**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 4522**

**Columns: META-ANALYSIS**

**TIPS improves liver-transplantation-free survival in cirrhosis with refractory ascites: An updated meta-analysis**

Bai M *et al*. TIPS improved survival in refractory ascites

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**Received:** July 4, 2013 **Revised:** October 8, 2013

**Accepted:** November 2, 2013

**Published online:**

**Abstract**

**AIM:** To compare the liver-transplantation-free (LTF) survival rates between transjugular intrahepatic portosystemic shunts (TIPS) and paracentesis patients groups by an updated meta-analysis that pools the effects of both number of deaths and time to death.

**METHODS:** MEDLINE, EMBASE, and the Cochrane Library were searched from the inception to October, 2012. LTF, liver transplantation, liver-disease-related death, non-liver-disease-related death, recurrent of ascites, hepatic encephalopathy (HE) and severe HE, and hepatorenal syndrome were assessed as outcomes. LTF survival was estimated by a hazard ratio (HR) with a 95%CI. Other outcomes were estimated by odds ratios (OR) with 95% CI. Sensitivity analyses were performed on the effects of potential outliers in the studies according to the risk of bias and the study characteristics.

**RESULTS:** Six randomized controlled trials with 390 patients were included. In comparison to paracentesis, TIPS significantly improved LTF survival (HR = 0.61, 95%CI: 0.46-0.82, *P* < 0.001). TIPS also significantly decreased liver-disease-related death (OR = 0.62, 95%CI: 0.39-0.98, *P* = 0.04), recurrent ascites (OR = 0.15, 95%CI: 0.09-0.24, *P* < 0.001) and hepatorenal syndrome (OR = 0.32, 95%CI: 0.12-0.86, *P* = 0.02). However, TIPS increased the risk of hepatic encephalopathy (OR = 2.95, 95%CI: 1.87-4.66, *P* = 0.02) and severe hepatic encephalopathy (OR = 2.18, 95%CI: 1.27-3.76, *P* = 0.005).

**CONCLUSION:** TIPS significantly improved the LTF survival of cirrhotic patients with refractory ascites and decreased the risk of recurrent ascites and hepatorenal syndrome with the cost of increased risk of hepatic encephalopathy compared with paracentesis. Further studies are warranted to validate the survival benefit of TIPS in clinical practice setting.

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**Key words:** Transjugular intrahepatic portosystemic shunt; Ascites; paracentesis; Survival; Meta-analysis

**Core tip:** We evaluated the effects of transjugular intrahepatic portosystemic shunts (TIPS) *vs* paracentesis on the liver-transplantation-free (LTF) survival in patients with cirrhosis and refractory ascites. Both the number of deaths and the time to death were considered in the present meta-analysis. We found out that TIPS significantly improved LTF survival, liver-disease-related death, recurrence of ascites, and hepatorenal syndrome; however, TIPS increased the post-TIPS hepatic encephalopathy risk.

Bai M, Qi XS, Yang ZP, Yang M, Han GH, Fan DM. TIPS improves liver-transplantation-free survival in cirrhosis with refractory ascites: an updated meta-analysis.

**Available from:**

**DOI:**

**INTRODUCTION**

Refractory ascites is observed in 5%-10% of advanced cirrhosis cases and has a one-year mortality rate of 20%-50%[[1-3](#_ENREF_1)]. Liver transplantation is the only definitive treatment for these patients, but the procedure is limited by donor liver resources and high cost. Repeated large-volume or total-volume paracentesis with intravenous albumin infusion is currently recommended as the first-line treatment for patients with refractory ascites[[4](#_ENREF_4),[5](#_ENREF_5)]. Although therapeutic paracentesis relieves symptoms rapidly with few technical complications, it does not correct the underlying mechanisms of ascites formation and has negative effects on systemic hemodynamics and renal function[[2](#_ENREF_2)]. Although surgical portal-caval shunts are effective in the treatment of refractory ascites by reducing the portosystemic pressure gradient (PSG), these shunts have been abandoned because of the high post-operation morbidity and mortality rates[[6](#_ENREF_6)]. Transjugular intrahepatic portosystemic shunts (TIPS) decompress the PSG and correct the formation of ascites in most cases without the need for general anesthesia avoiding the risk of major surgery[[4](#_ENREF_4),[5](#_ENREF_5),[7](#_ENREF_7)].

Several randomized controlled trials (RCTs) have compared uncovered TIPS with paracentesis in the management of refractory ascites in cirrhosis patients[[8-13](#_ENREF_8)]. Despite the demonstration by these studies that TIPS was effective in controlling ascites, it was associated with an increased risk of hepatic encephalopathy (HE) and controversial results in survival benefits[[8-13](#_ENREF_8)]. Based on the data reported in the literatures about the five available RCTs[[8-12](#_ENREF_8)], four previous meta-analyses concluded that TIPS could not significantly decrease patient mortality when compared with paracentesis[[6](#_ENREF_6),[14-16](#_ENREF_14)]. It is notable that all four of these meta-analyses simply combined the number of deaths without considering the effect of the time to death. Thereafter, a meta-analysis by Salerno *et al*[[17](#_ENREF_17)] pooled individual patient data from four RCTs to overcome this inappropriate survival analysis and demonstrated that TIPS significantly improved liver-transplantation-free (LTF) survival. However, the impossibility of collecting individual patient data from all of the identified RCTs is a potential drawback for the meta-analysis conducted by Salerno *et al*[[17](#_ENREF_17)] and Higgins *et al*[[18](#_ENREF_18)]. Most likely, the inconsistent conclusions among these meta-analyses were due in part to the hesitation of recommending TIPS as the primary therapy[[4](#_ENREF_4),[5](#_ENREF_5)]. After these meta-analyses, one additional RCT was published in 2011[[13](#_ENREF_13)]. Thus, it is useful to conduct an updated meta-analysis with an appropriate survival analysis method to evaluate the effect of TIPS on LTF survival in cirrhosis patients with refractory ascites.

The purpose of the present study was to update the previous meta-analyses to evaluate the effect of TIPS on patient survival by appropriate survival analysis. LTF survival was employed as the primary endpoint. Additionally, the causes of death, the number of patients who underwent liver transplantation, the frequency of recurrent ascites, the risk of HE, and the incidence of hepatorenal syndrome were evaluated.

**MATERIALS AND METHODS**

***Searching for and selection of studies***

Eligible studies were identified by a comprehensive search of MEDLINE, EMBASE, and the Cochrane Library from their inceptions to October 2012. The following key words were used in our search: ascites, TIPS, paracentesis, and RCT. Reference lists in primary study publications, review articles, editorials, and the proceedings of international congresses were also manually examined.

The following criteria were employed for study selection: (1) study publication: full-text in the English language; (2) study design: RCT; (3) study participants: cirrhotic patients with refractory or recurrent ascites; (4) study interventions: TIPS *vs* large-volume or total-volume paracentesis (with/without intravenous albumin); (5) one or more of the following outcomes estimated: LTF survival, liver transplantation, cause of death (liver-disease-related death or non-liver-disease-related death), recurrence of ascites, HE, and hepatorenal syndrome.

***Outcomes and definitions***

LTF survival (primary endpoint): patient survival without liver transplantation. Liver transplantation: number of patients who underwent liver transplantation. Liver-disease-related death: number of patients who died of liver-disease-related causes, including hepatic failure, variceal bleeding, hepatorenal syndrome, and hepatocellular carcinoma. Non-liver-disease-related death: number of patients who died of non-liver-disease-related causes, such as sepsis, cerebrovascular accident, and cardiac dysfunction[[16](#_ENREF_16)]. Recurrence of ascites: number of patients who required a new paracentesis after the interventions. HE and severe HE: number of patients who presented with HE after intervention and the number of patients with severe HE (grades III/IV HE according to Conn *et al*[[19](#_ENREF_19)] or equivalent classification), respectively. Hepatorenal syndrome: number of patients with type 1 or type 2 hepatorenal syndrome.

***Risk of bias assessment***

According to the Cochrane risk of bias tool[[18](#_ENREF_18)], the following six items were used in the assessment of risk of bias: generation of random allocation sequence, concealment of allocation sequence, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

***Data extraction***

Determination of trial eligibility and extraction of data were performed independently by two investigators (Bai M and Qi X). Agreements on disagreements were made through discussion. The following data were extracted: patient selection criteria, number of patients screened, number of patients allocated to each study group, detailed information of interventions, study design, duration of follow-up, age, gender, etiology of cirrhosis, Child-Pugh class and score, HE, history of GI bleeding, serum bilirubin, serum albumin, serum creatinine, serum sodium, technical results, method of randomization, allocation concealment, blinding, analysis methods, description of drop-outs, and detailed data of outcome measures.

***Statistical analysis***

For outcomes reported as time-to-event variables, the hazard ratios (HRs) are the most appropriate measures to be pooled because both the number of events and the time to events are important[[20](#_ENREF_20),[21](#_ENREF_21)]. The Log (HR) and its standard error for a study are needed to evaluate the pooled HRs. These values were calculated according to the methods described by Parmar *et al*[[22](#_ENREF_22)] and Tierney *et al*[[20](#_ENREF_20)]. In summary, randomization ratio, number of analyzed patients, number of observed events, number of expected events, HR and its 95%CI, logrank variance, logrank observed-minus-expected events, and *P*-value of logrank test were all used when available. When these variables were insufficient, Kaplan-Meier curves were employed to calculate the Log (HR) and its standard error. These calculations were accomplished by the calculation spreadsheet provided by Tierney *et al*[[20](#_ENREF_20)]. For outcomes reported as binary variables, the numbers of observed events were extracted and odds ratios (OR) were used to evaluate the pooled effect. Heterogeneity was assessed by the *χ2* test and the *I2* statistic. Upon confirmation that significant heterogeneity was absent, trials were combined using a fixed-effect model. Otherwise, the results of both fixed-effect and random-effect model were reported. To assess the stability of results, sensitivity analyses were performed on the effects of potential outlier studies according to the risk of bias and the study characteristics. A p-value of 0.05 was adopted as the criterion for statistical significance. All analyses were performed using Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2011.

**RESULTS**

Among the 155 identified publications, 40 duplicates were excluded. The remaining 115 papers underwent detailed examination, and 109 were subsequently excluded (Figure 1). Six RCTs including 390 patients reported between 1996 and 2011 were ultimately included in the meta-analysis[[8-13](#_ENREF_8)].

***Characteristics of the selected trials***

The characteristics of the six included RCTs are summarized in Table 1. The control treatment was large-volume paracentesis[[9](#_ENREF_9),[12](#_ENREF_12),[13](#_ENREF_13)] and total paracentesis[[8](#_ENREF_8),[10](#_ENREF_10),[11](#_ENREF_11)] in three studies each. Intravenous albumin infusion was prescribed after paracentesis in four studies[[8](#_ENREF_8),[11-13](#_ENREF_11)], employed when clinically indicated in one study[[9](#_ENREF_9)], and used when patients had a creatinine clearance of less than 60 mL/min in the remaining study[[10](#_ENREF_10)]. In five studies[[8](#_ENREF_8),[9](#_ENREF_9),[11-13](#_ENREF_11)], refractory ascites was defined according to the criteria reported by the International Ascites Club in 1996[[23](#_ENREF_23)]. Two trials included patients with recidivant ascites, which was defined as more than three episodes of tense ascites within a 12-mo period despite the administration of standard treatment[[9](#_ENREF_9),[12](#_ENREF_12)].

Five of the studies employed survival as the primary endpoint[[8](#_ENREF_8),[9](#_ENREF_9),[11-13](#_ENREF_11)], and one study used recurrent ascites as such[[10](#_ENREF_10)]. The frequencies of recurrence of ascites, HE, and liver transplantation were reported in all studies. Severe HE and hepatorenal syndrome were reported in four[[8](#_ENREF_8),[10-12](#_ENREF_10)] and two trials[[8](#_ENREF_8),[12](#_ENREF_12)], respectively.

***Characteristics of patients in the selected trials***

Table 2 summarizes the characteristics of the patients in the six selected trials. The numbers of randomized patients were at least 60 in all trials except for the study by Lebrec *et al*[10], which only enrolled 25 patients. The percentage of Child-Pugh C patients was 26%-33% in four studies[[8-10](#_ENREF_8),[13](#_ENREF_13)], and 76% in the study by Salerno *et al*[[12](#_ENREF_12)]. Baseline serum concentrations of bilirubin, albumin, creatinine, and sodium were not significantly different between the TIPS and paracentesis groups in all studies.

***Technical results***

Table 3 presents the technical results of the included RCTs. The TIPS technical success rate was at least 89% in five studies[[8](#_ENREF_8)[9](#_ENREF_9),[11-13](#_ENREF_11)] but was only 77% in the study by Lebrec *et al*[[10](#_ENREF_10)]. The average post-TIPS PSGs were 14 mmHg in one study[[10](#_ENREF_10)], and lower than 12 mmHg in all others[[8](#_ENREF_8),[9](#_ENREF_9),[11-13](#_ENREF_11)]. Severe procedure-related complications were reported in three trials, including cardiac arrhythmias[[10](#_ENREF_10)], hemolytic anemia[[8](#_ENREF_8)], and cerebrovascular embolism[[12](#_ENREF_12)]. The proportions of TIPS dysfunction ranged from 30% to 87%. The TIPS-assisted patency rates were higher than 80% in five studies[[8](#_ENREF_8),[9](#_ENREF_9),[11-13](#_ENREF_11)]. However, more than 50% of the TIPS patients in the study by Lebrec *et al*[[10](#_ENREF_10)] did not have TIPS-assisted patency during the follow-up.

***Risk of bias assessment***

All of the studies were unblinded to participants, personnel, and outcome assessment, employed intention-to-treat analysis with description of drop-outs, did not demonstrate the method of generation of random allocation sequence, and reported all of the outcomes described in the methods section (Table 4). The study by Rössle *et al*[[9](#_ENREF_9)] did not state the concealment of the allocation sequence, while the others concealed the randomization numbers with sealed opaque envelopes (Table 4)[[8](#_ENREF_8),[10-13](#_ENREF_10)].

***LTF survival***

LTF survival was directly reported in four studies[[8](#_ENREF_8),[9](#_ENREF_9),[11](#_ENREF_11),[12](#_ENREF_12)]. Because no patient underwent liver transplantation during the follow-up in the study by Narahara *et al*[[13](#_ENREF_13" \o "Narahara, 2011 #88)], the LTF survival in this study was certainly equal to the overall survival]. Thus, the LTF survival HRs were available in five RCTs[[8](#_ENREF_8),[9](#_ENREF_9),[11-13](#_ENREF_11)]. Compared with the paracentesis group, the LTF survival of the patients in the TIPS group was significantly increased in two studies[[12](#_ENREF_12),[13](#_ENREF_13)], was almost significantly increased in one study[[9](#_ENREF_9)], and was nearly equivalent in two studies[[8](#_ENREF_8),[11](#_ENREF_11)]. After pooling the five studies with 365 patients, the estimated LTF survival was significantly in favor of the TIPS group using a fixed-effects model (HR = 0.61, 95%CI: 0.46-0.82, *P* < 0.001) without significant heterogeneity (*I2* = 19%, *P-*value for heterogeneity = 0.30, Figure 2).

In the study by Lebrec *et al*[[10](#_ENREF_10)] patient LTF survival was not assessed. Only one patient in the paracentesis group underwent liver transplantation during follow-up. Thus, the estimated LTF survival of the patients in the paracentesis group would be higher than the overall survival, and the estimated LTF survival of the patients in the TIPS group would be similar to the overall survival. Therefore, we performed an additional sensitivity analysis that included the overall survival of this study to estimate a conservative pooled HR of LTF survival. The results significantly favored the TIPS group that underwent fixed-effect modeling (HR = 0.68, 95%CI: 0.51-0.89, *P* = 0.006, Figure 2) and tended to favour the TIPS group that underwent random-effect modeling (HR = 0.72, 95%CI: 0.46-1.13, *P* = 0.16, *I2* = 61%, *P-*value for heterogeneity = 0.03, Figure 2).

The subgroup analysis that included the two studies with both refractory and recidivant ascites patients[[9](#_ENREF_9),[12](#_ENREF_12)] demonstrated that LTF survival significantly favored TIPS without significant heterogeneity (HR = 0.52, 95%CI: 0.33-0.83, *P* = 0.006, *I2* = 0%, *P-*value for heterogeneity = 0.55, Figure 3). Furthermore, the subgroup analysis that included the three studies with only refractory ascites patients[[8](#_ENREF_8),[11](#_ENREF_11),[13](#_ENREF_13)] also demonstrated that LTF survival significantly favored TIPS without significant heterogeneity (HR = 0.68, 95%CI: 0.47-0.97, *P* = 0.04, *I2* = 48%, *P*-value for heterogeneity = 0.15, Figure 3).

***Other outcomes***

The proportions of liver-disease-related death were 30% and 40% in the TIPS and paracentesis groups, respectively. The OR of liver-disease-related death was 0.62 without significant heterogeneity (95%CI: 0.39-0.98, *P* = 0.04, *I2* = 31%, *P-*value for heterogeneity = 0.21, Table 5). The pooled proportions of non-liver-disease-related death were not significant different between the two groups (OR = 1.27, 95%CI: 0.68-2.38, *P* = 0.46, *I2* = 0%, *P-*value for heterogeneity = 0.64, Table 5).

The proportions of patients who underwent liver transplantation ranged from 0% to 30%[[8-12](#_ENREF_8)]. No significant difference was observed between the TIPS and the paracentesis groups in the numbers of patients who underwent liver transplantation (OR = 0.94, 95%CI: 0.53-1.67, *P* = 0.83, *I2* = 0%, *P-*value for heterogeneity = 0.94, Table 5).

TIPS was significantly more effective on the reduction of recurrent ascites than paracentesis in four of the included RCTs[[8](#_ENREF_8),[9](#_ENREF_9),[11](#_ENREF_11),[12](#_ENREF_12)] but was not significantly more effective in the other two studies[[10](#_ENREF_10),[13](#_ENREF_13)]. The overall proportions of patients with recurrent ascites were 51% for the TIPS group and 87% for the paracentesis group (OR = 0.15, 95%CI: 0.09-0.24, *P* < 0.001). Values for this variable showed no statistically significant heterogeneity (*I2* = 2%, *P-*value for heterogeneity = 0.40, Table 5).

HE occurred more frequently in the patients who underwent TIPS procedures (51% *vs* 29%). The OR of any degree of HE between the two groups was 2.95 (95%CI: 1.87-4.66, *P* < 0.001) without significant heterogeneity (I2 = 11%, *P-*value for heterogeneity = 0.35, Table 5). Patients treated with TIPS presented significantly higher risk of severe HE than those treated with paracentesis (39% *vs* 23%, OR = 2.18, 95%CI: 1.27-3.76, *P* = 0.005, Table 5).

Hepatorenal syndrome was assessed in two studies with 136 patients[[8](#_ENREF_8), [12](#_ENREF_12)] and was less frequently observed in the TIPS group (9% *vs* 24%, OR = 0.32, 95%CI: 0.12-0.86, *P* = 0.02, *I2* = 0%, *P-*value for heterogeneity = 0.34, Table 5).

***Potential outlier studies and sensitivity analyses***

The study by Lebrec *et al*[[10](#_ENREF_10)] was considered an outlier for the following two reasons: (1) it was the only trial that employed survival as a secondary endpoint; and (2) it achieved the lowest successful TIPS placement rate, the highest post-TIPS PSG, and the lowest TIPS-assisted patency rate, indicating a less refined TIPS technique compared with the subsequent trials published 4-15 years later[[6](#_ENREF_6),[8](#_ENREF_8),[9](#_ENREF_9),[11-13](#_ENREF_11)]. Sensitivity analyses that excluded this trial yielded very similar results (Figure 2, Table 5).

**DISCUSSION**

This updated meta-analysis, including appropriate survival analysis of six RCTs, shows that TIPS significantly improves LTF survival and decreases the risk of liver-disease-related death in cirrhotic patients with refractory ascites. Additionally, the rates of recurrent ascites and hepatorenal syndrome were significantly reduced, but the risk of HE was significantly increased in the patients who underwent TIPS in comparison to those who underwent paracentesis.

Four previously reported meta-analyses only evaluated the number of deaths without considering the effect of time to deaths. All of them showed similar mortality between the TIPS group and the paracentesis group[[6](#_ENREF_6),[14-16](#_ENREF_14)]. According to the PRISMA Statement, the HR is the most appropriate measure to be pooled, because both the number of deaths and the time to the death are important to time-to-event outcomes[[21](#_ENREF_21)]. For example, in the meta-analysis by D'Amico *et al*[[6](#_ENREF_6)], the pooled mortality was not significantly different (OR = 0.90, 95%CI: 0.44-1.81). Despite excluding the outlier RCT by Lebrec *et al*[[10](#_ENREF_10)] which was the only trial that favored paracentesis on survival, the pooled mortality of the remaining four RCTs was still not significantly different (OR = 0.74, 95%CI: 0.40-1.37)[[6](#_ENREF_6)]. However, if the HRs of the same four RCTs were pooled, the benefit of TIPS on survival was significant (HR = 0.68, 95%CI: 0.50-0.94). This heterogeneity suggested that these two groups of patients had similar numbers of deaths but different survival times. Thus, the HRs were pooled in our present meta-analysis[[20](#_ENREF_20),[21](#_ENREF_21)]. Conversely, because liver transplantation has a very important role in the survival of patients with end-stage liver cirrhosis, this meta-analysis evaluated LTF survival, which isolated the important effect of liver transplantation on survival.

The accumulated LTF survival was available for five of the six included RCTs[[8](#_ENREF_8),[9](#_ENREF_9),[11-13](#_ENREF_11)]. All five of these trials evaluated LTF survival using a Kaplan-Meier curve and log-rank test, which gave us facilities to estimate survival difference between the TIPS group and the paracentesis group by pooling the HRs.

After pooling the HRs of the five RCTs, the estimated LTF survival was significantly improved by TIPS compared with paracentesis. Similar improvements were observed when the study by Lebrec *et al* was excluded as an outlier. Furthermore, two of the six RCTs included patients with recidivant ascites (three recurrences of ascites within 12 mo), which represents an earlier stage and has a potentially better prognosis than patients with refractory ascites (recurrence within 4 wk)[[23](#_ENREF_23)]. Thus, subgroup analyses were performed and showed that TIPS significantly improved LTF survival regardless of if recidivant ascites patients were included or not in the trials.

In a previous study that showed relatively poor survival with TIPS[[10](#_ENREF_10)], the technical failure rate was more than twofold higher than the remaining five RCTs (23% *vs* < 11%)[[8](#_ENREF_8),[9](#_ENREF_9),[11-13](#_ENREF_11)], and all three of the patients with unsuccessful TIPS procedures died within 3 mo after TIPS. All of these characteristics obviously had a negative contribution to the survival of the TIPS group. We pooled the overall survival of this study in a sensitivity analysis to demonstrate a conservative result, which also showed an improvement of LTF survival in the TIPS group. All of these results suggest that TIPS could improve LTF survival in selected cirrhotic patients with refractory ascites.

An improvement of LTF survival was also reported in a previous meta-analysis that pooled individual patient data from four RCTs[[17](#_ENREF_17)]. The present study confirmed the effect of TIPS on LTF survival with appropriate survival analysis by pooling data from the literature from six available RCTs. The consistency of survival improvement in these two meta-analyses with different methods makes us more confident that TIPS can do better than paracentesis in the management of refractory ascites.

The improvement of LTF survival in the patients who underwent a TIPS procedure is mostly attributed to the reduction of liver-disease-related deaths, especially deaths related to severe complications of portal hypertension. Three studies reported the number of deaths caused by massive variceal bleeding, and all three of the studies showed a lower risk of this type of death in the TIPS group[[9-11](#_ENREF_9)]. Another cause of the improved LTF survival is that TIPS prolonged the time to liver transplantation, which was reported by two of the enrolled trials[[11](#_ENREF_11),[12](#_ENREF_12)].

TIPS dramatically reduced the incidences of recurrent ascites in the present meta-analysis. This result was consistent with the results of previous meta-analyses[[6](#_ENREF_6),[14-17](#_ENREF_14)]. TIPS procedure also has a positive effect on renal function[[2](#_ENREF_2),[24](#_ENREF_24)]. Thus, it is reasonable that the risk of developing hepatorenal syndrome was reduced by TIPS by more than a half when compared to paracentesis (from 24% to 9%). Because spontaneous bacterial peritonitis and hyponatremia occurs more frequently in patients with ascites, TIPS most likely can reduce these events by eliminating the ascites and improving renal function[[4](#_ENREF_4),[17](#_ENREF_17)]. Because hepatorenal syndrome, spontaneous bacterial peritonitis, and hyponatremia are usually associated with high mortality, TIPS most likely improves patient survival by reducing these complications[[4](#_ENREF_4),[17](#_ENREF_17)].

Furthermore, the pooled results showed that TIPS increased the risk of HE and severe HE by almost twofold in comparison to paracentesis (HE: 51% *vs* 29%, severe HE: 39% *vs* 23%). Similar results were also found in the sensitivity analyses. Although almost all of the post-TIPS HE could be successfully managed by medical treatment[[8-13](#_ENREF_8),[25](#_ENREF_25),[26](#_ENREF_26)], the reduction level of PSG should be considered with caution, especially in patients with high post-TIPS HE risk (old age, previous HE or high Child-Pugh class)[[27-29](#_ENREF_27)].

One limitation of this meta-analysis is that all of the included RCTs were open-label designed, which could most likely bias the results by affecting the judgment of actual outcomes, especially subjective outcomes (*i.e.,* HE)[[30](#_ENREF_30)]. Because blinding is unavailable for these two obviously different interventions, the results presented are most likely the highest quality evidences we can currently obtain. Furthermore, only one of the six RCTs provided raw data by Child-Pugh class[[8](#_ENREF_8)]. Thus, the subgroup analysis according to liver function is not evaluated in this meta-analysis. However, patient survival was improved by TIPS in both the study including a high proportion of Child-Pugh C patients (76%)[[12](#_ENREF_12)] and the study including a low proportion of Child-Pugh C patients (33%)[[12](#_ENREF_12)]. This result indicates that TIPS may be superior to paracentesis regardless of Child-Pugh classes. Additionally, only 48% (median, range from 21% to 77%, Table 1) of the screened patients could be included in the RCTs, which suggests that studies based on real clinical practice scenarios are needed to validate the universal nature of the results of the present meta-analysis.

In conclusion, this updated meta-analysis of literature data from six RCTs shows that TIPS significantly improves the LTF survival, the control of refractory ascites, and the prevention of hepatorenal syndrome in patients with cirrhosis and refractory ascites. The increased risk of HE is a major drawback of the TIPS procedure. Further studies based on real clinical practice scenarios are needed.

**COMMENTS**

***Background***

The survival benefit of transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients with refractory ascites requires further evaluations. Previous meta-analyses of the data reported in the literature considered only the number of deaths, but not the time to death. Furthermore, an additional study on this subject has been recently published. The primary aim is to compare the liver-transplantation-free (LTF) survival between TIPS and paracentesis groups by pooling the effects of both number of deaths and time to death.

***Research frontiers***

A meta-analysis was conducted to evaluate the effectiveness of TIPS *vs* paracentesis in patients with cirrhosis and refractory ascites.

***Innovations and breakthroughs***

In the present meta-analysis of randomized controlled trials, it was observed that TIPS significantly improved the LTF survival of patients with cirrhosis and refractory ascites. Additionally, TIPS was superior to paracentesis in liver-disease-related death, recurrence of ascites, and hepatorenal syndrome. However, patients who underwent TIPS were associated with an increased risk of hepatic encephalopathy (HE) and severe HE.

***Applications***

The results of the present meta-analysis suggest that TIPS could potentially be recommended as the first-line treatment for patients with cirrhosis and refractory ascites.

***Terminology***

LTF survival (primary endpoint): patient survival without liver transplantation. Liver-disease-related death: number of patients who died of liver-disease-related causes including hepatic failure, variceal bleeding, hepatorenal syndrome, and hepatocellular carcinoma. Recurrence of ascites: number of patients requiring a new paracentesis after the interventions. HE and severe HE: the number of patients presenting with HE after intervention and the number of patients with severe HE (grades III/IV HE or equivalent classification), respectively. Hepatorenal syndrome: number of patients with type 1 or type 2 hepatorenal syndrome.

***Peer review***

The effects of TIPS *vs* paracentesis for patients with cirrhosis and refractory ascites have been investigated for more than two decades. The present meta-analysis included the updated data and found out that TIPS could improve the LTF survival rate and alleviate recurrence of ascites, hepatorenal syndrome, and liver-disease-related death alone with an increase in HE risk. The paper is exciting and important and brings forth new knowledge.

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**P-Reviewer:** Busk TM **S-Editor:** Zhai HH **L-Editor: E-Editor:**

**Figure 1 Randomized controlled trials selection flowchart.** RCT: Randomized controlled trial.

**Figure 2 Liver-transplantation-free survival in trials compared transjugular intrahepatic portosystemic shunt with paracentesis.** Forest plots represent HR and 95%CI.

**Figure 3 Subgroup analyses of liver-transplantation-free survival in trials compared transjugular intrahepatic portosystemic shunt with paracentesis.** Forest plots represent HR and 95%CI.

**Table 1 Characteristics of the included studies**

RCT: Randomized controlled trial; NR: Not reported; TIPS: Transjugular intrahepatic portosystemic shunt; Para: Paracentesis; TP: Total paracentesis; LVP: Large-volume paracentesis; HE: Hepatic encephalopathy; PVT: Portal vein thrombosis; HVT: Hepatic vein thrombosis; HCC: Hepatocellular carcinoma; INR: International normalized ratio; PLT: Platelet count; GI: Gastrointestinal; HRS: Hepatorenal syndrome.

**Table 2 Characteristics of the patients in the included studies**

All of the comparisons between groups were not statistic significant (*P* > 0.05) in any of the included studies. TIPS: Transjugular intrahepatic portosystemic shunt; HE: Hepatic encephalopathy; NR: Not reported; GI: Gastrointestinal.

**Table 3 Technical results of the included studies *n* (%)**

Data are expressed as absolute numbers (percentage) or mean ± SD. TIPS: Transjugular intrahepatic portosystemic shunt; PSG: Portosystemic pressure gradient.

**Table 4 Risk of bias assessment of the included studies**

NR: Not reported.

**Table 5 Results of each study and pooled estimations of recurrence of ascites, hepatic encephalopathy, severe hepatic encephalopathy, gastrointestinal bleeding and hepatorenal syndrome with sensitivity analysis**

a*P* < 0.05, b*P* < 0.01; No significant heterogeneity was observed among these meta-analyses (*I2*= 0-31%, *P* > 0.05). All of these meta-analyses were performed under fixed-effect model. TIPS: Transjugular intrahepatic portosystemic shunt; Para: Paracentesis; HE: Hepatic encephalopathy.