Research Article

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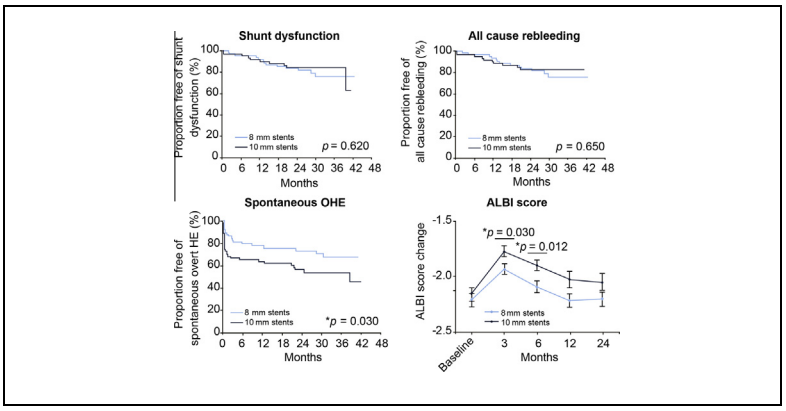
# Eight millimetre covered TIPS does not compromise shunt function but reduces hepatic encephalopathy in preventing variceal rebleeding

## Graphical abstract




## Highlights

- Shunt patency and rebleeding rate were non-different between groups.
- 8 mm group showed lower spontaneous overt hepatic encephalopathy risk.
- Liver function reserve was better in 8 mm stents group.

## Authors

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## Lay summary

The optimal diameter for transjugular intrahepatic portosystemic shunt (TIPS) remained uncertain. This study showed that TIPS with 8 mm covered stents did not compromise shunt patency, or influence the efficacy of variceal rebleeding prevention compared to TIPS with 10 mm stents, but reduced the risk of spontaneous overt hepatic encephalopathy and the incidence of severe encephalopathy. Moreover, liver function reserve was also better in the 8 mm stents group, suggesting that 8 mm TIPS stents should be preferred for the prevention of variceal rebleeding in cirrhotic patients.

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Research Article

EASL JOURNAL OF HEPATOLOGY

Cirrhosis

# Eight millimetre covered TIPS does not compromise shunt function but reduces hepatic encephalopathy in preventing variceal rebleeding

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**Background & Aims**: Currently, there are no recommendations in guidelines concerning the preferred diameter of stents for transjugular intrahepatic portosystemic shunt (TIPS), owing to the lack of adequate evidence. We therefore compared 8 mm stents with 10 mm stents, to evaluate whether 8 mm stents would achieve similar shunt function, with less hepatic encephalopathy (HE) and better liver function.

**Methods**: Cirrhotic patients were randomly assigned to receive TIPS with an 8 mm or 10 mm covered stent to prevent variceal rebleeding. The primary endpoint was shunt dysfunction. All-cause rebleeding, orthotopic liver transplantation (OLT)-free survival, their composite endpoint, overt HE (overall and spontaneous) and liver function were designated as the secondary endpoints.

**Results**: From July 2012 to January 2014, 64 and 63 patients were allocated to the 8 mm and 10 mm groups, respectively. During a median follow-up of 27 months in both arms, dysfunction rates (16% *vs.* 16% at two years, $p = 0.62$), two-year rebleeding (16% *vs.* 17%, $p = 0.65$), OLT-free survival (95% *vs.* 86%, $p = 0.37$), and the composite endpoint ($p = 0.62$) were not statistically different between the groups. Despite a marginal decrease in overall overt HE, there were significantly fewer spontaneous overt HE incidents in the 8 mm group within two years (27% *vs.* 43%, $p = 0.03$), with a risk reduction of 47%. Notably, patients receiving 8 mm stents also developed less hepatic impairment.

**Conclusions**: TIPS with 8 mm covered stents showed similar shunt function to TIPS with 10 mm stents, but halved the risk of spontaneous overt HE and reduced hepatic impairment. Therefore, 8 mm TIPS stents should be preferred for the prevention of variceal rebleeding in cirrhotic patients.

**Lay summary:** The optimal diameter for transjugular intrahepatic portosystemic shunt (TIPS) remained uncertain. This study showed that TIPS with 8 mm covered stents did not compromise shunt patency, or influence the efficacy of variceal rebleeding prevention compared to TIPS with 10 mm stents, but reduced the risk of spontaneous overt hepatic encephalopathy and the incidence of severe encephalopathy. Moreover, liver function reserve was also better in the 8 mm stents group, suggesting that 8 mm TIPS stents should be preferred for the prevention of variceal rebleeding in cirrhotic patients.



## Introduction

Since its introduction into clinical practice, transjugular intrahepatic portosystemic shunt (TIPS) has been recommended by guidelines and Baveno consensus.[1–7] TIPS has been used widely in patients with portal hypertension complications not amenable to standard therapy for nearly 30 years.[8] However, no consensus has been reached regarding the key issue of stent diameter selection,[5,9] owing to the theoretical dilemma that larger stents would achieve better shunt patency and more sufficient portal decompression, but increase the risk of hepatic encephalopathy (HE), and vice versa.[10] Early studies suggested that a stent diameter greater than the general calibre of the portal and hepatic veins would result in excessive risk of HE, without additional benefits

Keywords: Transjugular intrahepatic portosystemic shunt; Variceal bleeding; Liver cirrhosis; Stent diameter; Hepatic encephalopathy.

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from portal decompression,[11,12] which was the rational for using 10 mm stents rather than larger ones. Unfortunately, the HE incidence has remained relatively high, ranging from 21%–53% at one year, even since the advent of covered stents in 2004 (Table S1).[13–19]

To explore the possibility of further reducing the incidence of HE, the only study to date comparing 8 mm and 10 mm stents in TIPS was conducted in 2010. It was prematurely stopped, before any difference could be detected, due to unsatisfactory shunt dysfunction in the small stent arm.[20] In contrast, a recent study reported adequate shunt function and an inspiringly low overt HE rate of 18% in two years with the exploratory use of 8 mm covered stents in TIPS.[21] In line with these findings, our team observed that 8 mm stents did not lead to reduced shunt patency or insufficient decompression, but decreased the HE incidence.[22] These disagreements,[10,23,24] along with the lack of head-to-head studies on the association between stent diameter and shunt function, particularly in regions where patients' body surface area is smaller[25] and hepatitis B viral (HBV) infection is the major aetiology of cirrhosis,[26] such as China, suggest that the outcome of TIPS with stents of different diameters requires more robust data.[23]

We hypothesized that 8 mm stents would not compromise shunt patency or increase the risk of rebleeding, but could reduce HE, especially overt HE incidence, and liver function impairment. Therefore, we designed the current prospective trial.

## Patients and methods

### *Study design*

This was a randomized controlled trial, performed by a single tertiary hospital, comparing TIPS with 8 mm and 10 mm covered stents for the prophylaxis of variceal rebleeding in cirrhotic patients. TIPS was performed immediately after randomization, preferably within 1–2 days.

### *Inclusion and exclusion criteria*

The eligibility criteria were as follows: 1) liver cirrhosis detected by clinical and imaging features and validated by biopsy when radiological imaging was inconclusive; 2) variceal haemorrhage occurred 5 to 42 days prior and standard treatment for secondary prophylaxis failed; 3) age 18 to 75 years; 4) adequate liver and renal function: Child-Pugh score ≤13, aspartate aminotransferase (ALT) and alanine aminotransferase (AST) <5× upper limit of normal (ULN), alkaline phosphatase <4× ULN, international normalized ratio (INR) <2.3, serum creatinine <1.5× ULN; and 5) written informed consent.

The exclusion criteria were as follows: 1) hepatocellular carcinoma or other malignancies; 2) severe active infection (>grade II, NCI-CTCAE 3.0); 3) hypertension with systolic pressure >150 mmHg or diastolic pressure >90 mmHg despite proper management; 4) heart failure >NYHA II, coronary heart disease, or arrhythmia requiring treatment; 5) portal vein thrombosis; 6) absolute contraindications for TIPS; 7) overt HE; 8) spontaneous bacterial peritonitis; 9) previous TIPS or surgical shunting; 10) liver transplantation candidates; and 11) female patients who were pregnant or lactating.

### *Randomization*

The randomization scheme was obtained by a clinical research coordinator using a web-based allocation system (http://openrct.fmmu.edu.cn) with Pocock and Simon's minimization method[27] at a ratio of 1:1 on the basis of balancing patients according to baseline age, gender (male and female) and Child-Pugh class (A, B and C). The patients, investigators performing the TIPS procedure and caregivers were not blinded to the assignments and did not participate in the data collection and analysis, whereas follow-up investigators (collecting data and assessing endpoints) and the statistician were blinded to the assignment.

### *TIPS*

Patients were randomly assigned to receive TIPS with 8 mm or 10 mm polytetrafluoroethylene-covered stents (Fluency®, Bard, Inc., Tempe, AZ, USA), with local anaesthesia at puncture site.[22,26,28] Specifically, after successful puncture, an 8 mm balloon was used in every patient to dilate the liver parenchyma, and a Fluency® stent with nominal diameter of 8 mm or 10 mm was subsequently implanted according to randomization schemes. The optimal stent position, with the cephalic end of the stent extended to the hepatocaval junction and the caudal end parallel to the vascular wall of the main portal vein, was required; an additional Cordis® (Johnson & Johnson, Inc., New Brunswick, NJ, USA) stent with the same diameter was implanted to achieve such a position when necessary.[22] During the procedure, the portosystemic pressure gradient (PPG) was obtained preoperatively (baseline PPG) and immediately after stent placement (immediate PPG). For the first 59 patients recruited to the current study, an additional PPG measurement was performed, within 24–72 h, after the TIPS procedure (short-term PPG). PPG values at each time point were obtained by averaging the results of three repeated measurements using Mindray monitor (Mindray, Inc., Shenzhen, China). Considering that anticoagulation is not recommended in TIPS guidelines and might influence the primary endpoint, no anticoagulants were used. Similarly, no prophylactic treatment was given to prevent HE occurrence.

### *Endpoints and definitions*

The primary endpoint was shunt dysfunction (shunt stenosis or occlusion), evidence of which, namely occlusion, stenosis, a reduction in portal blood flow velocity >50% or to <28 cm/s, or a change in direction of blood flow within intrahepatic branches (identified by ultrasound) alongside high-risk varices (identified by endoscopy) was validated with angiography. Shunt dysfunction was defined as shunt stenosis ≥50%, complete occlusion, a PPG >12 mmHg or a 25% increase in PPG if the initial value after stent placement was >12 mmHg.[26,29]

The secondary endpoints included the following: 1) all-cause rebleeding; 2) orthotopic liver transplantation (OLT)-free survival; 3) overt HE; 4) spontaneous overt HE; 5) hepatic myelopathy (HM); 6) liver function; 7) a post-hoc analysis of the composite endpoint of rebleeding and death, along with the competing risk analyses of major endpoints with death and OLT being competing events; and 8) albumin-bilirubin (ALBI) score: $(\log_{10}\text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$[9] and the CLIF Consortium acute decompensation score (CLIF-C AD): $10 \times ([0.03 \times \text{age}] + [0.66 \times \ln(\text{creatinine})] + [1.71 \times \ln(\text{INR})] + [0.88 \times \ln(\text{WBC})] - [0.05 \times \text{Na}^+] + 8)$,[30] as well as the number of patients requiring hospital admission and length of stay in hospital.

All-cause rebleeding was defined as recommended in the Baveno V consensus.[6] The HE grade was recorded; covert HE (minimal or grade I), overt HE (≥grade II) and HM were defined as recommended in recent guidelines.[31] Spontaneous overt HE was defined as at least one episode of overt HE without any identifiable precipitants. OLT-free survival referred to the time from the TIPS procedure to the end of the follow-up, OLT or death.

### *Follow-up*

Scheduled follow-ups were performed at months one, three, and six; and every six months thereafter or whenever the patient had a clinical relapse or other event requiring hospital admission, including the following assessments: clinical manifestations, physical examination, shunt patency evaluation (including ultrasound and endoscopy), HE, and laboratory tests. Between two scheduled follow-ups, a telephone follow-up was performed to record the patient's condition and details of clinical events. Patients were followed until death or when the last enrolled patient had been followed up for two years.

Shunt revision was considered when dysfunction was detected. Patients with severe HE (>grade II), recurrent/persistent HE (≥2 episodes of overt HE within six months or a long-existing pattern of behavioural alterations interspersed with relapses of overt HE) would be considered for shunt reduction.[31]

### *Sample size calculation*

The required sample size was calculated according to the shunt dysfunction rates from a previous randomized controlled trial: 6/12 (50%) *vs.* 2/9 (22%) for TIPS with 8 mm and 10 mm stents, respectively, in patients with variceal bleeding.[20] We conservatively considered 25% for 10 mm stents; hence, the difference between the two groups was 25%. To achieve a power of 80% and a two-sided significance level of 0.05 with a loss-to-follow-up rate of 10%, a total of 126 patients were needed, with 63 in each group.

*Statistical analyses*

Continuous variables are presented as the means ± standard deviation or medians (interquartile ranges) and were compared by independent sample *t* tests or paired-sample *t* tests accordingly. Categorical and ordinal variables are presented as frequencies or percentages and were compared using Fisher's exact and Mann-Whitney U tests, respectively. Time-to-event outcomes were evaluated with Kaplan-Meier curves and log-rank test. Cox regression model was used to identify independent predictors. Events developed during follow-up were encoded as time-dependent variables when included in analyses. Variables with *p* values <0.1 in univariate analysis were incorporated into the multivariate analysis, in which two-tailed *p* values <0.05 were considered statistically significant. Logistic regression was used when analysing binary dependents. Post-hoc competing risk survival analyses were performed, with death and OLT as competing events, using Gray's test. Unbalanced factors between groups were treated as covariates for adjusting survival using Cox regression. Statistical analyses were performed using IBM SPSS statistics version 22.0 (IBM, Inc., Chicago, IL, USA), GraphPad Prism version 6.0 (GraphPad Software, Inc., La Jolla, CA, USA) and the cmprsk package in R version 3.3.2 (Stanford University, Stanford, CA, USA). Follow-up investigators and statisticians had access to all of the data and can vouch for the integrity of data analyses.

*Ethics*

The study protocol, informed consent, case report forms and other relevant documents were registered and approved by the ethics committee of Xijing Hospital. The study was conducted in accordance with the Helsinki Declaration and good clinical practices. The study is registered at Clinicaltrials.gov NCT01410591.

For further details regarding the materials used, please refer to the Supplementary material and the CTAT table.

## Results

*Recruitment and randomization*

Recruitment was performed from July 2012 to January 2014, and the final follow-up was completed in January 2016. A total of 134 patients were evaluated for eligibility, 127 were finally enrolled (Fig. 1). The main reasons for exclusion were refusal to participate (n = 3), portal vein thrombosis (n = 2) and non-cirrhotic portal hypertension (n = 2). Sixty-four and 63 patients were assigned to the 8 mm and 10 mm groups, respectively. No patients were lost to follow-up.

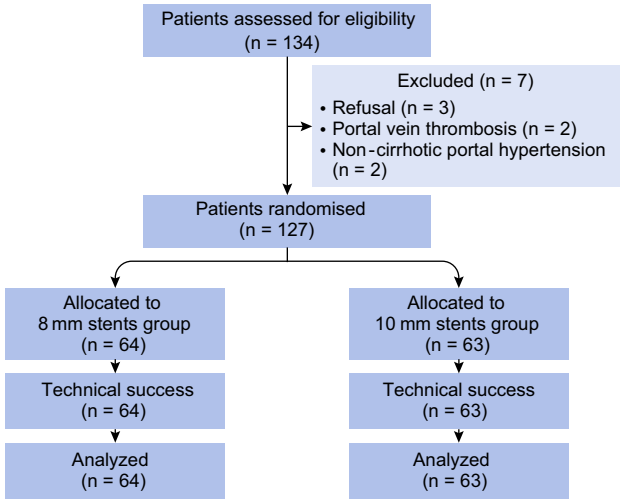


**Fig. 1. Study design and flow chart.**

*Baseline characteristics*

The patients' baseline characteristics are shown in Table 1. The two groups were comparable with respect to most features, except for a very small difference in age. Among 92 patients with HBV infection, 53 patients with negative HBV-DNA at admission continued previous antiviral treatment, the other 39 patients were treated with nucleoside analogue (entecavir). Rates of virologic response were comparable between 8 mm and 10 mm groups.

*Interventions and PPG*

TIPS procedures were successfully performed in all patients. To achieve optimal stent position, an additional stent was implanted in three patients from the 8 mm group and one from the 10 mm group. PPG significantly decreased immediately after stent placement in both arms, with no difference between groups (26.2 ± 4.3 to 8.2 ± 3.0 mmHg *vs.* 24.9 ± 4.3 to 7.4 ± 3.0 mmHg, $p = 0.130$, Fig. 2). Among all 127 patients, 59 patients from the 8 mm group and 58 from the 10 mm group reached a PPG <12 mmHg (92.2% *vs.* 92.1%, $p = 0.979$). Of the 10 patients who did not reach this threshold, five in the 8 mm group and five in the 10 mm group had an average PPG decrease of 54% (31.6 ± 3.4 mmHg to 14.4 ± 1.9 mmHg) and 52% (31.6 ± 3.4 mmHg to 14.4 ± 1.9 mmHg), respectively; a PPG decrease >20% was achieved in all 10 of these patients. Short-term PPGs in the first 59 patients were significantly higher than immediate PPGs in both the 8 mm (8.7 ± 3.1 mmHg to 11.3 ± 3.5 mmHg, $p = 0.002$, Fig. S1A) and 10 mm stent groups (7.7 ± 2.8 mmHg to 10.5 ± 3.6 mmHg, $p = 0.004$, Fig. S1B), with no statistical difference ($p = 0.397$, Fig. 2). The major procedure-related complication was intraperitoneal bleeding in one patient from the 8 mm group and two patients from the 10 mm group (1.6% *vs.* 3.2%, $p = 0.619$); all of which were non-fatal and were controlled. After the procedure, concurrent ascites resolved in 22/32 patients from the 8 mm group and 26/35 patients from the 10 mm group (68.8% *vs.* 74.3%, $p = 0.787$).

*Primary endpoint*

The median follow-up times for the 8 mm and 10 mm stent groups were 26.9 (0.7–42.6) and 26.9 (0.4–41.4) months, respectively. A total of 23 patients (13 from the 8 mm group *vs.* 10 from the 10 mm group) exhibited 25 shunt dysfunctions. Among these patients, seven underwent revision (five received one revision; the other two received two revisions each). The cumulative incidence of shunt dysfunction at one and two years for the 8 mm and 10 mm stent groups were non-different (8.1% *vs.* 8.4% and 16.3% *vs.* 15.6%, respectively, log-rank $p = 0.620$, hazard ratio (HR): 1.23, 95% CI: 0.54–2.79, Fig. 3A) with a power of 0.97. Since age was not balanced between groups, we adjusted the survival curve to this covariate, the result of which ($p = 0.559$, Fig. S3A), as well as that of post-hoc competing risk analyses (Gray's test $p = 0.538$, Fig. S4A) were consistent with the above findings. Cox regression identified male gender and older age as independent predictors. The main reasons for not undergoing revision were refusal for economic reasons (eight patients) and death before revision could be performed, despite ultrasound evidence of shunt occlusion or stenosis (eight patients).

**Table 1. Baseline characteristics.**

| Variables | 8 mm group (n = 64) | 10 mm group (n = 63) | *p* value |
|---|---|---|---|
| Gender | | | 0.587 |
| Male | 41 (64.1) | 37 (58.7) | |
| Female | 23 (35.9) | 26 (41.3) | |
| Age (years) | 49.4 ± 11.0 | 52.0 ± 9.7 | <0.001 |
| Aetiology | | | 0.233 |
| Hepatitis B virus | 50 (78.1) | 42 (66.7) | |
| Hepatitis C virus | 4 (6.3) | 5 (7.8) | |
| Autoimmune liver disease | 3 (4.7) | 1 (1.6) | |
| Alcohol misuse | 0 (0.0) | 2 (3.2) | |
| Primary biliary cirrhosis | 1 (1.5) | 0 (0.0) | |
| Miscellaneous | 2 (3.1) | 2 (3.2) | |
| Unknown | 4 (6.3) | 11 (17.5) | |
| Child-Pugh class | | | 0.938 |
| A | 36 (56) | 35 (56) | |
| B | 25 (40) | 25 (39) | |
| C | 3 (4) | 3 (5) | |
| MELD score | 11.4 ± 3.0 | 10.6 ± 2.5 | 0.119 |
| Total bilirubin (mg/dl) | 1.3 ± 0.6 | 1.5 ± 0.9 | 0.258 |
| Albumin (g/dl) | 36.1 ± 6.0 | 35.7 ± 4.7 | 0.678 |
| Alanine aminotransferase (U/L) | 35.8 ± 47.7 | 37.9 ± 29.0 | 0.768 |
| Aspartate aminotransferase (U/L) | 39.5 ± 27.9 | 46.2 ± 30.8 | 0.201 |
| Alkaline phosphatase (U/L) | 109.1 ± 73.1 | 118.8 ± 80.8 | 0.480 |
| γ-glutamyl transferase (U/L) | 42.9 ± 40.6 | 63.2 ± 83.9 | 0.084 |
| Creatinine (mg/dl) | 1.0 ± 0.3 | 0.90 ± 0.1 | 0.096 |
| Blood urea nitrogen (mg/dl) | 15.3 ± 9.0 | 14.9 ± 7.8 | 0.822 |
| $Na^+$ (mEq/L) | 140.0 ± 3.2 | 139.7 ± 4.1 | 0.658 |
| $K^+$ (mEq/L) | 3.9 ± 0.4 | 3.8 ± 0.5 | 0.402 |
| Venous ammonia level (μg/dl) | 74.4 ± 34.1 | 76.9 ± 35.6 | 0.692 |
| Pre-TIPS PPG (mmHg) | 26.2 ± 4.3 | 24.9 ± 4.3 | 0.112 |
| Pre-TIPS ascites | 32 (50) | 35 (56) | 0.595 |
| Duration from last bleeding to randomization (days) | 17 (8–35) | 17 (11–35) | 0.904 |
| Duration of follow-up (months) | 26.9 (0.7–42.6) | 26.9 (0.4–41.4) | 0.265 |
| Virological response | | | 0.335 |
| Complete response | 45 (90) | 34 (81) | |
| Partial response | 5 (10) | 7 (17) | |
| Non-response | 0 (0) | 1 (2) | |

MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt; PPG, portosystemic pressure gradient.

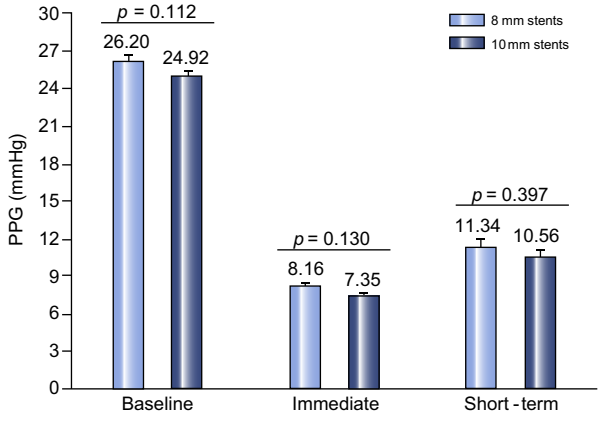


**Fig. 2. Comparison of immediate and short-term PPG measurements between the 8 mm and 10 mm groups.** Student's *t* test was used to compare PPG, PPG at each time point were non-difference between groups. PPG, portosystemic pressure gradient.

*Secondary endpoints*

During follow-up, 13 patients from the 8 mm group and 10 from the 10 mm stent group experienced all-cause rebleeding. Among these patients, five in the 8 mm group and six in the 10 mm group had variceal rebleeding, diagnosed by endoscopy. The one- and two-year incidence rates of all-cause rebleeding were 6.5% *vs.* 10.1% and 16.3% *vs.* 17.1%, for the 8 mm and 10 mm groups, respectively (log-rank $p = 0.650$, HR: 1.21, 95% CI: 0.53–2.74, fig. 3C). Neither the adjusted survival ($p = 0.548$, Fig. S3B) or Gray's test ($p = 0.562$, Fig. S4B) detected a difference. Post-hoc analysis of the composite endpoint of all-cause rebleeding and death showed similar results: (23.4% *vs.* 28.6% at two years, log-rank $p = 0.615$, HR: 0.86, 95% CI: 0.47–1.37, fig. 3B).

Overt HE occurred in 55 patients, including 23 patients in the 8 mm stent group and 32 in the 10 mm stent group. Immediate PPGs, in patients with and without overt HE, were not significantly different (7.86 ± 3.00 *vs.* 7.69 ± 2.97, $p = 0.757$), logistic regression for PPG and overt HE occurrence showed consistent results (OR: 1.931, 95% CI: 0.492–7.576, $p = 0.346$). Nine patients experienced

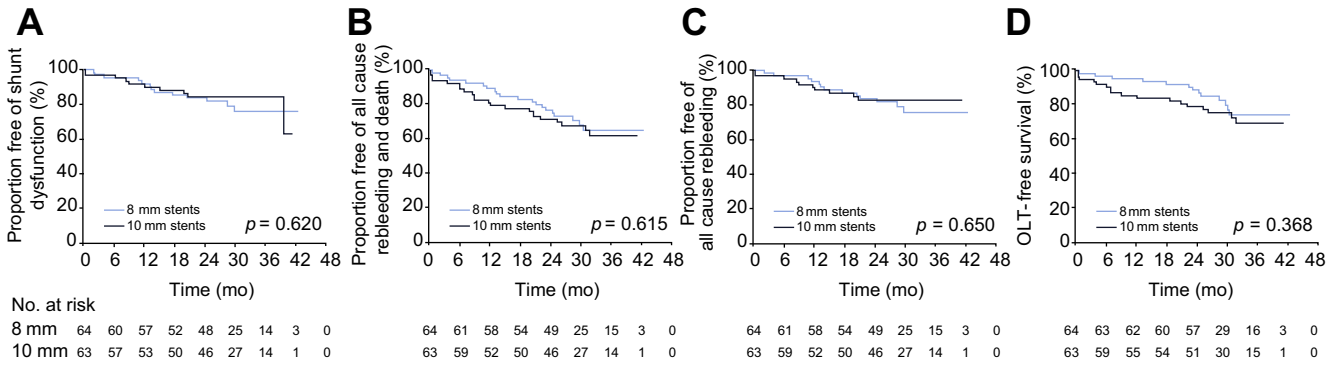


**Fig. 3. Kaplan-Meier curve of post-TIPS shunt function and survival.** Proportion free of shunt dysfunction (A), proportion free of all-cause rebleeding or death (B), all-cause rebleeding (C) and OLT-free survival (D) using Kaplan-Meier method are shown. Mo, month; OLT, orthotopic liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt.

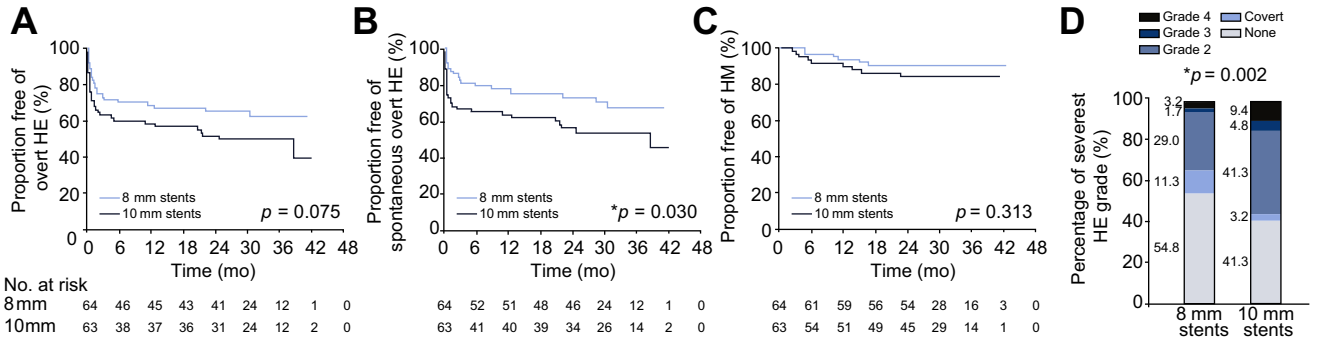


**Fig. 4. Kaplan-Meier curve of HE and HM, with percentage bar chart of HE grade.** Proportion free of overt HE (A), spontaneous overt HE (B), and HM (C) using Kaplan-Meier method are shown. The HR in the 8 mm stent group was 0.53 (95% CI 0.30–0.94) for spontaneous overt HE. The percentage of the most severe HE grade (D) was compared with Mann-Whitney *U* test, and was significantly different in the two groups. HE, hepatic encephalopathy; HM, hepatic myelopathy; HR, hazard ratio; Mo, month.

recurrent HE, including three patients from the 8 mm group and six from the 10 mm group. All six patients with persistent HE were from the 10 mm group. The rate of recurrent/persistent HE in the 8 mm group was significantly lower (5% *vs.* 19%, $p = 0.014$). The two-year cumulative incidence rates of overt HE for the 8 mm and 10 mm groups were 34.4% and 48.0%, respectively, with a marginal difference (log-rank $p = 0.075$, fig. 4A). The survival curve adjusted to age ($p = 0.086$, Fig. S3C) and competing risk analysis (Gray's test $p = 0.079$, Fig. S4C) reported consistent results. Cox regression identified group assignment as the only predictor of spontaneous overt HE (Table 3).

During follow-up, spontaneous overt HE occurred in 49 patients, suggesting that only six patients with overt HE had an identifiable precipitant, a result most likely due to the setting of bypass creation and liver injury after TIPS. More than half of these patients (30 patients, 61%) were from the 10 mm group. The two-year cumulative rates were significantly lower in the 8 mm group (26.6% *vs.* 43.2%, log-rank $p = 0.030$, HR: 0.53, 95% CI: 0.30–0.94, fig. 4B), as were the adjusted survival curve ($p = 0.039$, adjusted HR: 0.54, Fig. S3D) and competing risk model (Gray's test $p = 0.032$, HR: 0.54, Fig. S4D). The percentages of severest grade HE episodes were significantly different between the groups (Fig. 4D, $p < 0.001$).

The cumulative incidence of HM did not differ between 8 mm and 10 mm groups (10% *vs.* 16%, log-rank $p = 0.313$, HR 0.951, 95% CI: 0.215–1.635, fig. 4C).

Laboratory tests during the follow-up period demonstrated comparatively better liver function in the 8 mm group, with higher albumin levels together with lower total bilirubin (TBIL) and AST levels at several time points (Fig. 5A–C). The dynamic change in the ALBI score also favoured 8 mm stents, with significantly lower scores at months three and six (Fig. 5D), whereas CLIF-C AD score showed no significant results (Fig. S5). The number of patients requiring hospital admission was significantly less in the 8 mm group (53.1% *vs.* 76.2%, $p < 0.001$), whereas the lengths of hospital stay were non-different (11 [0–30] *vs.* 14 [2–40], $p = 0.099$).

In total, 30 patients (24%) died. The reasons are listed in Table 2. One patient from the 10 mm group underwent OLT at month 25. OLT-free survivals in the 8 mm and 10 mm groups at one year were 95.3% *vs.* 85.7%, and at two years were 89.1% *vs.* 79.4%, with no significant difference (log-rank $p = 0.369$, HR: 0.72, 95% CI: 0.35–1.47, Fig. 3D). The only predictor of survival for the entire cohort was bilirubin (Table 3), whereas in 92 patients with HBV infection, age and virologic response to antiviral treatment were identified as risk factors (Table S2).

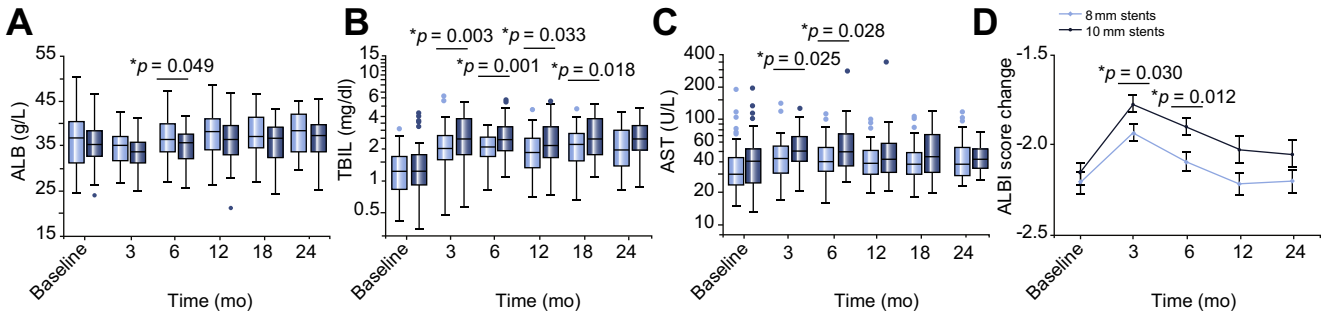


**Fig. 5. Boxplots of liver function and line chart of ALBI scores.** ALB (A), TBIL (B) and AST (C) in the 8 mm group (light blue bars) and 10 mm group (dark blue bars) were compared with Student's *t* test. Line chart of ALBI scores (D) is shown. ALB, albumin; ALBI, albumin-bilirubin; AST, aspartate aminotransferase; Mo, month; TBIL, total bilirubin.

**Table 2. Causes of death.**

| Cause | 8 mm group | 10 mm group | Total |
|---|---|---|---|
| Liver failure | 6 (20%) | 8 (26%) | 14 (46%) |
| Upper gastrointestinal rebleeding | 2 (7%) | 2 (7%) | 4 (14%) |
| HCC rupture | 1 (3%) | 0 (0%) | 1 (3%) |
| Renal failure | 0 (0%) | 1 (3%) | 1 (3%) |
| Other | 1 (3%) | 4 (14%) | 5 (17%) |
| Unknown | 3 (10%) | 2 (7%) | 5 (17%) |
| Total | 13 (43%) | 17 (57%) | 30 (100%) |

HCC, hepatocellular carcinoma.

## Discussion

The ideal stent diameter in TIPS should be sufficient to maintain shunt patency, provide adequate decompression, and equally, if not more importantly, avoid exposing patients to an excessively high risk of HE.[12] Whether it is 8 mm or 10 mm stents that can achieve this subtle balance has remained controversial, up to now.[21,23,24] Our study suggests a favourable overall outcome with 8 mm stents and lends support to their use in TIPS for the prevention of variceal rebleeding with the following findings: (1) the similar shunt patency and rebleeding rate of TIPS with 8 mm and 10 mm stents, within a larger population; (2) the advantage of 8 mm stents in reducing spontaneous overt HE and severe and recurrent/persistent HE; (3) the merit of 8 mm stents in alleviating the deterioration of liver function impairment and clinical condition after TIPS.

The improvement of shunt patency with covered stents has been acknowledged,[14,32] yet the association between stent diameter and dysfunction has remained unclear.[10] Indeed, in the only prospective study comparing TIPS with covered stents of different diameters, 8 mm stents demonstrated a potentially higher risk of shunt dysfunction;[33] however, the primary endpoint was HE rather than patency, rendering this finding an exploratory observation, rather than sufficient clinical evidence.[24] Therefore, we opted for shunt dysfunction as the primary outcome measure.

As hypothesized, 8 mm stents did not compromise shunt patency. Moreover, the 8% incidence of shunt dysfunction, in both groups of our study, was comparable to the 14% for covered stents in the landmark study on covered and bare grafts.[14] In

**Table 3. Univariate and multivariate analysis of factors associated with post-TIPS outcomes.**

| Outcomes | Univariate analysis* | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| Shunt dysfunction | | | | | | |
| Gender (male *vs.* female) | 12.254 | 2.148–69.89 | 0.005 | 5.186 | 1.597–16.84 | 0.006 |
| Age (per year increase) | 1.102 | 1.023–1.188 | 0.011 | 1.064 | 1.011–1.120 | 0.017 |
| Albumin (per g/L increase) | 0.902 | 0.800–1.016 | 0.090 | | | |
| BUN (per mg/dl increase) | 1.284 | 0.582–1.718 | 0.094 | | | |
| Spontaneous overt HE† | | | | | | |
| Group (8 mm *vs.* 10 mm) | 0.565 | 0.287–1.112 | 0.099 | 0.527 | 0.295–0.938 | 0.030 |
| ALT (per IU/L increase) | 0.981 | 0.959–1.003 | 0.096 | | | |
| Survival | | | | | | |
| Platelets (per $10^9$ cell/L increase) | 0.992 | 0.985–1.000 | 0.046 | | | |
| Bilirubin (per mg/dl increase) | 1.034 | 0.997–1.072 | 0.072 | 1.664 | 1.128–2.455 | 0.010 |
| Creatinine (per mg/dl increase) | 1.032 | 1.006–1.060 | 0.017 | | | |

ALT, alanine aminotransferase; BUN, blood urea nitrogen; CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio; PPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

* Only variables introduced in multivariate analysis (*p* value <0.1 in the univariate analysis) are shown. Variables selected for univariate analysis included gender, age, group, aetiology (viral and non-viral), white blood cell, red blood cell, platelets, international normalized ratio, alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, γ-glutamine transaminase; Na, K, BUN, creatinine, ammonia, ascites, baseline PPG, immediate PPG, and time from last bleeding to randomization.

† Shunt dysfunction was encoded as a time-dependent variable and was included.

contrast, Riggio *et al.* reported an extraordinarily high incidence of 50%, approaching that of bare grafts[14] in 8 mm stents.[20] Despite this discrepancy, our findings might be more reliable for the following reasons. Firstly, our study and that by Bureau *et al.* were both designed primarily to analyse shunt dysfunction, with an adequate sample size and follow-up, thereby guaranteeing the power of test for this endpoint. Secondly, previous findings suggest that about half of shunt dysfunction occurrences can be attributed to suboptimal stent position.[32] Both our study and that by Bureau *et al.* paid close attention to achieving optimal stent position, to control possible confounding bias.[22,34] Whereas, it cannot be excluded that stent position might have contributed to such a high dysfunction incidence in the study by Riggio *et al.*, where the effect of polytetrafluroethylene was almost offset.[20] Thirdly, since non-standardized assessment of shunt dysfunction would lead to varied actuarial probabilities (Table S1),[13,14,16,20,21,32,35] we proposed a clearer and more feasible step-wise evaluation approach, *i.e.*, using clinical manifestations as complementary indications for assessment, ultrasound and endoscopy as preliminary screening for suspicious signs, and angiography as final validation of dysfunction. This helped to ensure sensitivity and avoid excessive angiography, thereby improving the reliability of our results. Regarding the predictors of shunt dysfunction, the study comparing covered and bare stents identified only bare stents as a risk factor,[14] whereas in the current study, where only covered stents were used, older age and male gender were the risk factors. The reason for this requires more in-depth study.

Our study demonstrated no significant difference in rebleeding rates between groups, both of which were comparable to those published in recent randomized trials (Table S1). However, Riggio *et al.*[20] reported a higher rebleeding rate in patients from the 8 mm group (annual incidence 58%) and explained it as a probable result of a higher PPG. In contrast, both immediate PPG and short-term PPG were similar between the two arms in our study. Similarly, a previous study comparing 10 mm and 12 mm bare stents demonstrated a non-different PPG between the groups,[12] suggesting that a 2 mm difference in diameter may not cause a remarkable discrepancy in pressure gradient, and consequently may not lead to different efficacy in preventing rebleeding. In addition, one recent study reported that early PPG, at 24 h after TIPS, was higher than the immediate value under general anaesthesia, and was predictive of patient outcome.[36] However, our study found that PPG slightly increased at 24–72 h in both groups even when all patients were locally anaesthetized, and did not demonstrate predictive ability (Fig. S2), suggesting that studies specialized on this issue with larger sample sizes are needed. Taken together, the similarities in shunt patency, rebleeding rate and PPG suggest that 8 mm stents did not compromise shunt function and therefore, were as effective as 10 mm stents.

In terms of overt HE, the 8 mm group presented a marginal but non-significant advantage. Nevertheless, the lower spontaneous overt HE incidence favoured the 8 mm stents with an HR of 0.53. This discrepancy could possibly be explained by a difference in their nature: HE episodes secondary to a precipitating event were triggered by this very cause; however, for spontaneous episodes, the underlying condition was more likely to be deteriorated liver function.[37] Indeed, a better liver function reserve in 8 mm stents supported this idea (Fig. 5). Moreover, smaller stents were advantageous for lowering the incidence of recurrent/persistent HE and severe HE, which was in alignment with the favourable outcome of shunt reduction or occlusion as a therapy for refractory HE.[35,38–42] However, compared with remedial shunt reduction, 8 mm stents have the significant advantage of being able to protect against, rather than treat, HE.

Our study has several limitations. Firstly, the single-centre nature may limit its representativeness. However, quality control was ensured because all procedures were completed by the same experienced team. Secondly, the covered stents we used were Fluency® rather than Viatorr®. However, only the former was available in China when this study was launched, and it was used in both groups, so it may not influence the result of between-group comparison. Thirdly, covert HE was not tested before TIPS. Nevertheless, similar baseline liver function and venous ammonia levels between the groups suggested a balanced patient distribution. Finally, the population enrolled in the current study comprised Chinese patients whose body surface areas are smaller[25] and HBV infection was the main aetiology of cirrhosis, and spontaneous overt HE was not the primary endpoint used for the sample size calculation; hence, caution should be applied when extrapolating the results, and further investigations will be needed.

In conclusion, the present study suggests that 8 mm covered stents in TIPS may achieve a favourable clinical outcome with non-compromised shunt function, nearly halved spontaneous overt HE risk and better liver function reserve. Therefore 8 mm covered stents should be favoured for the prevention of variceal rebleeding in cirrhotic patients.

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**Conflict of interest**

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

**Authors' contributions**

Qiuhe Wang: telephone follow-up, data collection, evaluation of clinical events, endpoint assessment, statistical analysis, and writing and revising the manuscript. Yong Lv: statistical analysis and revising the manuscript. Ming Bai: study conception and design, drafting of the study hypothesis, informed consent, and study protocol. Zhengyu Wang: data collection, schemed follow-up, telephone follow-up, and endpoint assessment. Haibo Liu: telephone follow-up and data collection. Chuangye He: study design, patient recruitment, patient administration, and TIPS surgery. Jing Niu: patient randomization, data collection and regular follow-up. Wengang Guo: study design and TIPS surgery. Bohan Luo: data collection. Zhanxin Yin: study design, TIPS surgery, patient administration, and critical revision of the manuscript.

Wei Bai: TIPS surgery, patient administration and revision of the manuscript. Hui Chen, Enxin Wang, and Dongdong Xia: revision of the manuscript. Xiaomei Li, Jie Yuan, and Na Han: data collection. Hongwei Cai and Jielai Xia: design of computer randomization system. Tao Li and Jianhong Wang: study design, ultrasound-guided percutaneous puncture of the portal vein. Huahong Xie and Hongbo Zhang: study design and endoscopic therapy.

Kaichun Wu and Daiming Fan: study supervision, study design, critical revision of the manuscript, and funds collection. Guohong Han: study supervision, study conception and design, patient recruitment, patient administration, TIPS surgery, critical revision of the manuscript, and funds collection.

All authors gave final approval of the version to be published.

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**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2017.05.006.

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*Author names in bold designate shared co-first authorship*

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