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Clinical efficacy of transjugular intrahepatic portosystemic shunt created through left or right branches of the portal vein: A meta-analysis

Shaobo Zhai [a,b], Qi Cui [b], Fang Dong [b], Shiqi Wen [b], Moubo Si [b], Quan Chen [b,c,*]

[a] Gansu University of Chinese Medicine, Lanzhou, 730000, People's Republic of China
[b] Gansu Province People's Hospital, Lanzhou, 730000, People's Republic of China
[c] Key Laboratory of Molecular Diagnostics and Precision Medicine for Surgical Oncology in Gansu Province, Gansu Provincial Hospital, Lanzhou, 730000, Gansu, People's Republic of China

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ABSTRACT

Background and aim: Transjugular intrahepatic portosystemic shunt (TIPS) is a technique successfully used to treat portal hypertension and its complications. However, the choice of the branch, left (L) or right (R), of the portal vein resulting in a better outcome is still under debate. Therefore, this meta-analysis aims to evaluate which branch has a better curative effect on patients treated with TIPS.

Methods: PubMed, EMBASE, Web of science, Cochrane Library databases, Wanfang database and CBM were used for our search in October 2019 and updated in June 2021. The following parameters were used in evaluation: overall mortality, hepatic encephalopathy, shunt dysfunction, variceal rebleeding and rate of postoperative ascites.

Results: There were seven studies included. The sample size was 1940. A lower risk of mortality was observed in TIPS-L-treated patients compared with TIPS-R-treated ones (OR = 0.65, 95% CI = 0.50–0.85, p = 0.002). A lower risk of shunt dysfunction was observed in TIPS-L-treated patients compared with TIPS-R-treated ones (OR = 0.53, 95% CI = 0.33–0.87, p = 0.01). And the TIPS-L group had a significantly higher hepatic encephalopathy-free rate than the TIPS-R group (OR = 0.59, 95% CI = 0.44–0.78, p = 0.0002). However, the rate of rebleeding (OR = 0.75, 95% CI = 0.55–1.03, p = 0.07) and incidence of postoperative ascites (OR = 1.14, 95% CI = 0.86–1.51, p = 0.38) was not statistically significant between the two groups.

Conclusions: Based on the currently available evidence, the technique of TIPS through the left branch of the portal vein can significantly reduce the occurrence of overall postoperative mortality, hepatic encephalopathy and shunt dysfunction.

1. Introduction

Portal hypertension is a common complication of cirrhosis.[1,2] Nowadays, the transjugular intrahepatic portosystemic shunt (TIPS) has become very popular in the treatment of portal hypertension caused by cirrhosis,[3] becoming a standard treatment option when pharmacological and endoscopic interventions fail.[4] Since its development, many queries have been put forward about TIPS, and some of them have been resolved, such as questions regarding the comparison between the curative effect of TIPS and the traditional method, the comparison of the covered stent and the bare stent, and the side effects and positive effects of TIPS.[5–10] However, the choice of which branch, left (L) or right (R), of the portal vein that results in a better outcome is still under debate, and only a few studies have evaluated the effect of this choice.[11–17]

Therefore, a meta-analysis to evaluate which branch should be selected to obtain a better outcome is of utmost importance, thus solving the above debate. The aim of our study was to assess which branch of the portal vein should be selected to obtain better outcomes after TIPS.

2. Methods

This work was carried out according to the statement for Preferred Reporting Items for Systematic reviews and Meta-Analyses for studies that evaluate health-care interventions.[18]

* Corresponding author. Gansu Province People's Hospital of Vascular Surgery department, No. 204 Dong-Gang West Road, Lanzhou, 730000, People's Republic of China.
E-mail address: 13919093907@126.com (Q. Chen).

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2.1. Search strategy

Six major databases were used for our search in October 2019 and updated in June 2021, including PubMed, EMBASE, Web of Science, Cochrane Library, Wanfang database, and CBM. The search for eligible studies was performed using database-specific subject headings, known as Medical Subject Headings (MeSH) terms, the thesaurus associated with each database, and the population, intervention, control, and outcomes (PICO) format to frame and answer the clinical or healthcare-related questions. The specific search strategy was as follows: (Hypertension, Portal [Title/Abstract]) AND (Portasystemic Shunt, Transjugular Intrahepatic [Title/Abstract]). No publication date, language, or status restrictions were applied. Indeed, non-English language articles were also included in our meta-analysis to minimize language bias.

2.2. Eligibility criteria

The inclusion criteria were as follows: all cohort studies and randomized controlled studies comparing the curative effect of TIPS-L and TIPS-R. In accordance with the PICO process, 1) the participants had liver cirrhosis, 2) the participants were patients who underwent TIPS, 3) the interventional and control groups were compared based on the curative effect of TIPS-L and TIPS-R, and 4) the outcome indicators were determined to be overall mortality, hepatic encephalopathy (HE), rebleeding, ascites, and shunt dysfunction.

The exclusion criteria were as follows: 1) no full text available, and 2) liver cirrhosis was not the cause of portal hypertension. Additionally, if the outcome indicators overlapped between two or more studies, only the two with similar follow-up duration were included.

2.3. Data extraction

Two independent reviewers (Zhai, Cui) extracted the following data from the included studies: the first author, publication year, country where the study was conducted, number of patients, period of enrollment, albumin levels, number of events (death, HE, origin of bleeding, and ascites), age, gender, and Child–Pugh score. The main parameters used to evaluate the effect of TIPS were the presence of HE and overall mortality. The minor parameters were the presence of shunt dysfunction, ascites, and rebleeding. Any discrepancies between the two reviewers were resolved by discussion to reach an agreement, or by discussion with a third person (Si). The data are presented in Table 1.

2.4. Quality assessment

Randomized controlled studies were assessed using the Jadad composite scale, which assesses randomization, blinding, and withdrawals. The quality scale ranges from 0 to 5; a score of 2 or less is considered a low-quality report, while a score of at least 3 is considered a high-quality report. The Newcastle-Ottawa scale was used to assess cohort studies.[19] In total, seven studies assessed case selection, comparability, and outcomes. The results of the quality assessment are presented in Table 1.

2.5. Statistical analysis

Meta-analyses were conducted using the Review Manager version 5.3. The odds ratios (ORs) of each study were pooled using fixed-effect models. Forest plots were drawn. For data evaluation, patients were divided into two groups: the TIPS-L-treated group and the TIPS-R-treated group. Heterogeneity was explored by trials using the chi-square ($\chi 2$) test, which included the inconsistency factor. Heterogeneity was defined as a p-value of less than 0.05 or an I^2 greater than 50%. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes. The type of stent may also influence the curative effect of TIPS on portal hypertension.[9] A subgroup analysis was performed according to the type of stent (covered stent and bare stent). Subgroup analysis was also carried out in studies with $I^2 > 50\%$ and/or $p < 0.1$ and those with $I^2 < 50\%$ with positive outcome indicators.

3. Results

Study selection and characteristics: A total of 3334 articles were initially identified using our search strategy. After excluding irrelevant articles, seven were considered eligible. A flowchart of this process is shown in Fig. 1. The sample size was 1940 in all seven included studies. The characteristics of the two different groups are summarized in Table 1. The included studies were published between 2009 and 2021, and among them, one was a randomized study,[13] and the other six were non-randomized studies.[11,12,14–17] All included studies reported HE,[11–17] while six reported overall mortality.[11–15,17] Meanwhile, five studies provided cumulative data regarding the rate of rebleeding[12,13,15–17] and shunt dysfunction[13–17]; whereas, only three of the seven included studies provided cumulative data regarding the rate of postoperative ascites.[12,13,16]

Overall mortality: Six included studies provided cumulative data regarding mortality.[11–15,17] A lower risk of mortality was observed in TIPS-L-treated patients compared with TIPS-R-treated patients (OR = 0.65, 95% CI = 0.50–0.85, $p = 0.002$) (Fig. 2). The heterogeneity among the studies was not statistically significant ($I^2 = 6\%$, $p = 0.38$).

The subgroup meta-analysis demonstrated that the pooled OR was 0.71 (95% CI = 0.53–0.96, $p = 0.02$) (Fig. 4) in four studies where covered stents were used, while it was 0.46 (95% CI = 0.26–0.83, $p = 0.01$) (Fig. 4) in two studies where bare stents were used.

Hepatic encephalopathy: All included studies provided cumulative data regarding the rate of occurrence of HE.[11–17] The results of the meta-analysis suggested that the TIPS-L group had a significantly better HE-free rate than the TIPS-R group (OR = 0.59, 95% CI = 0.44–0.78, $p = 0.0002$) (Fig. 2). The heterogeneity among the studies was statistically significant ($I^2 = 57\%$, $p = 0.03$).

Subgroup meta-analysis demonstrated that the pooled OR was 0.62 (95% CI = 0.43–0.87, $p = 0.01$) (Fig. 4) in five studies where covered stents were used, while it was 0.54 (95% CI = 0.34–0.87, $p = 0.01$) (Fig. 4) in two studies where bare stents were used.

Shunt dysfunction: Five studies provided cumulative data regarding shunt dysfunction.[13–17] A lower risk of shunt dysfunction was observed in TIPS-L-treated patients than in TIPS-R-treated patients (OR = 0.53, 95% CI = 0.33–0.87, $p = 0.01$) (Fig. 2). The heterogeneity among the studies was not statistically significant ($I^2 = 33\%$, $p = 0.20$).

Subgroup meta-analysis demonstrated that the pooled OR was 0.46 (95% CI = 0.26–0.79, $p = 0.006$) (Fig. 5) in four studies wherein covered stents were used, while it was 1.00 (95% CI = 0.33–3.00, $p = 1.00$) (Fig. 4) in one study that used bare stents.

Rate of rebleeding: Five of the seven included studies provided cumulative data regarding the rate of rebleeding.[12,13,15–17] The results of the meta-analysis demonstrated that the rate of rebleeding between the two groups was not statistically significant (OR = 0.75, 95% CI = 0.55–1.03, $p = 0.07$) (Fig. 3). The heterogeneity among the studies was also not statistically significant (I2 = 0%, $p = 0.96$).

Incidence of postoperative ascites: Three of the seven included studies provided cumulative data regarding the rate of postoperative ascites.[12,13,16] The results of the meta-analysis demonstrated that the rate of postoperative ascites between the two groups was not statistically significant (OR = 1.14, 95% CI = 0.86–1.51, $p = 0.38$) (Fig. 3). The heterogeneity among the studies was also not statistically significant (I2 = 49%, $p = 0.38$).

3.1. Sensitivity analysis and publication bias

Sensitivity analysis was carried out by evaluating the influence of a single study on the overall pooled estimates by excluding one study in each turn. Our results suggested that the influence of each individual dataset on the pooled OR was statistically significant when comparing

Table 1
General information and quality score of the included studies.

Author	Year	Country	Age (Mean ± SD)	Sex m/f	Sample size	Previous ascites	Previous hepatic encelphalopathy	Origin of bleeding	Child-pugh class(A/B/C)	Child-pugh score	INR for prothrombin time	Meld score	albumin	The score of quality assessment
			TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	TIPS-L TIPS-R	
Bai M [11]	2014	China	50.0 ± 12.8 52.5 ± 12.3	151/70 58/28	221/86	147/66	7/2	NA	94/110/17 32/47/7	7.1 ± 1.6 7.3 ± 1.7	NA NA	11.1 ± 3.3 11.1 ± 3.5	33.4 ± 5.0 32.9 ± 5.9	7
Luo SH [12]	2019	China	44.48 ± 18.23 40.8 ± 17.76	398/539 166/141	937/307	384/117	NA	653/236	79/729/137 25/160/122	NA NA	16.03 ± 7.31 18.46 ± 5.17	13.19 ± 7.35 12.26 ± 8.47	29.14 ± 7.22 31.23 ± 6.52	7
Chen L [13]	2009	China	47.4 ± 11.4 46.4 ± 10.7	27/9 26/6	36/32	17/19	6/3	36/32	12/18/6 10/20/2	8.1 ± 2.5 7.7 ± 2.1	1.3 ± 0.5 1.3 ± 0.7	12.4 ± 3.9 12.0 ± 4.2	29.9 ± 6.4 30.9 ± 6.1	5
Chen SL [14]	2016	China	50.2 ± 12.7 51.8 ± 12.5	25/10 33/15	35/48	6/8	N/A	29/40	N/A	7.42 ± 1.74 8.14 ± 1.89	N/A	N/A	N/A	6
Zheng H [15]	2019	China	53.7 ± 12.9 55.9 ± 10.9	26/8 24/10	34/34	15/16	N/A	34/34	N/A	6.50 ± 1.33 6.94 ± 1.46	N/A	6.40 ± 4.73 7.14 ± 5.22	N/A	6
Zhou XC [16]	2014	China	N/A	N/A	30/32	N/A	4/5	N/A	9/17/4 8/21/3	N/A	N/A	N/A	N/A	5
Zhou Y [17]	2021	China	56.6 ± 11.1 55.5 ± 12.3	33/21 31/23	54/54	13/9	N/A	N/A	40/14/0 36/18/0	5,93 ± 1.1 5.67 ± 1.14	1.24 ± 0.16 1.22 ± 0.12	4.82 ± 5.28 5.12 ± 3.57	35.52 ± 4.18 35.59 ± 5.11	6

TIPS: transjugular intrahepatic portosystemic shunt; L: left; R: right; INR: international normalized ratio.

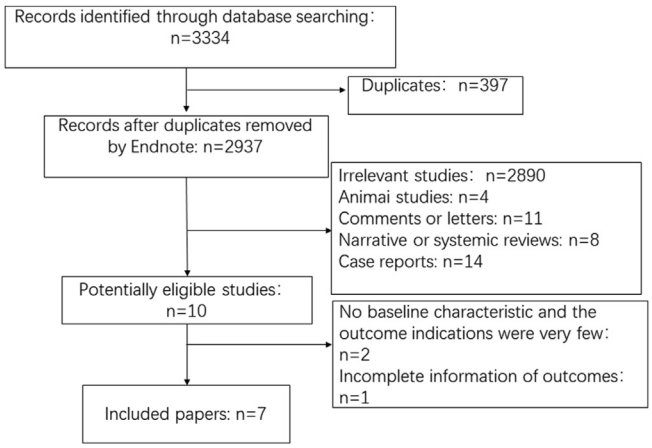

Fig. 1. Flowchart of study inclusion.

TIPS-L and TIPS-R with regards to the absence of HE. However, the difference in the overall survival rates between TIPS-L and TIPS-R was not statistically significant. This phenomenon might be explained by two main points[1]: the number of studies we collected was too small, and[2] the type of stent in each study was different. Meanwhile, the results of the subgroup meta-analysis verified these points. Since only seven available studies were included in this meta-analysis, publication bias was not meaningful enough for the clinical outcomes obtained.[20]

4. Discussion

TIPS is widely accepted as an alternative to surgery in controlling the complications of portal hypertension, such as variceal bleeding, refractory ascites, hepatorenal syndrome, hepatic hydrothorax, and even hepatopulmonary syndrome.[4,8] However, some contradictions arose in the selection of which branch of the portal vein to use when performing TIPS. Lei Chen and Ming Bai[11,13] suggested that the TIPS-L group had a significantly better outcome than the TIPS-R group in terms of overall survival and the rate of HE occurrence. Nevertheless, other scientists think that the right portal vein is easier to puncture compared with the left. The difficulty and risk of failure in puncturing the left portal vein made them conclude that TIPS-R is more advantageous than TIPS-L. Thus, it was important to conduct this meta-analysis so that the choice of branch selection could become easier for surgeons.

TIPS can effectively control portal hypertension by reducing portal venous pressure. However, HE is one of the most challenging complications of TIPS.[21] Some studies[21] suggested that the incidence of HE is always high after TIPS (approximately 18%–45%). This is common because more blood is diverted through the stent, and there is a rapid increase in blood ammonia levels, leading to cerebral edema and portosystemic encephalopathy after TIPS. In this condition, balancing the requirement of decompression of the portal venous system and reducing the incidence of HE is a problem. Our meta-analysis suggested that the TIPS-L group had a significantly better HE-free rate than the TIPS-R group. This phenomenon might be explained by the fact that the main portal vein accepts reflux blood from the splenic and superior mesenteric veins. However, it was not fully balanced and entered the left and right branches of the portal vein. The right branch mainly receives blood from the superior mesenteric vein and the left branch, mainly from the splenic vein22. Furthermore, ammonia concentration in the blood is mostly localized in the superior mesenteric vein, and the main cause of HE is high blood ammonia concentration. In addition, from an anatomical point of view, the right branch of the portal vein supplies a larger portion of the right liver, and liver function impairment is aggravated if blood flow is partially or completely diverted. Our subgroup meta-analysis showed no significant influence of the type of stent on HE in the two groups. This result might be due to the small sample size in the subgroup meta-analysis, precluding the possibility of statistical significance.

On the other hand, we found a lower risk of mortality in TIPS-L-treated patients than in the TIPS-R-treated patients. This phenomenon might be explained by most HE neurotoxins, such as ammonia, derived

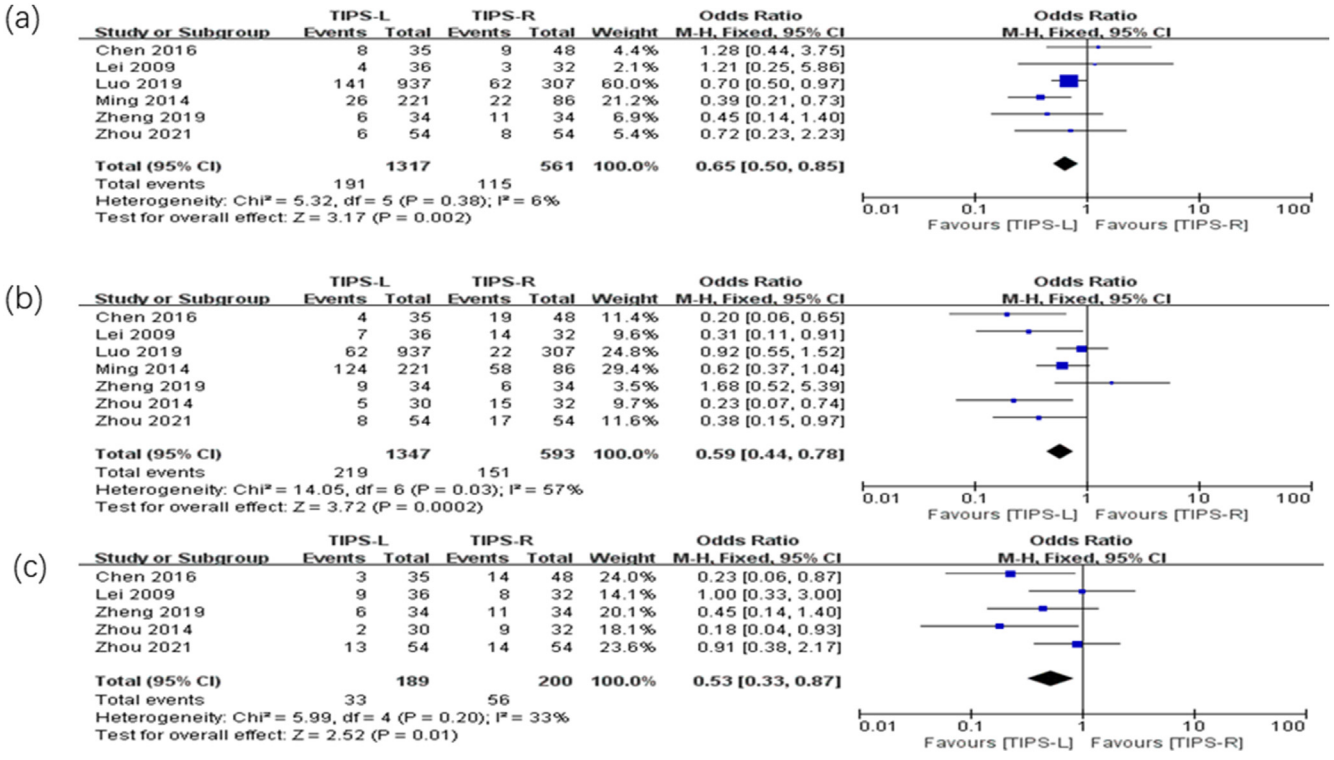

Fig. 2. Forest plots of meta-analyses comparing the overall mortality(a), hepatic encephalopathy(b) and shunt dysfunction(c) between TIPS-L group and TIPS-R group. CI, confidence interval.

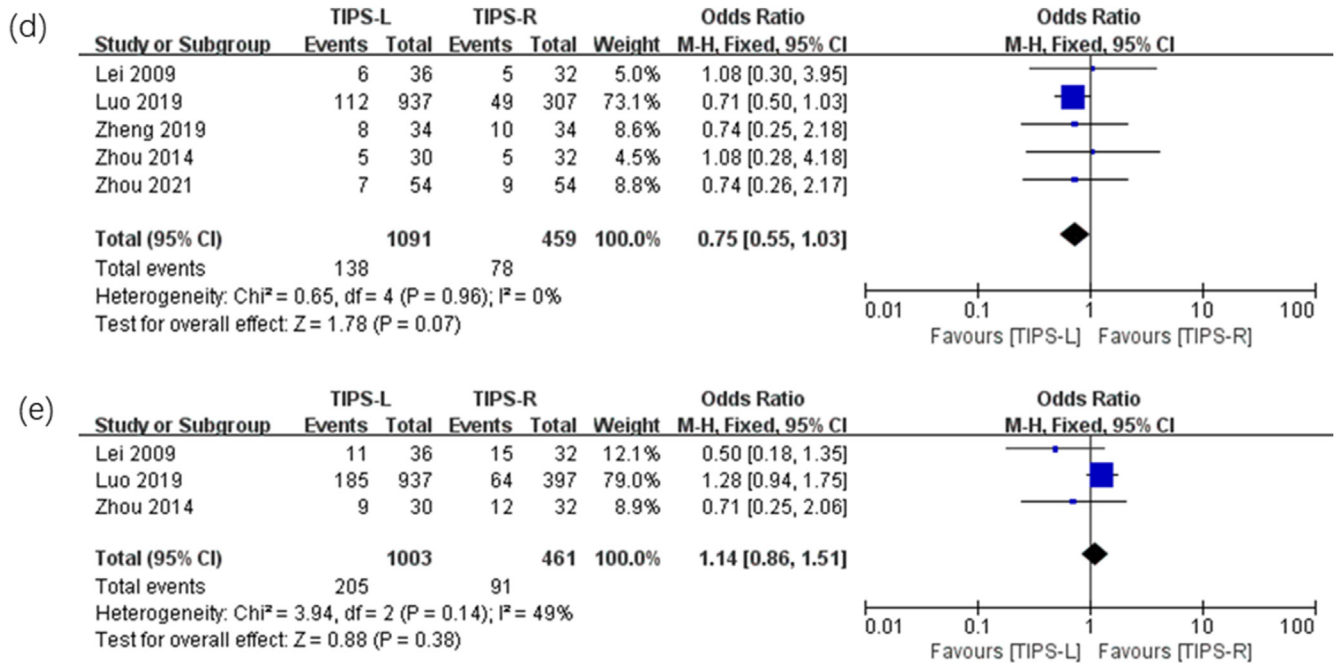

Fig. 3. Forest plots of meta-analyses comparing the rate of rebleeding (d), and incidence of postoperative ascites (e) between TIPS-L group and TIPS-R group. CI, confidence interval.

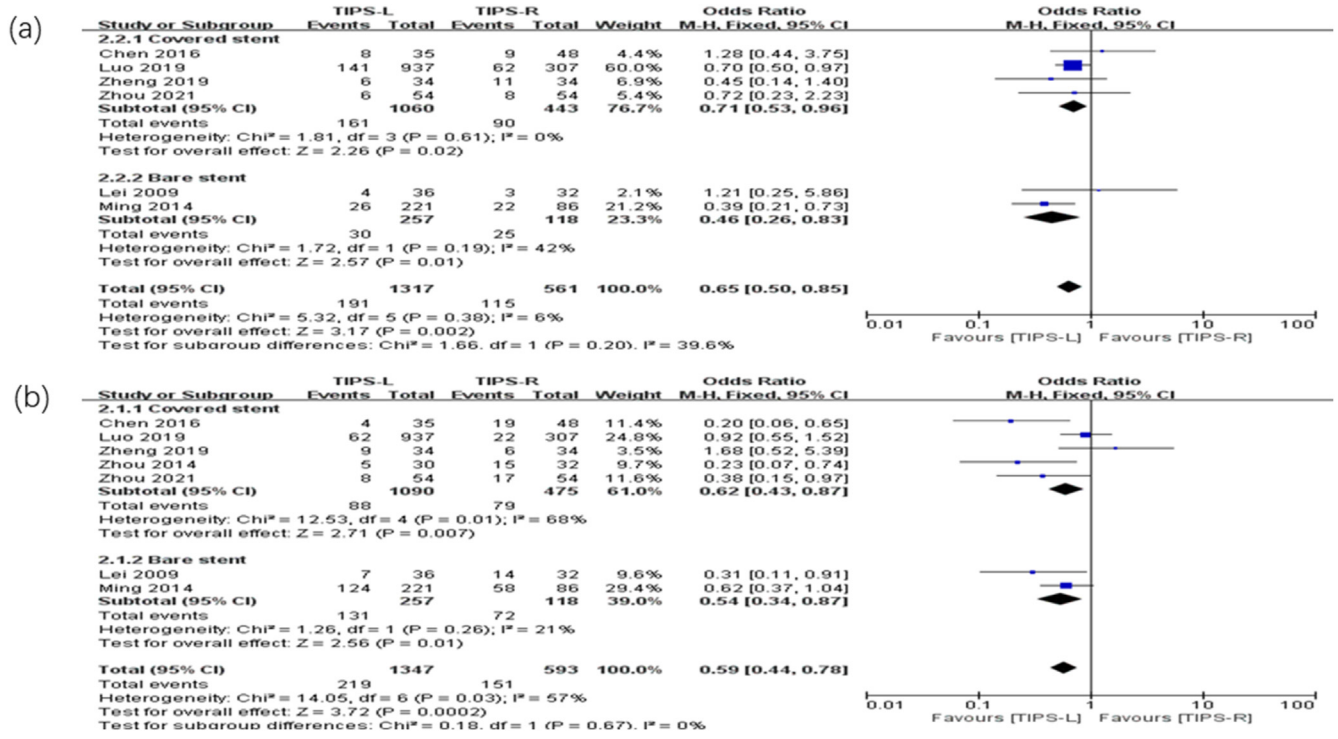

Fig. 4. Forest plots of subgroup meta-analysis comparing the overall mortality(a) and hepatic encephalopathy(b) between TIPS-L group and TIPS-R group according to the type of stents. CI, confidence interval.

from the intestine. The blood in the superior mesenteric vein mainly reaches the right portal vein12. Thus, TIPS placement through the right portal vein may theoretically lead to increased neurotoxins in the systemic circulation. This condition leads to an increased incidence of HE and decreased survival.[23] Although some studies suggested that the two groups did not have any difference in overall survival,[13] the authors of this study considered that the reason for these results may be the short observation period and relatively small sample size. Our subgroup meta-analysis also showed no significant influence of stent type on the overall mortality of the two groups. At the very least, this result might demonstrate that the differences in stent types do not significantly affect the overall mortality of either group.

Shunt dysfunction is a common complication of TIPS. Our meta-analysis revealed a lower risk of shunt dysfunction in TIPS-L-treated

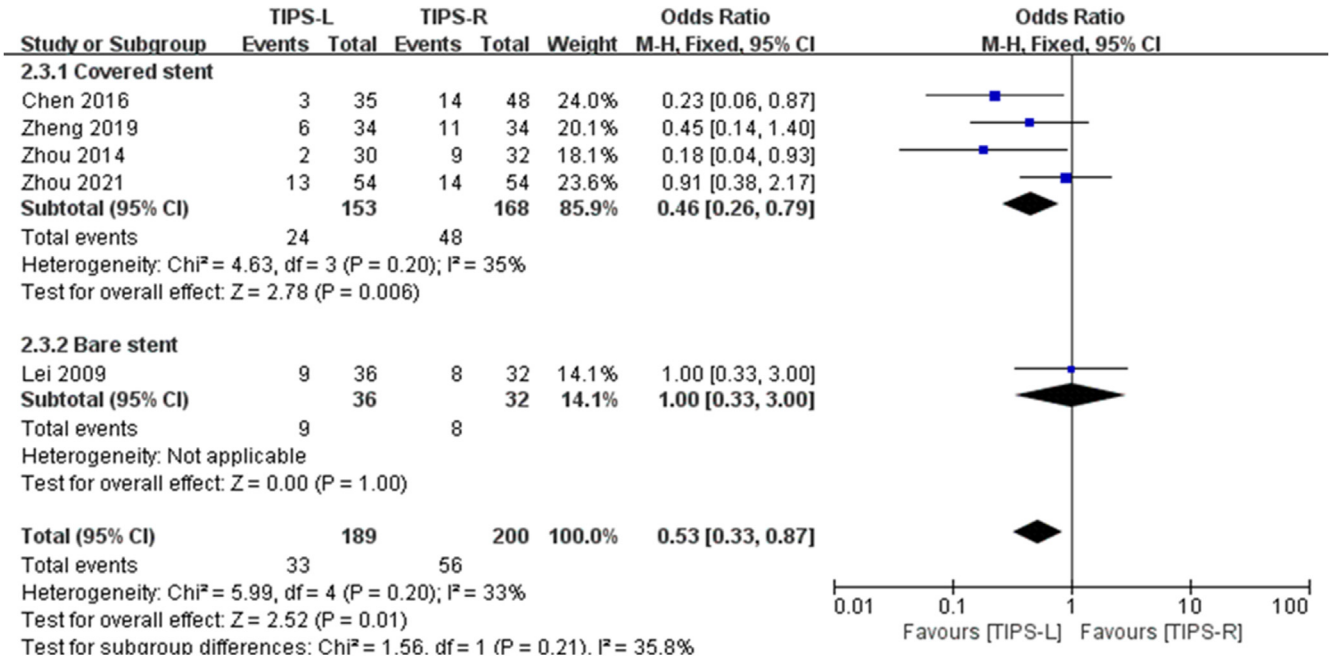

Fig. 5. Forest plots of subgroup meta-analysis comparing the shunt dysfunction between TIPS-L group and TIPS-R group according to the type of stents. CI, confidence interval.

patients compared to TIPS-R-treated patients. For this phenomenon, we considered that it may be related to the following reasons[1]: according to hemodynamic analysis, the hemodynamics in the left branch of the portal vein follows the hydrodynamic law pertaining to laminar shear stress, wherein blood flow cannot easily cause platelet accumulation and thrombosis[2]; through anatomical analysis, the shunt channel from the left portal vein to the hepatic vein is short, which is conducive to blood shunting in the distributary channel. In addition, according to the subgroup meta-analysis concerning the type of TIPS stents, the subgroup results of the bare stent group were inconsistent with the main result. This result confirms the suggestions of Qi[9] that the covered stent group might have a lower shunt dysfunction than the bare stent group.

No statistically significant difference was found between the two groups regarding the rate of rebleeding and incidence of postoperative ascites. Gastrointestinal rebleeding was efficiently prevented in both the TIPS-L and TIPS-R groups.[13] Dunne[24] claimed that TIPS is more effective in reducing variceal rebleeding in selected patients with advanced cirrhosis than the current standard of care. Similarly, both TIPS-L and TIPS-R were efficient in treating ascites. After stent implantation, ascites were successfully controlled in both groups.[13] Notably, the heterogeneity among studies was not statistically significant, suggesting that the statistical results were stable.

Our study has several limitations. First, the number of articles comparing the two groups was small, which could generate more potential bias. Second, the brand and type of stents used in the six studies were different, making these studies heterogeneous.[8] Third, as there were no intact data regarding re-hospitalization and cost in our studies, this resulted in fewer outcome indicators. Therefore, more studies comparing these two groups should be conducted to ensure less potential bias in the future. In addition, it is important to emphasize the role and effects, both positive and negative, of TIPS in the recovery phase of liver transplantation.

5. Conclusions

Based on the currently available evidence, a meta-analysis comparing TIPS-L and TIPS-R in the treatment of portal hypertension demonstrated that the TIPS-L group had significantly better outcomes than the TIPS-R group in terms of overall mortality, HE, and shunt dysfunction. However, the rate of rebleeding and the incidence of postoperative ascites were not significantly different between the two groups.

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Declaration of competing interest

None.

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