08, 0.58] (*P*=0.002)*	I^2=76% (*P*=0.0001)	
Bare stents or unknown	16/1328	0.28 [0.19, 0.40] (*P*<0.00001)*	I^2 = 48% (*P*=0.02)	
Mean diameter of TIPS stents				I^2=34% (*P*=0.22)
≤10 cm	12/1011	0.24 [0.17, 0.32] (*P*<0.00001)	I^2=38% (*P*=0.09)	
>10 cm	7/629	0.25 [0.12, 0.51] (*P*=0.0001)*	I^2=64% (*P*=0.01)	
NR	5/545	0.39 [0.13, 1.14] (*P*=0.08)*	I^2=79% (*P*=0.0006)	
Patients with Child-Pugh class C cirrhosis				I^2=80% (*P*=0.007)
≥40%	6/553	0.18 [0.07, 0.46] (*P*=0.0004)*	I^2=72% (*P*=0.003)	
<40%	14/1320	0.27 [0.21, 0.36] (*P*<0.00001)	I^2=43% (*P*=0.04)	
NR	4/312	0.40 [0.14, 1.13] (*P*=0.0002)*	I^2=75% (*P*=0.0003)	
Study quality				I^2=0% (*P*=0.66)
High	16/1311	0.27 [0.17, 0.42] (*P*<0.00001)*	I^2=52% (*P*=0.009)	
Low	8/874	0.27 [0.13, 0.54] (*P*=0.0002)*	I^2=75% (*P*=0.0003)	
Follow-up time				I^2= 80% (*P*=0.03)
≤18 months	12/1111	0.24 [0.14, 0.40] (*P*<0.00001)*	I^2=57% (*P*=0.008)	
>18 months	12/1074	0.30 [0.18, 0.51] (*P*<0.0001)*	I=64% (*P*=0.001)	
(B) All-cause mortality	24/2165	0.84 [0.63, 1.12] (*P*=0.23)*	I^2=48% (*P*=0.005)	
Site of bleeding				I^2=0% (*P*=0.85)
EVB	15/1289	0.82 [0.57, 1.19] (*P*=0.29)*	I^2=49% (*P*=0.02)	
GVB	3/326	1.42 [0.79, 2.55] (*P*=0.24)	I^2=0% (*P*=0.61)	
EVB and GVB	6/550	0.69 [0.37, 1.30] (*P*=0.25)*	I^2=57% (*P*=0.04)	
Type of study design				I^2=96% (*P*<0.00001)
Randomized studies	17/1327	1.04 [0.81, 1.33] (*P*=0.77)	I^2=16% (*P*=0.27)	
Non-randomized studies	7/838	0.55 [0.33, 0.93] (*P*=0.03)*	I^2=55% (*P*=0.04)	
Type of ET				I^2=74% (*P*=0.008)
EIS or/and glue	10/754	0.88 [0.63, 1.22] (*P*=0.44)	I^2=40% (*P*=0.09)	
ELB or/and glue	10/860	0.83 [0.61, 1.13] (*P*=0.24)	I^2=29% (*P*=0.18)	
Glue	3/326	1.42 [0.79, 2.55] (*P*=0.24)	I^2=0% (*P*=0.61)	
EIS/ELB	1/225	0.30 [0.17, 0.53] (*P*<0.0001)	NR	
Type of TIPS stents				I^2=0% (*P*=0.74)
Bare stents or unknown	16/1328	0.88 [0.60, 1.27] (*P*=0.49)*	I^2=51% (*P*=0.009)	
Covered or/and bare stents	8/837	0.83 [0.59, 1.15] (*P*=0.25)	I^2=48% (*P*=0.06)	
Mean diameter of TIPS stents				I^2=72% (*P*=0.03)
≤10 cm	12/1011	0.95 [0.72, 1.26] (*P* = 0.73)	I^2 = 35% (*P* = 0.11)	
>10 cm	7/629	0.68 [0.35, 1.30] (*P*=0.24)*	I^2=67% (*P*=0.006)	

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NR	5/525	0.88 [0.56, 1.36] (P=0.56)	I^2=14% (P=0.33)	
Patients with Child-Pugh class C cirrhosis				I^2=90% (P<0.0001)
≥40%	6/553	0.48 [0.23, 0.97] (P=0.04)*	I^2=67% (P=0.01)	
<40%	14/1300	0.94 [0.72, 1.23] (P=0.64)	I^2=0% (P=0.49)	
NR	4/312	1.32 [0.82, 2.14] (P=0.25)	I^2=0% (P=0.80)	
Study quality				I^2=78% (P=0.03)
High	16/1291	0.97 [075, 1.25] (P = 0.79)	I^2 =36% (P = 0.08)	
Low	8/874	0.69 [0.43, 1.12] (P=0.14)*	I^2=56% (P=0.03)	
Follow-up time				I^2=94% (P<0.0001)
≤18 months	12/1091	0.66 [0.43, 1.03] (P=0.07)*	I^2=49% (P=0.03)	
>18 months	12/1074	1.03 [0.78, 1.34] (P=0.85)	I^2 =29% (P=0.16)	
(C) Bleeding-related death	21/1862	0.21 [0.13, 0.32] (P<0.00001)	I^2=4% (P=0.40)	
Site of bleeding				I^2=0% (P=0.83)
EVB	14/1240	0.21 [0.13, 0.36] (P<0.0001)	I^2=29% (P=0.14)	
GVB	1/72	0.33 [0.03, 3.37] (P=0.35)	NR	
EVB and GVB	6/550	0.18 [0.08, 0.42] (P<0.0001)	I^2=0% (P=0.89)	
Type of study design				I^2=70% (P=0.07)
Randomized studies	16/1278	0.30 [0.17, 0.51] (P<0.0001)	I^2=0% (P=0.49)	
Non-randomized studies	5/584	0.12 [0.05, 0.25] (P<0.00001)	I^2=0% (P=0.68)	
Type of ET				I^2=11% (P=0.34)
EIS or/and glue	9/705	0.29 [0.16, 0.54] (P<0.0001)	I^2=37% (P=0.12)	
ELB or/and glue	10/860	0.20 [0.09, 0.42] (P<0.0001)	I^2=0% (P=0.95)	
Glue	1/72	0.33 [0.03, 3.37] (P=0.35)	NR	
EIS/EBL	1/225	0.07 [0.02, 0.29] (P=0.0003)	NR	
Type of TIPS stents				I^2=0% (P=0.77)
Covered or/and bare stents	6/583	0.18 [0.07, 0.47] (P=0.0004)	I^2=0% (P=0.83)	
Bare stents or unknown	15/1279	0.21 [0.13, 0.35] (P<0.00001)	I^2=23% (P=0.19)	
Mean diameter of TIPS stents				I^2=0% (P=0.56)
≤10 cm	12/1011	0.28 [0.15, 0.53] (P<0.0001)	I^2=0% (P=0.81)	
>10 cm	7/629	0.18 [0.06, 0.60] (P=0.005)*	I^2=51% (P=0.06)	
NR	2/222	0.13 [0.03, 0.53] (P=0.004)	I^2=0% (P=0.75)	
Patients with Child-Pugh class C cirrhosis				I^2=0% (P=0.56)
≥40%	6/553	0.17 [0.05, 0.64] (P=0.009)*	I^2=55% (P=0.05)	
<40%	13/1151	0.24 [0.14, 0.43] (P<0.0001)	I^2=0% (P=0.71)	
NR	2/158	0.19 [0.02, 1.63] (P=0.13)	I^2=0% (P=0.65)	
Study quality				I^2=62% (P=0.10)
High	14/1093	0.30 [0.17, 0.52] (P<0.0001)	I^2=10% (P=0.35)	
Low	7/769	0.13 [0.07, 0.27] (P<0.00001)	I^2=0% (P=0.78)	
Follow-up time				I^2=78% (P=0.03)
≤18 months	11/942	0.15 [0.08, 0.28] (P < 0.00001)	I^2 =3% (P = 0.42)	
>18 months	10/920	0.30 [0.16, 0.55] (P=0.0001)	I^2=0% (P=0.44)	
(D) Post-treatment hepatic encephalopathy	24/2177	1.82 [1.34, 2.47] (P=0.0001)*	I^2=47% (P=0.006)	
Site of bleeding				I^2=32% (P=0.23)
EVB	15/1289	1.81 [1.40, 2.33] (P<0.00001)	I^2=42% (P=0.04)	
GVB	3/338	4.93 [0.42, 57.30] (P=0.20)*	I^2=84% (P=0.002)	
EVB/GVB	6/550	1.80 [1.21, 2.67] (P=0.004)	I^2=38% (P=0.16)	
Type of study design				I^2=61% (P=0.11)
Randomized studies	17/1327	2.04 [1.57, 2.66] (P<0.00001)	I^2=35% (P=0.08)	
Non-randomized studies	7/850	1.51 [0.80, 2.83] (P=0.20)*	I^2=66% (P=0.007)	
Type of ET				I^2=60% (P=0.06)
EIS or/and glue	10/754	2.01 [1.45, 2.79] (P<0.0001)	I^2=41% (P=0.08)	
ELB or/and glue	10/860	1.40 [1.01, 1.95] (P=0.04)	I^2=25% (P=0.21)	
Glue	3/338	4.93 [0.42, 57.3] (P=0.020)*	I^2=84% (P=0.002)	
EIS/EBL	1/225	2.79 [1.57, 4.97] (P=0.0005)	NR	
Type of TIPS stents				I^2=43% (P=0.19)
Bare stents or unknown	16/1328	2.08 [1.62, 2.67] (P<0.00001)	I^2=37% (P=0.07)	
Covered or/and bare stents	8/849	1.52 [0.82, 2.80] (P=0.18)*	I^2=60% (P=0.01)	

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Mean diameter of TIPS stents				I^2=14% (P=0.31)
≤10 cm	12/1011	1.84 [1.17, 2.91] (P=0.009)*	I^2=48% (P=0.03)	
>10 cm	7/629	2.27 [1.57, 3.27] (P<0.0001)	I^2=27% (P=0.22)	
NR	5/537	1.58 [0.70, 3.59] (P=0.27)*	I^2=66% (P=0.02)	
Patients with Child-Pugh class C cirrhosis				I^2=0% (P=0.71)
≥40%	6/553	1.37 [0.75, 2.50] (P=0.31)*	I^2=53% (P=0.06)	
<40%	14/1312	2.04 [1.54, 2.70] (P<0.00001)	I^2=44% (P=0.04)	
NR	4/312	2.16 [0.74, 6.25] (P=0.16)*	I^2=68% (P=0.03)	
Study quality				I^2=0% (P=0.99)
High	16/1303	1.91 [1.46, 2.51] (P<0.00001)	I^2=43% (P=0.04)	
Low	8/874	1.74 [0.99, 3.07] (P=0.06)*	I^2=60% (P=0.01)	
Follow-up time				I^2=52% (P=0.15)
≤18 months	12/1103	1.63 [1.04, 2.56] (P=0.03)*	I^2=54% (P=0.01)	
>18 months	12/1074	2.03 [1.31, 3.16] (P=0.002)	I^2=44% (P=0.05)	

TIPS: transjugular intrahepatic portosystemic shunt; ET: endoscopic therapy; *n*: number; OR: odds ratio; CI: confidence intervals; NR: not reported.

P<0.05 for χ^2 test was considered to have a significant heterogeneity in statistics.

*All data were calculated using a random-effects model when the heterogeneity was significant (I^2 >50%).

3 DISCUSSION

This study showed that during a mean follow-up period of 12 to 61 months, the incidence of VRB in TIPS group was only 15.4%, which was significantly lower than that in ET group (41.7%). Previous meta-analyses regarding the efficacy of TIPS for the prevention of VRB have confirmed that TIPS could significantly reduce the risk of rebleeding but increase the risk of hepatic encephalopathy without affecting survival[31, 32]. The results of meta-analysis were consistent with our conclusions. It is suggested that TIPS is more effective than ET for the secondary prophylaxis of VRB.

All of the previous randomized studies comparing TIPS with ET except for the study by Garcia-Villarreal[14] have showed only reduced rebleeding-related mortality but not overall mortality. The most important finding from our study was that studies including a high proportion (≥40%) of patients with Child-Pugh class C cirrhosis had a lower mortality after TIPS (30.3%) compared to ET (52.7%) without any increased incidence of PTE in our subgroup analysis. Jalan and his colleagues also proved that TIPS could improve the 1-year survival of the patients with Child-Pugh class C cirrhotic disease compared to ET[30]. Although previous study reported similar conclusion about TIPS to our results, the larger sample size evaluated in our study provided greater confidence in confirming the findings of previous reports.

This striking finding might be associated with the following facts. First, this may be associated with the study design. Previous studies were constructed with sufficient statistical power to stress on the differences in rebleeding rate but not mortality, and obviously larger number of smple size is required to demonstrate the latter. In comparison, the survival was emphasized in our study. Twenty-four studies were eligible and they included 1120 subjects treated with TIPS and 1065 subjects treated with ET. Apart from 17 randomized controlled trials, 7 non-randomized trials were also included in our meta-analysis. The sample size of our study was much larger than any previous meta-analysis. The improved survival in our study may be related with the larger sample size. Second, the improved survival in our study conld be related to the relative proportion of patients with Child class C liver disease. Most of previous trials, by reason of exclusion of very ill patients, had no more than 40% of their included studies with Child class C disease. A large proportion of Child classes A and B patients would be expected to dilute this effect. It is able to be believed that any survival benefit would be demonstrated best in the group of patients with the worst prognosis. We believe that the improved survival could be related to the large absolute number of Child class C patients in our study. Third, a majority of the included studies were more recently performed. Thus, the technical improvements in TIPS might be considered as other explanation for the lower mortality of post-TIPS. Hence, these finding suggest that TIPS improves survival in patients with severe (Child class C) liver disease, and should be considered the preferred choice of therapy in cirrhosis for secondary prophylaxis.

Another important aspect of this study that we would like to highlight is the problem of complications of therapy, in particular that of hepatic encephalopathy. Initial or worsened hepatic encephalopathy may be observed in 22% to 50% of patients after TIPS[33]. Due to the significant risk of PTE, an exploration of new approaches out of above complications will be of considerable clinical significance. In recent years, covered stents have been introduced as a valid alternative to bare stents in TIPS. Compared with the bare stents, covered stents could decrease the incidence of TIPS dysfunction by permitting endothelial lining and avoiding bile leakage into shunt lumen. In our subgroup analysis, we found that covered TIPS in the studies of a greater proportion (≥40%) of patients with Child-Pugh class C cirrhosis did not increase the risk of hepatic encephalopathy compared to ET (OR=1.52, 95% CI=0.82-2.80, P=0.18). In a recently published RCT, TIPS with covered stents demonstrated a markedly higher patency rate without increasing hepatic encephalopathy compared to bare stents after a long-term follow-up[34]. The result of RCT was consistent with the subgroup analysis, reinforcing the validity of our conclusions. Furthermore, a recent meta-analysis

demonstrated that the use of covered-stents could even reduce the post-TIPS HE risk[35]. Although covered TIPS did not improve overall survival in our results, it did not increase the risk of hepatic encephalopathy. With this improvement of covered stent, the role of TIPS in the treatment of variceal rebleeding of cirrhotic patients probably would be up-graded in the near future.

The strengths of our study were as follows. First, subgroup analyses were performed to explore potential causes. To minimize potential bias, we performed subgroup analysis according to the site of bleeding, type of study design, type of ET, type of TIPS stents, mean diameter of TIPS stents, proportion of patients with Child-Pugh class C cirrhosis, study quality and follow-up time. Although significant heterogeneity was observed in the meta-analysis of rebleeding, a random-effects model was used to produce a conservative result with wider CIs. Second, 24 studies were eligible for our meta-analysis. Such a large number of included studies developed the possibility of firm conclusions and conducting adequate subgroup analyses.

Our meta-analysis had several limitations. First, the risk stratification of liver disease are not uniform. An earlier study performed risk stratification using the HVPG measurement[28]. Recent years, the severity of liver disease is expressed by Child-Pugh classification[21]. The high risk of risk stratification was performed using HVPG ≥20 mmHg[28], Child-Pugh B with active bleeding or Child-Pugh C up to 13 points[21]. It should be noted that the definitions of "high risk" were heterogenous among the studies. There is a need to identify criteria that can select patients with a very poor prognosis, in whom TIPS could achieve a favourable outcome. Second, English was restricted to the publication language in our meta-analysis, which might have produced the potential selection bias. Third, 7 of these trials were retrospective and nonrandomized studies, which might also have produced the potential selection bias due to the absence of a prior well-organized study protocol. The selection of nonrandomized trials for our meta-analysis was based on the consideration that these retrospective studies could reflect real-world data[36].

In summary, TIPS had a survival benefit in patients with severe (Child class C) liver disease, and TIPS with covered stent did not increase the risk of hepatic encephalopathy. Hence, we conclude that TIPS with covered stent might be considered the preferred choice of therapy in patients with severe liver disease for secondary prophylaxis.

Conflict of Interest Statement

The authors declare no conflict of interest related to this publication.

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