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Anticoagulation after transjugular intrahepatic portosystemic shunt for portal hypertension

A systematic review and meta analysis

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Abstract

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is widely applied to decrease portal hypertension. Because of the lack of strong evidence, it is controversial whether anticoagulation should be performed after TIPS. This meta-analysis aimed to assess the safety and efficacy of anticoagulation for patients with portal hypertension following TIPS.

Methods: Studies making comparisons between combination treatment and TIPS alone were searched in China National Knowledge Infrastructure, Cochrane Library, PubMed, the Wan Fang electronic databases, and EMBASE, delivered between the earliest accessible date and September 4, 2021. The RevMan version 5.3 was applied to conduct all statistical analyses. I^2 index statistic was used to assess heterogeneity.

Results: Five eligible studies were selected, and total 707 patients were enrolled. According to the meta-analysis, compared to TIPS alone, TIPS + anticoagulation led to much lower incidence of portal vein thrombosis (PVT; odds ratio [OR] = 0.39, 95% confidence interval [CI] 0.18–0.84, $P = .02$) as well as low heterogeneity ($P = 0.36$, $I^2 = 3\%$). Other index like the stent dysfunction rate (OR = 1.27, 95% CI 0.71–2.77, $P = .42$), bleeding rate (OR = 1.27, 95% CI 0.71–2.77, $P = .42$), and incidence of hepatic encephalopathy (OR = 0.87, 95% CI 0.56–1.36, $P = .55$) showed no statistical significance.

Conclusions: In certain patients with portal hypertension, anticoagulation following TIPS may not be required. However, for patients who do not have a PVT before TIPS, post-TIPS anticoagulation can decrease the incidence of PVT. Nonetheless, further research is still required.

Abbreviations: HE = hepatic encephalopathy, PVT = potal vein thrombosis, TIPS = transjugular intrahepatic portosystemic shunt.

Keywords: anticoagulation, interventional, portal hypertension, TIPS

1. Introduction

Portal hypertension can cause a series of serious complications, like refractory ascites and esophagogastric variceal bleeding; cirrhosis is the most prevalent and primary cause of portal hypertension.[1] Transjugular intrahepatic portosystemic shunt (TIPS) is extremely efficient in lowering portal pressure.[2] To relieve portal pressure, a shunt between the portal vein and the hepatic vein is created in the hepatic parenchyma.[3,4] After nearly 30 years of continuous exploration and development, especially with the clinical practice of specialized covered stents, TIPS prognosis has made a vast improvement.[5,6] However, the long-term stent patency rate after TIPS is still unsatisfactory.[7] The main factors affecting abnormalities[8,9] are as follow: trauma to vascular tissue and liver tissue caused by the puncture procedure in TIPS, which initiates the exogenous coagulation process; the implanted stent is a foreign body, which activates the endogenous coagulation process; incomplete deployment of the implanted stent and distortion of the stent into an angle after release; excessive intimal hyperplasia in the shunt; and the growth of liver tissue into the stent. Previous studies have shown that anticoagulation such as heparin therapy in patients with cirrhosis significantly improved the prognosis and survival of patients.[10,11] Theoretically, anticoagulation after TIPS may reduce the incidence of this complication. Nonetheless, a majority of relevant research were anecdotal in nature and had tiny sample sizes. Clinically, anticoagulation after TIPS is controversial and the relevant evidence-based medicine has been lacking.[12]

Currently, there are limited data on anticoagulation after TIPS in individuals with portal hypertension. As a result, we would like to conduct a systematic review of the published data

PJ and X-YC contributed equally to this work.

Ethics statement: The data from this meta-analysis were based on previous studies, this study did not require ethical approval or patient consent.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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on anticoagulation after TIPS to provide a foundation for clinical treatment.

2. Study selection

2.1. Ethics statement

Because the data from this meta-analysis were based on previous studies, this study did not require ethical approval or patient consent.

2.2. Strategy for search

To collect valuable data, we searched the Sino Med databases, Web of Science, Chinese National Knowledge Infrastructure, PubMed, EMBASE, Wan Fang, VIP, as well as Cochrane Library in a systematic way, with no language restrictions and with a focus on human studies; likewise, we explored ClinicalTrials.gov for accessible results of ongoing research. The following strategies for search were used: The terms "Portasystemic Shunt, Transjugular Intrahepatic" or "TIPSS" or "Shunt, Transjugular Intrahepatic Portosystemic" or "Portosystemic Shunt, Transjugular Intrahepatic" or "Shunt, Transjugular Intrahepatic Portasystemic" or "Transjugular Intrahepatic Portasystemic Shunt", "Anticoagulants" or "Anticoagulation Agents" or "Agents, Anticoagulation" or "Anticoagulant Agents" or "Agents, Anticoagulant" or "Anticoagulant Drugs" or "Drugs, Anticoagulant" or "Anticoagulant", and their combinations were used. PJ and X-YC separately screened all abstracts, and full-text reports of appropriate studies were acquired for another screen. We also looked up the relevant references in the articles we found.

2.3. Criteria for inclusion

1. Patients having portal hypertension.
2. Clinical tests applying TIPS with anticoagulation medicines or making comparisons between TIPS anticoagulation and TIPS therapy alone for the therapies of portal hypertension patients.
3. Studies involving stent stenosis rate, stent occlusion rate, incidence of bleeding, and related information about the source data could be assessed.
4. Anticoagulation drug conference summaries and thesis papers related to anticoagulation drugs with TIPS for portal hypertension patients. All of the above, with no publication language restrictions.

2.4. Criteria for exclusion

1. Tests, current events review, case reports, reviews, and other meta-analyses and studies that did not offer all of the information needed to assess the study quality.
2. Only the most recent studies were considered for repeated publications, repetition, or material from the same research, and the others were eliminated.
3. Limitation to animals or cells.

2.5. Extraction of data and evaluation of quality

Two independent reviewers (PJ and X-YC) extracted and reviewed all data from the experimental reports. The third author (JQ) was invited to participate in the resolution of

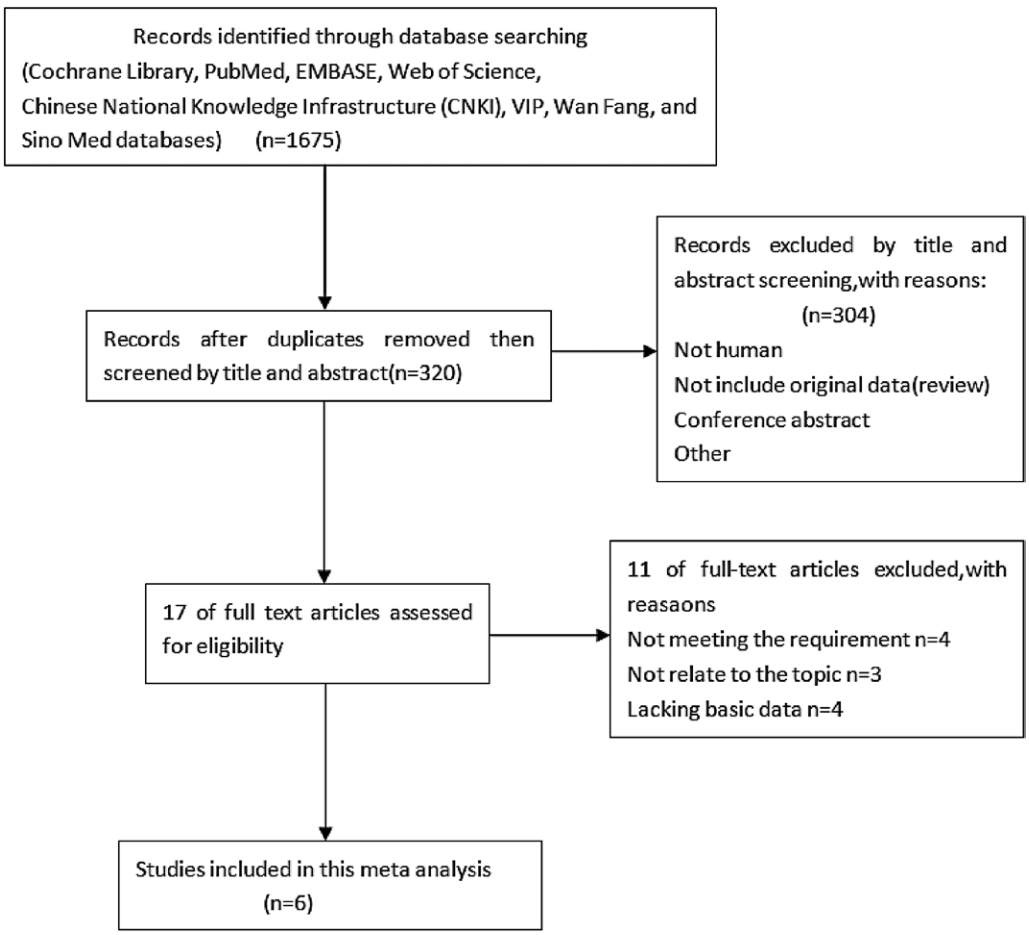

Figure 1. Flowchart of electronic database search results.

disputes if necessary. The third author (JQ) was asked to take part in the resolution of disputes if necessary. In the meanwhile, the grounds for the exclusion of studies have been recorded: authors, nation, study design, year of publication, sex of patients, as well as number of patients were among the basic data retrieved; data about the state of liver function (Child A/B/C); and moreover, some information on the experimental content was supplied, like study approaches and results of rates of stent stenosis and stent occlusion, as well as the occurrence of adverse events (bleeding, variceal bleeding rate, and hepatic encephalopathy). All data were contained in the TIPS alone and TIPS anticoagulaiton groups. Two authors (PJ and X-YC) worked independently to extract the data and then input the requisite data into Review Manager software (RevMan version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration; 2014, Copenhagen, Denmark).

2.6. Statistical analysis

Review Manager software was used to examine all of the included studies. The Q test combined with the I^2 test was first performed to evaluate the overall heterogeneity of the studies for each meta-analysis. If the heterogeneity of the included studies was acceptable ($I^2 < 50\%$ or $P > .05$), a fixed-effects model was considered. If the heterogeneity was large ($I^2 \geq 50\%$ or $P < .05$), a random-effects model was considered. Forest plots were chosen to show study-level and summary-level outcomes.[13]

Each included RCT was assessed according to the Cochrane Collaboration's instrument for estimating bias risk.[14] The Newcastle-Ottawa Scale is used to assess the included cohort studies.[15] In addition, it was not possible to process the publication bias. Finally, sensitivity analysis was performed by removing studies one by one to evaluate the effect of every study on the overall result.

3. Results

3.1. Characteristics of patient

After the titles and abstracts were screened, the search strategies determined 1675 suitable studies, of which 1355 were duplicates or removed; and 313 studies were subsequently excluded for various reasons, as presented in Figure 1. At last, 6 studies consisting of 3 RCTs and 3 cohort studies were covered in this meta-analysis. Four studies were from China, 2 studies were from Germany, and all studies were written in English. In total, 707 patients were enrolled, including 239 patients who underwent TIPS treatment alone and 468 patients who underwent TIPS + anticoagulation treatment. The characteristics of all study populations are listed in Table 1. The quality evaluation of the RCTs and the cohort studies is respectively shown in Tables 2 and 3. Three RCTs were all low risk and the 3 cohort studies scored 5 to 9 points.

Stent dysfunction including shunt stenosis and occlusion was reported in 5 studies. A fixed-effects model was chosen for stent dysfunction on the basis of the heterogeneity evaluation results ($P = .25$, $I^2 = 25\%$). The stent dysfunction rates of TIPS + anticoagulation combination were not significantly different from those of TIPS alone (odds ratio [OR] = 0.7, 95% confidence interval [CI] 0.37–0.33, $P = .28$; Fig. 2).

Five studies reported data for bleeding rates, and heterogeneity evaluation among these studies showed no significance ($P = .76$, $I^2 = 0$). Thus, the results were pooled by the fixed-effects model. Meta-analysis showed that the bleeding rates of TIPS + anticoagulation combination were not significantly different from those of TIPS alone (OR = 1.27, 95% CI 0.71–2.77, $P = .42$, Fig. 3).

Table 1
Characteristics of studies included in the meta-analysis.

Study	Year	Country	Therapy	Age (y)	Sex (M/F)	Alcohol/virology (B/C)/other	Child-Pugh A/B/C	Post-TIPS of PVT*	Incidence of bleeding†	Variceal bleeding	Shunt dysfunction‡	Hepatic encephalopathy	Study design	Follow-up time
Wang[26]	2016	China	W	54.5 ± 12.9	17/14	0/(26/2)/3	12/17/2	5	2	1	2	7	RCT	1 yr
			T	55.0 ± 12.2	21/12	5/(23/2)/3	12/15/6	9	2	0	3	6		1 yr
Zhang et al[27]	2020	China	W	51.7 ± 14.2	19/8	5/14/8	0/0/27	4	2	2	2	6	CCT	23.8 ± 9.9 mo
			T	51.4 ± 10.5	42/14	10/36/10	0/0/56	24	0	4	4	16		25.0 ± 10.4 mo
Ly[31]	2021	China	T	53.6 ± 11.9	51/37	5/69/6/8	22/51/15	1	11	1	NA	23	CCT	21.4 mo
			T + A	52.3 ± 11.1	120/77	5/150/10/32	67/113/17	3	30	1	NA	59		41.4 mo
Theilmann[23]	1994	Germany	ASA	56.8 ± 11	16/5	19/0/1/1	NA	NA	0	0	5/15	NA	RCT	3 mo
			T	49 ± 10	20/3	18/3/2/0	NA	NA	0	0	5/19	NA		3 mo
Tang et al[28]	2017	China	T	58.4 ± 6.5	14	NA	NA	NA	NA	NA	5	NA	CCT	1 yr
			T + A	58.4 ± 6.5	168	NA	NA	NA	NA	NA	17	NA		48 mo
Sauer[24]	1996	Germany	T + P	59 ± 7.5	17/7	18/3/3	12/12/0	NA	1	1	11	4	RCT	3 mo
			T	63 ± 4	16/9	15/8/2	10/15/0	NA	2	1	12	4		3 mo

AC = anticoagulation, CCT = clinical controlled studies, NA = not available, PVT = portal vein thrombosis, RCT = randomized controlled trial, T = TIPS alone (control group), TIPS = transjugular intrahepatic portosystemic shunt.
*Newly formed and progressive PVT after TIPS.
†Including bleeding conditions that need to be treated excluded variceal bleeding.
‡Including shunt stenosis and occlusion.

Table 2

Methodological quality assessment of randomized controlled trials: the Cochrane Collaboration's tool for assessing risk of bias.

Study (year)	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Sauer et al (1996)[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Wang et al (2016)[26]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Theilmann et al (1994)[25]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear

Table 3

Methodological quality assessment of cohort studies: the Newcastle-Ottawa Scale.

First author (year)	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Selection of exposure	Outcome of interest was fiter start of study	Control for important factor	Assessment of outcome	Sufficient follow-up	Adequacy of follow-up of cohorts
Lv (2021)[31]	★	★	★	★	★★	★	★	★
Tang et al (2017)[28]	★	★	☆	☆	★	★	★	★
Zhang et al (2020)[27]	★	★	☆	☆	★	★	★	☆

★Article is given a point for meeting the corresponding criterion.

☆Indicates no point.

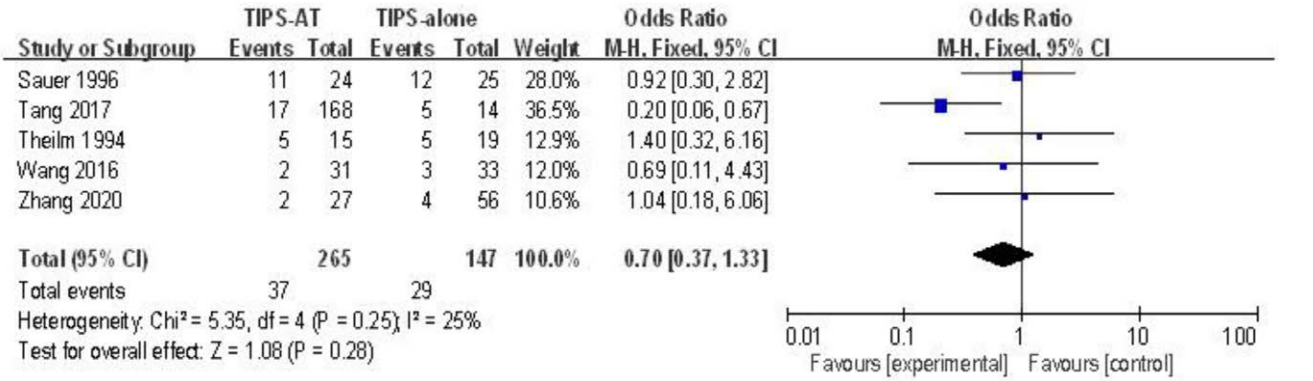

Figure 2. Forest plot of included studies demonstrating effective of AT + TIPS compare TIPS alone on stent dysfunction. AT = anticoagulation, CI = confidence interval, M-H = Mantel-Haenszel, TIPS = transjugular intrahepatic portosystemic shunting.

Incidence of hepatic encephalopathy (HE) rates were reported in 4 studies. A fixed-effects model was chosen for pooling the outcomes because no obvious heterogeneity was found in these studies (P = .88, I^2 = 0%). The results indicated that the HE rate of the combination therapy was not significantly different from that of TIPS alone (OR = 0.87, 95% CI 0.56–1.36, P = .55; Fig. 4).

Three studies reported data for recurrent portal vein thrombosis (PVT) rate. According to the results of heterogeneity evaluation among these studies (P = .36, I^2 = 3%), a fixed-effects model was chosen. The results showed that the recurrent PVT rate of the combination therapy was significantly lower than that of TIPS alone (OR = 0.39, 95% CI 0.18–0.84, P = .02; Fig. 5).

Studies were divided into subgroups according to following-up time (within 1 year, 1 year, and over 1 year) to show the comparison of efficacy and security between TIPS + anticoagulation and TIPS alone. For patients whose follow-up time was over 1 year, the combined therapy group had a lower OR value

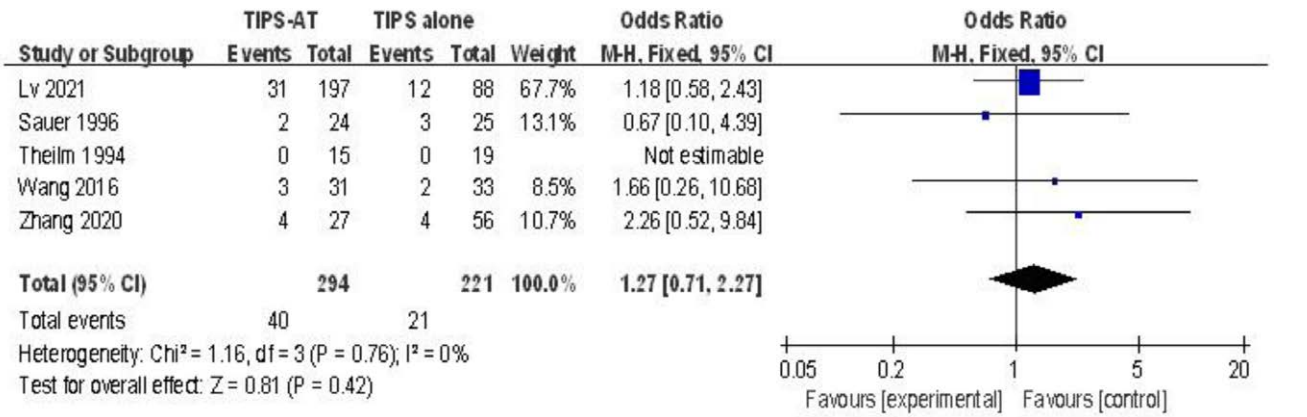

Figure 3. Forest plot of included studies demonstrating safety of AT + TIPS compare TIPS alone on bleeding rate. AT = anticoagulation, CI = confidence interval, M-H = Mantel-Haensze, TIPS = transjugular intrahepatic portosystemic shunting.

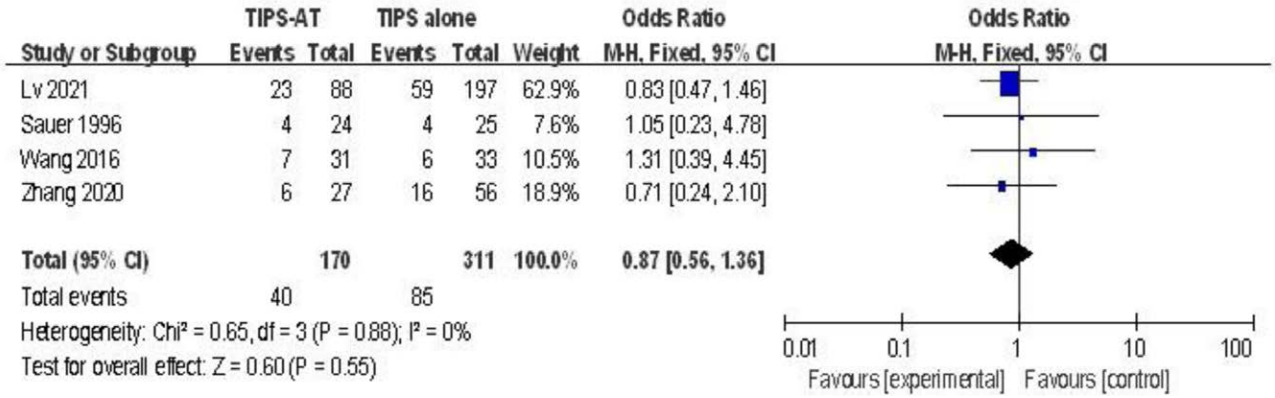

Figure 4. Forest plot of included studies demonstrating safety of AT + TIPS compare TIPS alone on incidence of HE. AT = anticoagulation, CI = confidence interval, M-H = Mantel-Haensze, TIPS = transjugular intrahepatic portosystemic shunting.

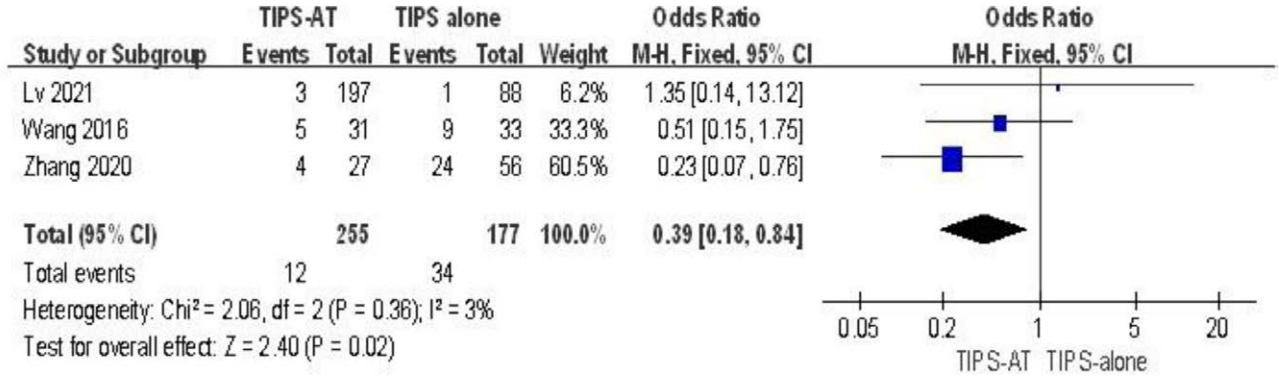

Figure 5. Forest plot of included studies demonstrating effectiveness of AT + TIPS compared to TIPS alone on appearing PVT after TIPS. AT = anticoagulation, CI = confidence interval, M-H = Mantel-Haensze, PVT = , TIPS = transjugular intrahepatic portosystemic shunting.

than the 1 year group in the presence of PVT (Fig. 6). Other indexes had no statistical significance.

No uniform standard exists for reporting complications among studies, and only descriptive analysis was performed in this meta-analysis. Minor complications occurred in all 6 included studies, including gingival hemorrhage, dizziness, and occasional hemorrhinia, which regressed or disappeared within a short time after support treatment. Five studies reported mortality, including liver failure, liver cancer, and recurrent variceal bleeding that did not relate to the TIPS or anticoagulation.

4. Discussion

Conventionally, cirrhosis was regarded as a hypocoagulable state.[16] However, recent studies changed this view.[17,18] In patients with cirrhosis, the intrahepatic coagulation and anticoagulation factors are severely impaired, but the other coagulation factors (such as von Willebrand factor and factor VIII and factor Xa) increase, which will cause an increase in thrombin production, and ultimately induce a state of hypercoagulable. Except for the potential risk of PVT, there is a tight connection between the activation of coagulation and the rapid development of liver fibrosis. Growing evidence showing the safety of anticoagulation in patients with cirrhosis indicates this method as well.[19,20] The most common complication of end-stage liver cirrhosis is portal hypertension. Cirrhotic portal hypertension is a multiorgan disease that manifests itself in a variety of ways involving HE, variceal bleeding, ascites, hepatorenal syndrome, among others.[21,22] TIPS has been shown to be a useful and minimally invasive treatment for portal hypertension and related complications,[21] but it brings some complications such as stent dysfunction, HE, and liver failure.[23] Considering the complications after TIPS creation, the efficacy and safety of anticoagulation deserve particular attention when it is combined with the TIPS procedure. In this meta-analysis, although post-TIPS anticoagulation was safe and did not significantly enhance the bleeding or HE risk, the initial aim of anticoagulation to improve stent patency was not achieved.

The RCTs conducted by by Sauer et al[24] and Theilmann et al[25] showed that the patency rate of stents was much lower than that in other studies[26–28] because they only used bare metal stents (Palmaz stent). Covered stents were more effective and safer than bare mental stent in TIPS.[29,30] Tang et al[28] indicated that the anticoagulation drugs significantly decreased the risk of stent stenosis compared to no medication (10% [17/168 vs 36% [5/14]; $P = .005$], which may be because of the lack of baseline comparability between groups.

For patients with PVT after TIPS, post-TIPS anticoagulation could decrease the risk of thrombosis, but in the study conducted by Zhang et al,[27] all included patients showed no existence of PVT before TIPS, but in other studies[26,31] patients were all complicated with PVT before TIPS, so when we exclude the study by Zhang et al[27], the results showed no significant difference (OR = 0.64, CI 95% 0.23–1.83, $P = .41$). Therefore, in patients combined with PVT, post-TIPS anticoagulation is not meaningful for the progression of PVT, because TIPS is sufficient. In contrast, in patients without preexisting PVT, anticoagulation could function and improve the patient's liver function. This is because

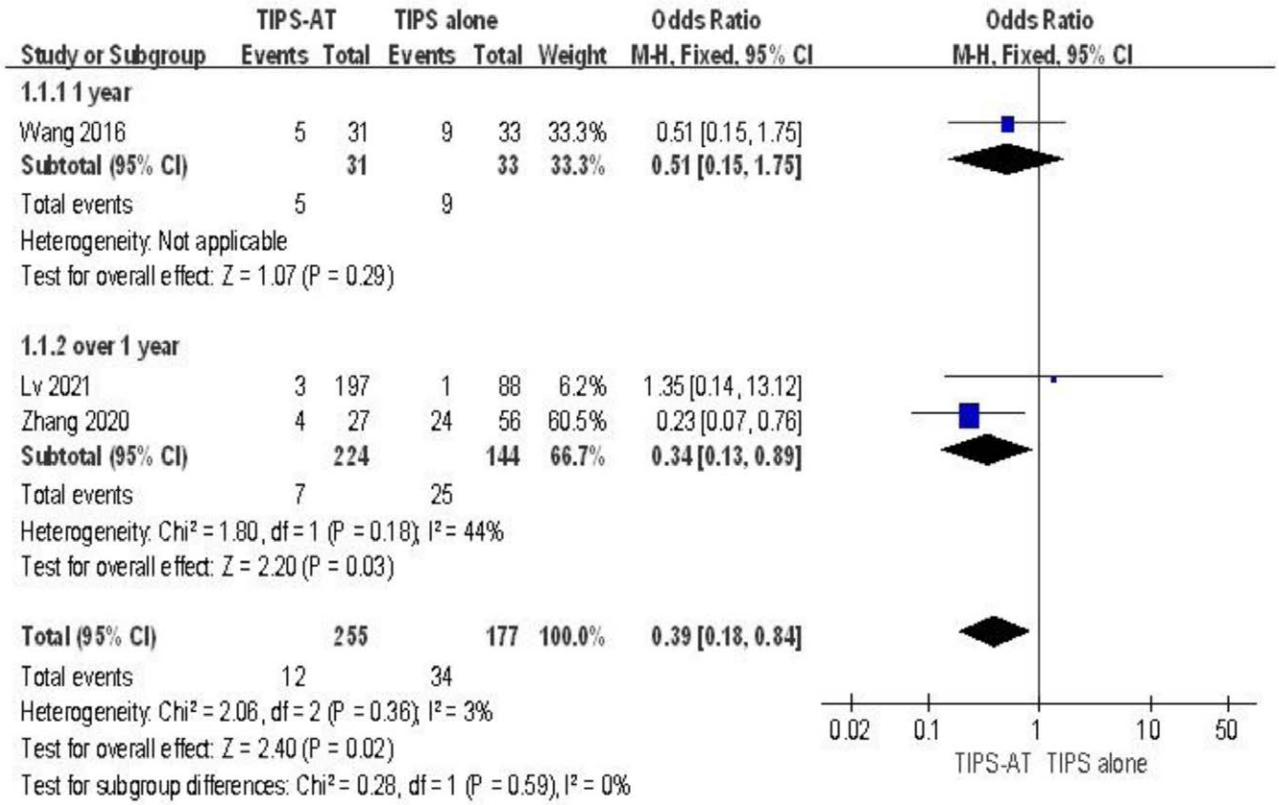

Figure 6. Forest plot of included studies demonstrating effective of different follow-up times. AT + TIPS compare TIPS alone on appearing PVT after TIPS. AT = anticoagulation, CI = confidence interval, M-H = Mantel-Haensze, TIPS = transjugular intrahepatic portosystemic shunting.

of the close relationship between the activation of coagulation and the rapid development of liver fibrosis.[32]

We found that anticoagulation following TIPS is safe in patients suffering from portal hypertension, but HE remains a problem, whether anticoagulation or not. The pathogenesis of HE has been incompletely understood since the first neuropathological descriptions of the disorder.[33] Post-TIPS HE is triggered by hepatocellular failure as well as portosystemic shunting and has been presented in 18% to 45% cirrhosis patients, and the incidence of refractory HE post-TIPS range between 3% and 8%,[34] which confirmed that a strong correlation exists between liver hemodynamics and the post-TIPS HE incidence.[35] Huang et al[36] reported that the cumulative HE rates were obviously lower in smaller stents. And Wang et al[26] showed that were spontaneous overt HE caused by the liver functions. Moreover, after TIPS, intervention of early positive dietary can obviously enhance the compliance of cirrhosis patients to consume a low-protein diet and lower the incidence of HE.[37] Therefore, better liver function reserve before TIPS, application of suitable diameter stent, and early positive dietary intervention can lower the incidence of HE.

The limitation of this meta-analysis was the relatively small sample size that included only 6 studies globally and unstandardized therapy (the type and dosage of anticoagulant drugs are not standardized, and there is no specific treatment protocol). Anticoagulant treatment measures were traditional antiplatelets and coumarins, and only 1 study[31] was conducted including direct oral anticoagulant (rivaroxaban). Additionally, 3 studies included were retrospective cohorts, which might have resulted in high heterogeneity.

In conclusion, the application of anticoagulant drugs in patients having portal hypertension anticoagulation seems not mandatory. However, post-TIPS anticoagulation can lower the risk of PVT in patients who do not have a PVT before the TIPS and do not increase the risk of bleeding and HE. In the future, large-scale and multicenter RCTs are needed to evaluate the safety, survival endpoints, and PVT recanalization of anticoagulation after TIPS.

Author contributions

Conceptualization: Xiaolin Zhang
Data curation: Pan Jiao, Xuying Chen
Investigation: Hongyan Zheng, Chao Li
Methodology: Xuying Chen, Jia Qin
Writing—original draft: Pan Jiao
Writing—review and editing: Xiaolin Zhang

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