Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial

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Summary

Background The survival benefit of early placement of transjugular intrahepatic portosystemic shunts (TIPS) in patients with cirrhosis and acute variceal bleeding is controversial. We aimed to assess whether early TIPS improves survival in patients with advanced cirrhosis and acute variceal bleeding.

Methods We did an investigator-initiated, open-label, randomised controlled trial at an academic hospital in China. Consecutive patients with advanced cirrhosis (Child-Pugh class B or C) and acute variceal bleeding who had been treated with vasoactive drugs plus endoscopic therapy were randomly assigned (2:1) to receive either early TIPS (done within 72 h after initial endoscopy [early TIPS group]) or standard treatment (vasoactive drugs continued to day 5, followed by propranolol plus endoscopic band ligation for the prevention of rebleeding, with TIPS as rescue therapy when needed [control group]). Randomisation was done by web-based randomisation system using a Pocock and Simon's minimisation method with Child-Pugh class (B *vs* C) and presence or absence of active bleeding as adjustment factors. The primary outcome was transplantation-free survival, analysed in the intention-to-treat population, excluding individuals subsequently found to be ineligible for enrolment. This study is registered with ClinicalTrials.gov, number NCT01370161, and is completed.

Findings From June 26, 2011, to Sept 30, 2017, 373 patients were screened and 132 patients were randomly assigned to the early TIPS group (n=86) or to the control group (n=46). After exclusion of three individuals subsequently found to be ineligible for enrolment (two patients in the early TIPS group with non-cirrhotic portal hypertension or hepatocellular carcinoma, and one patient in the control group due to non-cirrhotic portal hypertension), 84 patients in the early TIPS group and 45 patients in the control group were included in the intention-to-treat population. 15 (18%) patients in the early TIPS group and 15 (33%) in the control group died; two (2%) patients in the early TIPS group and one (2%) in the control group underwent liver transplantation. Transplantation-free survival was higher in the early TIPS group than in the control group (hazard ratio 0·50, 95% CI 0·25–0·98; p=0·04). Transplantation-free survival at 6 weeks was 99% (95% CI 97–100) in the early TIPS group compared with 84% (75–96; absolute risk difference 15% [95% CI 5–48]; p=0·02) and at 1 year was 86% (79–94) in the early TIPS group versus 73% (62–88) in the control group (absolute risk difference 13% [95% CI 2–28]; p=0·046). There were no significant differences between the two groups in the incidence of hepatic hydrothorax (two [2%] of 84 patients in the early TIPS group *vs* one [2%] of 45 in the control group; p=0·96), spontaneous bacterial peritonitis (one [1%] *vs* three [7%]; p=0·12), hepatic encephalopathy (29 [35%] *vs* 16 [36%]; p=1·00), hepatorenal syndrome (four [5%] *vs* six [13%]; p=0·10), and hepatocellular carcinoma (four [5%] *vs* one [2%]; p=0·68). There was no significant difference in the number of patients who experienced other serious adverse events (ten [12%] *vs* 11 [24%]; p=0·07) or non-serious adverse events (21 [25%] *vs* 19 [42%]; p=0·05) between groups.

Interpretation Early TIPS with covered stents improved transplantation-free survival in selected patients with advanced cirrhosis and acute variceal bleeding and should therefore be preferred to the current standard of care.

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Introduction

Acute variceal bleeding is a common and life-threatening complication occurring in patients with portal hypertension and is a leading cause of death in patients with cirrhosis.[1] The current recommended standard of care for acute variceal bleeding involves a combination of vasoactive drugs, prophylactic antibiotics, and endoscopic therapy.[2–5] This approach has improved patient outcomes. However, up to 10–20% of patients still experience treatment failure, requiring further intensive

Research in context

Evidence before this study

We searched PubMed, Embase, Web of Science, and the Cochrane Library for clinical trials published in English between Jan 1, 1980, and Jan 1, 2019, with the terms ("transjugular intrahepatic portosystemic shunt" OR "TIPS" OR "TIPSS") AND ("acute variceal bleeding" OR "acute variceal haemorrhage") AND "cirrhosis". Two randomised trials had been published, showing that, compared with drugs plus endoscopic treatment, early use of transjugular intrahepatic portosystemic shunt (TIPS; placed within 72 h of admission) was associated with significantly lower treatment failure and mortality in selected patients with cirrhosis and acute variceal bleeding. However, survival was not the primary endpoint of either of these trials. Furthermore, several observational studies have not confirmed the effect of early TIPS on survival. Additionally, whether the survival benefit associated with early TIPS can be achieved in a broader population remains unclear.

Added value of this study

Our study showed that among patients with advanced cirrhosis (Child-Pugh class B or C) and acute variceal bleeding, early TIPS is superior to drugs plus endoscopic treatment in improving transplantation-free survival, reducing failure to control bleeding, and new or worsening ascites, without increasing the risk of overt hepatic encephalopathy.

Implications of all the available evidence

Our results, observed in patients of Asian ethnicity with cirrhosis of viral aetiology, are consistent with those of earlier European trials where most patients had alcoholic liver cirrhosis, suggesting that ethnicity and aetiology of cirrhosis did not obviously influence the results. This study adds further evidence to support recommendations that early TIPS should be done in selected patients without contraindications.

management. In such patients, placement of a transjugular intrahepatic portosystemic shunt (TIPS) is successful in achieving haemostasis in 90–100% of patients. However, 6-week mortality remains high (35–55%).[6–8] This is probably because the severity of the underlying liver disease has worsened and additional organ dysfunction may have occurred after several failed endoscopic therapy attempts.[9–11]

The poor outcomes associated with the use of TIPS as a rescue treatment raises the question whether patients with predicted high-risk uncontrolled bleeding might benefit from a more aggressive therapeutic approach before treatment failure has occurred. This strategy was first explored in a randomised controlled trial by Monescillo and colleagues,[12] in which patients with hepatic venous pressure gradient (HVPG) of 20 mm Hg or greater receiving early TIPS (within 24 h of admission) had significantly fewer treatment failures and lower mortality than those undergoing standard therapy. However, the standard therapy used in the control group was not the current standard of care and the TIPS stents were uncovered. These drawbacks, together with the difficulty of performing HVPG measurements in many centres, especially in emergency situations, encouraged Garcia-Pagan and colleagues to do a subsequent multicentre randomised trial,[13] in which patient selection was based on clinical risk factors predicting failure to control bleeding. This study showed that early treatment with covered TIPS (within 72 h of admission) improved survival in a subset of patients with Child-Pugh C (score 10–13 points) or with Child-Pugh B and active bleeding at initial endoscopy. Nevertheless, survival was not the primary endpoint of the study, which increased the chances of a type I error.[14] Indeed, the survival benefit associated with early TIPS was not confirmed in several subsequent observational studies with a similar patient population.[15–17] Additionally, the trial of Garcia-Pagan and colleagues has been criticised for having a selection bias and including patients who were not representative of the entire population of patients with severe cirrhosis and variceal bleeding.[14,18,19] Thus, whether early TIPS confers a survival benefit in a broader population remains to be assessed.

We designed this randomised trial to evaluate whether early TIPS improves transplantation-free survival in patients with advanced cirrhosis and acute variceal bleeding compared with the current recommend standard care.

Methods

Study design and participants

This investigator-initiated, open-label, randomised, single-centre trial was conducted at Xijing Hospital of Digestive Diseases (a tertiary university hospital in China). The study protocol and amendments were approved by the ethics committee of Xijing Hospital and written informed consent was obtained from all the patients or their next of kin. Of note, none of the patients enrolled in this trial were included in our previous multicentre observational study.[20]

Inclusion criteria for the study were: liver cirrhosis (diagnosed based on clinical presentation, laboratory tests, images, or liver biopsies); age 18–75 years; endoscopy-proven acute variceal bleeding according to Baveno II definitions;[21] and Child-Pugh class B or C (<14 points). Exclusion criteria were: uncontrolled bleeding before randomisation; bleeding from isolated gastric or ectopic varices; severe cardiopulmonary diseases; spontaneous recurrent hepatic encephalopathy;

complete portal vein thrombosis or cavernoma; creatinine greater than 3 mg/dL; hepatocellular carcinoma or other extrahepatic malignancy; uncontrolled infection or sepsis; previous treatments with a surgical shunt, TIPS, or combined therapy with non-selective β-blockers plus endoscopic band ligation; contraindications to TIPS; pregnancy or breastfeeding; and declining to participate or unable to give informed consent.

Randomisation and masking

Eligible patients were randomly assigned in a 2:1 ratio to receive early TIPS (early TIPS group) or endoscopic plus drug treatment (control group). A 2:1 ratio was chosen on the basis of previous studies[12,13] that showed that early TIPS improved survival in selected patients with cirrhosis and acute variceal bleeding, and to encourage recruitment. After obtaining written informed consent, a research coordinator independent of the trial entered the patient's baseline data into a secure web-based randomisation system. After the data were checked for completeness and consistency, the system generated a unique study identification number and a treatment pack number, which corresponded to either early TIPS or standard treatment. Randomisation was dynamically balanced using the Pocock and Simon's minimisation method[22] with Child-Pugh class (B *vs* C) and presence or absence of active bleeding as adjustment factors. Due to the nature of the intervention, clinicians and patients were not masked to treatment allocation, but allocation was concealed to outcome assessors and investigators analysing data.

Procedures

In both groups, vasoactive drugs (octreotide, somatostatin, or terlipressin) or endoscopic band ligation (sclerotherapy if technically difficult or not feasible) within 12 h of admission and prophylactic antibiotics were used to control the initial bleeding episode.

For those randomly assigned to the early TIPS group, the TIPS procedure was done within 72 h (preferably within the first 24 h) after diagnostic endoscopy, with vasoactive drugs continued to the procedure and antibiotics used for 5–7 days from admission. All TIPS procedures were done under conscious sedation with local anaesthesia at the puncture site, as described previously.[23,24] An 8 mm covered stent (Fluency, Bard Peripheral Vascular, Tempe, Arizona, USA) was used and dilated to 8 mm to obtain a good portacaval pressure gradient (measured as the difference between the portal vein and the inferior vena cava pressures). TIPS revision with angioplasty or another stent placement was done when portal hypertensive complications re-emerged or Doppler ultrasonography indicated shunt dysfunction (ie, a reduction of portal blood flow velocity greater than 50% or below 28 cm/s, or a reversion of blood flow direction within the intrahepatic branches).[23,24]

Patients assigned to the control group received vasoactive drugs for up to 5 days. At day 6, propranolol was started with an initial dose of 20 mg twice daily and then titrated to reduce the resting heart rate by 25% but not below 55 beats per minute. An elective session of endoscopic band ligation was done within 7–14 days after initial endoscopic treatment and then every 14 days (plus or minus 3 days) thereafter until variceal eradication was achieved. Endoscopic band ligation was done with multiband devices (Wilson-Cook Medical, Winston-Salem, North Carolina, USA). Once variceal eradication was achieved, monitoring endoscopy was done every 6 months. Additional sessions of ligation were done if varices reappeared. TIPS placement was used as a rescue therapy if bleeding failed to be controlled or clinically significant rebleeding occurred.

Follow-up was done at patient visits to outpatient clinics, scheduled at 1 month, 3 months, and 6 months after randomisation and then every 6 months thereafter. At each visit, clinical, laboratory, and abdominal ultrasound evaluations were done and information on prespecified liver-related complications that may have occurred since the previous visit were collected by clinical research coordinators. These visits were supplemented by telephone interviews with a 1-month interval to determine the patient's clinical course and to remind patients to adhere to the scheduled follow-up. Additional urgent appointments were provided if recurrence of portal hypertensive complications, including hepatic encephalopathy, was suspected. Patients were followed until death, liver transplantation, a maximum of 2 years of follow-up, or 1 year after enrolment of the last patient.

For the **randomisation system** see http://openrct.fmmu.edu.cn

Outcomes

The primary endpoint was transplantation-free survival. Secondary endpoints were: failure to control bleeding or rebleeding defined as per the recommendations of the Baveno V workshop;[25] new or worsening ascites defined as an increase of at least one point in the ultrasound ascites score (0=none, 1=mild, 2=moderate, 3=massive) or sustained ascites up to a volume requiring paracentesis; overt hepatic encephalopathy, diagnosed and graded according to the West-Haven criteria;[26] and other complications of portal hypertension and adverse events.

Statistical analysis

With a randomisation ratio of 2:1, it was estimated that 114 patients would be required to achieve 80% power to detect a 25% difference in survival at a 5% significance level, assuming 1-year transplantation-free survival of 85% with early TIPS and 60% with standard treatment, which was based on previous studies.[12,13,27,28] Assuming a 5% drop-out rate, we aimed to enrol 120 patients (80 in early TIPS group and 40 in control group).

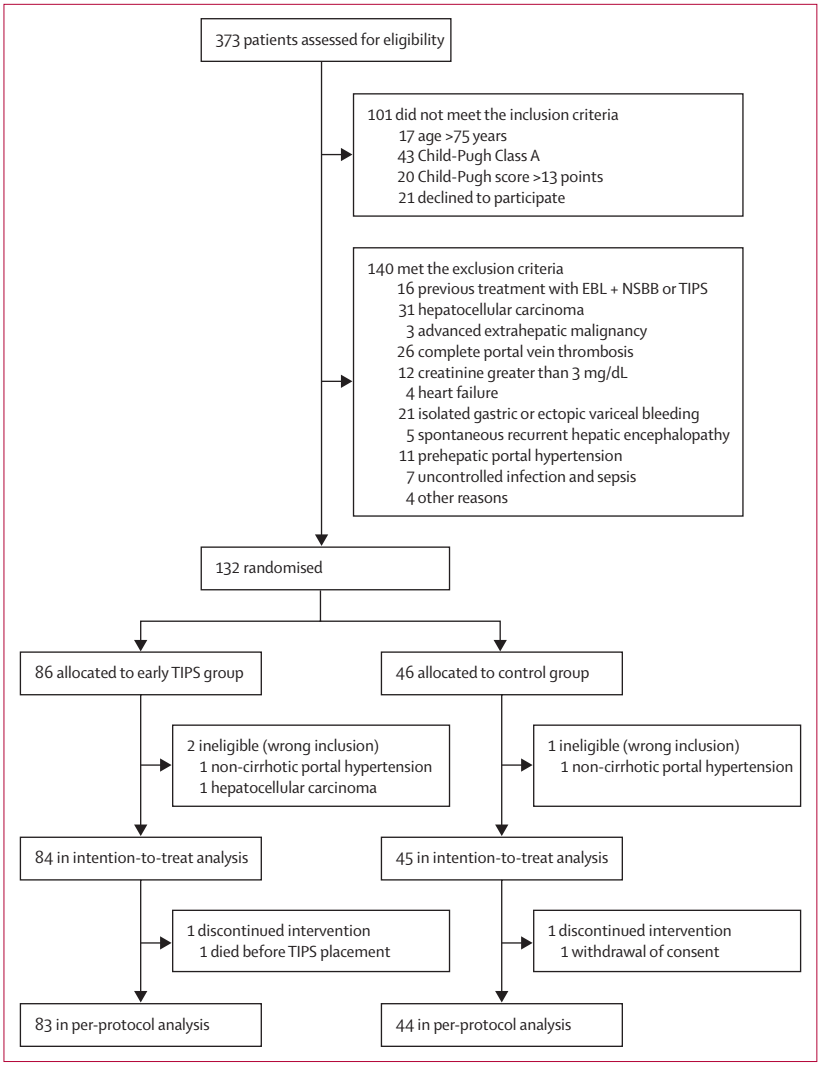

Figure 1: **Trial profile**
EBL=endoscopic band ligation. NSBB=non-selective β-blockers. TIPS=transjugular intrahepatic portosystemic shunt.

All analyses were done in the intention-to-treat population and were supplemented by per-protocol analyses. Comparisons between groups of variables were done with the Student *t* test, non-parametric Mann-Whitney *U* test, χ^2 test, or Fisher's exact test, as appropriate. Actuarial probability curves were constructed with the Kaplan-Meier method and compared with log-rank tests. Hazard ratios (HR) and absolute risk difference (ARD), with 95% CI, were calculated as an estimate of the effect size and its precision. ARD was calculated based on Kaplan-Meier estimates or event rates in each treatment group. Stepwise Cox regression analysis was used to identify independent predictors for transplantation-free survival, failure to control bleeding or rebleeding, new or worsening ascites, and overt hepatic encephalopathy. Variables with p values of less than 0·10 in univariate analyses were selected for the subsequent multivariate analysis. Redundant variables were not introduced in the final analysis to reduce possible colinearities. A post-hoc sensitivity analysis based on a competing risk approach (Fine and Gray method) was done to assess the effects of liver transplantation as a competing event on mortality. We did the same analysis, with all-cause deaths and liver transplantation as competing events, to assess the treatment effect on the first occurrence of the complications included in the secondary outcomes. Additionally, we tested treatment-by-subgroup interactions to assess whether any treatment effect differed in the pre-specified (Child-Pugh class [B/C] and early TIPS criteria [low-risk/high-risk][13]) and post-hoc subgroups (Model for End-Stage Liver Disease score [MELD] score [≤11/12–18/≥19][29]).

No interim analysis was done. A two-tailed p value of less than 0·05 was considered statistically significant in all analyses. All statistical calculations were done with SPSS 19.0 (IBM, Chicago, IL, USA) and R 3.5.1 (http://www.R-project.org) software packages. The study is registered with ClinicalTrials.gov, number NCT01370161.

Role of the funding source

The study funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 26, 2011, and Sept 30, 2017, 373 patients were screened for eligibility, of whom 241 patients were excluded; the remaining 132 patients were randomly assigned to the early TIPS group (n=86) or the control group (n=46; figure 1). After randomisation, three patients were excluded due to non-cirrhotic portal hypertension (one in each group) and hepatocellular carcinoma (one in the early TIPS group; figure 1). Therefore, the intention-to-treat population consisted of 84 patients in the early TIPS group and 45 in the control group (figure 1). One patient allocated to the early TIPS group died before TIPS placement, and one patient assigned to the control group withdrew consent before administration of propranolol; thus, 83 patients in the early TIPS group and 44 patients in the control group were included in the per-protocol population (figure 1).

Baseline characteristics were comparable between study groups (table 1). Final follow-up was completed on Sept 30, 2018; no patients were lost to follow-up. Median follow-up was 24·0 months (IQR 18·1–24·0) in the early TIPS group and 24·0 months (9·0–24·0) in the control group (p=0·06). Baseline characteristics of the high-risk subset of patients (Child-Pugh B with active bleeding or Child-Pugh C 10–13 points) are summarised in the appendix (p 12).

See Online for appendix

	Early TIPS group (n=84)	Control group (n=45)
Age (years)	50·7 (11·6)	50·9 (10·4)
Sex		
Male	53 (63%)	34 (76%)
Female	31 (37%)	11 (24%)
Aetiology of cirrhosis		
Chronic HBV infection	62 (74%)	34 (76%)
Chronic HCV infection	3 (4%)	4 (9%)
Alcoholic liver disease	2 (2%)	4 (9%)
Autoimmune hepatitis	3 (4%)	1 (2%)
Primary biliary cholangitis	4 (5%)	0 (0%)
Cryptogenic	10 (12%)	2 (4%)
HBV-DNA detectable	27 (32%)	15 (33%)
MELD score	14·0 (11·9–16·2)	13·4 (11·6–16·2)
MELD score		
<19	76 (90%)	41 (91%)
≥19	8 (10%)	4 (9%)
MELD-Na score	14·3 (12·0–16·8)	14·6 (12·2–17·5)
Child-Pugh score	8·0 (7·0–9·0)	8·0 (7·0–9·0)
Child-Pugh class		
Child-Pugh B without active bleeding	48 (57%)	25 (56%)
Child-Pugh B with active bleeding	17 (20%)	10 (22%)
Child-Pugh C ≤13 points	19 (23%)	10 (22%)
Interval from start of bleeding to randomisation (h)	24·3 (16·1)	24·7 (19·5)
Active bleeding at index endoscopy	25 (30%)	12 (27%)
Location of varices at index endoscopy		
Oesophageal varices only	59 (70%)	27 (60%)
Oesophageal and gastric varices	25 (30%)	18 (40%)
Size of varices (large)*	78 (93%)	42 (93%)
Previous encephalopathy	3 (4%)	0 (0%)
Ascites		
Mild	43 (51%)	28 (62%)
Moderate	17 (20%)	5 (11%)
Massive	14 (17%)	7 (16%)
White blood cell (×10⁹/L)	4·46 (2·79–7·91)	5·15 (3·68–7·36)
Platelet count (×10⁹/L)	56·0 (43·5–84·5)	53·0 (42·0–82·0)
Haemoglobin (g/L)	69·0 (59·0–84·0)	73·0 (62·0–84·0)
International normalised ratio	1·59 (1·37–1·85)	1·51 (1·33–97)
Bilirubin (mg/dL)	1·40 (1·12–2·07)	1·23 (0·90–1·82)
Albumin (g/L)	29·7 (26·3–32·6)	28·7 (24·7–33·1)
Creatinine (mg/dL)	0·96 (0·83–1·10)	0·96 (0·83–1·09)
Sodium (mmol/L)	138·5 (135·8–140·3)	139·8 (135·7–142·0)
Comorbidities†	10 (12%)	4 (9%)
Portal vein thrombosis	17 (20%)	7 (16%)
Body-mass index (kg/m²)	21·5 (20·0–22·9)	21·6 (19·8–23·3)
Heart rate at admission (beats/min)	77 (68–80)	75 (65–84)
Systolic blood pressure at admission (mm Hg)	106 (98–115)	108 (99–117)
Diastolic blood pressure at admission (mm Hg)	65 (60–72)	67 (59–73)
Mean arterial pressure (mm Hg)	78·6 (72·3–84·0)	80·0 (71·5–87·0)
Shock at time of admission‡	14 (17%)	7 (16%)
Patients transfused before randomisation	56 (67%)	26 (58%)
Blood transfusion before randomisation (units of packed red cells)	3·1 (3·2)	3·0 (2·9)
Initial endoscopic treatment		
Endoscopic band ligation	80 (95%)	42 (93%)
Endoscopic sclerotherapy	4 (5%)	3 (7%)
Initial pharmacological therapy		
Octreotide	38 (45%)	19 (42%)
Somatostatin	35 (42%)	22 (49%)
Terlipressin	11 (13%)	4 (9%)

Data are mean (SD), median (IQR), or n (%). MELD=Model for End-Stage Liver Disease. TIPS=transjugular intrahepatic portosystemic shunt. *Large defined as ≥5 mm. †Including hypertension, coronary artery disease, and diabetes. ‡Hypovolaemic shock defined as systolic blood pressure <100 mm Hg and heart rate >100 beats per min.

Table 1: **Baseline characteristics**

In the early TIPS group, all patients (except the patient who died before TIPS placement) underwent early TIPS placement (45 patients within 24 h, 28 in 24–48 h, and ten in 48–72 h). 68 (82%) patients received one stent; 15 (18%) required two stents. The mean portacaval pressure gradient dropped from 24·4 (SD 4·8) mm Hg before TIPS to 8·3 (2·4) mm Hg immediately after TIPS (p<0·0001, appendix p 3). After TIPS placement, 11 (13%) patients had a portacaval pressure gradient greater than 12 mm Hg, but a reduction in portacaval pressure gradient of more than 25% was achieved in all. Collateral embolisation was performed in 41 (49%) patients. 1-year and 2-year primary shunt patency rates were 90% (95% CI 83–97) and 79% (70–90), respectively (appendix p 3).

In the control group, 38 patients received propranolol with a median dose of 60 mg (range 10–180; appendix p 3). The administration of propranolol achieved an average 25% reduction of the median resting heart rate at 2 months (from 77 [IQR 66–85] to 58 [56–62] bpm), which was maintained throughout the course of the study (appendix p 3). In the remaining seven patients, propranolol was not initiated because of withdrawal of consent (n=1), receiving rescue TIPS (n=3), or early death (n=3). Variceal eradication was

	Early TIPS group (n=84)	Control group (n=45)	ARD (95% CI)*	HR (95% CI)	p value
Death or liver transplantation	17 (20%)	16 (36%)	−16% (−31 to −0·04)	0·50 (0·25 to 0·98)	0·04
Liver transplantation	2 (2%)	1 (2%)	−1% (−10 to 5)	0·87 (0·08 to 9·57)	0·91
Death	15 (18%)	15 (33%)	−15% (−32 to −0·2)	0·47 (0·23 to 0·96)	0·04
Cause of death†	..	..	..	..	0·66‡
Liver failure	6 (40%)	3 (20%)	..	..	..
Gastrointestinal bleeding	2 (13%)	4 (27%)	..	..	..
Sepsis/pneumonia	3 (20%)	2 (13%)	..	..	..
Multiorgan failure	0 (0%)	2 (13%)	..	..	..
Hepatorenal syndrome	0 (0%)	1 (7%)	..	..	..
Hepatocellular carcinoma	1 (7%)	1 (7%)	..	..	..
Unrelated to liver disease	3 (20%)	2 (13%)	..	..	..
Failure to control bleeding or rebleeding	11 (13%)	17 (38%)	−25% (−40 to −9)	0·26 (0·12 to 0·55)	<0·0001
Failure to control bleeding (≤5 days)	1 (1%)	6 (13%)	−12% (−25 to −3)	0·08 (0·01 to 0·68)	0·02
Early rebleeding (>5 days to 6 weeks)	1 (1%)	3 (7%)	−6% (−17 to 1)	0·12 (0·02 to 1·51)	0·16
Late rebleeding (>6 weeks to 2 years)	9 (11%)	8 (18%)	−7% (−22 to 5)	0·50 (0·19 to 1·29)	0·15
Sources of bleeding§	..	..	..	..	0·31‡
Variceal bleeding	9 (82%)	13 (76%)	..	..	..
Portal hypertensive gastropathy	1 (9%)	1 (6%)	..	..	..
Peptic ulcer bleeding	1 (9%	1 (6%)	..	..	..
Post-endoscopic therapy	0 (0%)	2 (12%)	..	..	..
New or worsening ascites	14 (17%)	20 (44%)	−27% (−44 to −11)	0·28 (0·14 to 0·55)	<0·0001
Refractory ascites	0 (0%)	4 (9%)	−9% (−21 to −2)	NE	0·01
Overt hepatic encephalopathy	29 (35%)	16 (36%)	−1% (−18 to 15)	0·89 (0·48 to 1·64)	0·72
More than one episode	13 (15%)	5 (11%)	4% (−9 to 15)	1·30 (0·46 to 3·65)	0·43
Episodes per patient¶	2·4 (1·3)	1·7 (1·2)	0·7% (−1·0 to 1·5)	NE	0·27**
Severe hepatic encephalopathy (grade III/IV)	5 (6%)	4 (9%)	−3% (−15 to 6)	0·61 (0·16 to 2·28)	0·73
Spontaneous overt hepatic encephalopathy	9 (11%)	4 (9%)	2% (−11 to 12)	1·12 (0·34 to 3·62)	0·67
Precipitating overt hepatic encephalopathy††	20 (24%)	12 (27%)	−3% (−19 to 12)	0·78 (0·38 to 1·60)	0·67

Data are n (%) or mean (SD), unless otherwise specified. ARD=absolute risk difference. HR=hazard ratio. TIPS=transjugular intrahepatic portosystemic shunt. *Calculated according to event rates in each treatment group. †Denominator is the total number of patients who died. ‡χ^2 test. §Denominator is the total number of patients with failure to control bleeding or rebleeding. ¶Episodes per patient with overt hepatic encephalopathy. **Student *t* test. ††In the early TIPS group, possible precipitating events for overt hepatic encephalopathy were constipation (n=8), higher protein intake (n=9), and shunt revision (n=3). In the control group, possible precipitating events were gastrointestinal bleeding (n=3), use of diuretics (n=3), infection (n=4), higher protein intake (n=1), and diarrhoea (n=1).

***Table 2*: Summary of outcome measurements in the intention-to-treat population**

achieved in 27 patients after a median of two endoscopic band ligation sessions (range one to five) and a median of 21 days (range 7–91). Of the patients who achieved variceal eradication, varices reappeared in four patients after a median of 163 days (range 64–390). In the remaining 18 patients, eradication was not achieved because of death (n=6), transfer to rescue TIPS (n=11), and non-compliance (n=1).

All patients in both groups received prophylactic antibiotics (ceftriaxone or norfloxacin) of 5–7 days in duration. All 42 HBV-DNA positive patients (except the patient who died early) were treated with entecavir. Undetectable HBV DNA was achieved in 38 patients (25 in the early TIPS group and 13 in the control group).

15 (18%) patients in the early TIPS group and 15 (33%) in the control group died during follow-up; two (2%) patients in the early TIPS group and one (2%) in the control group received a liver transplant. Causes of death are summarised in table 2.

Actuarial transplantation-free survival was higher in the early TIPS group than in the control group at 6 weeks (99% [95% CI 97–100] *vs* 84% [75–96]; ARD 15% [95% CI 5–48]; p=0·02 for ARD), at 1 year (86% [79–94] *vs* 73% [62–88]; ARD 13% [2–28]; p=0·046 for ARD), and at 2 years (79% [71–89] *vs* 64% [52–80]; ARD 15% [1–33]; p=0·04 for ARD). The HR for transplantation-free survival was 0·50 (95% CI 0·25–0·98; p=0·04). A competing risks analysis with liver transplantation as a competing event with mortality showed that the cumulative incidence of death was significantly reduced in the early TIPS group (subdistribution hazard ratio [sHR] 0·47 [95% CI 0·23–0·95]; Gray's test p=0·04). A competing risk analysis done with liver-related mortality, non-liver-related mortality, and liver transplantation as competing events,

showed that the effect of early TIPS was specific for liver-related deaths (appendix p 4). The effect of early TIPS on transplantation-free survival was also observed in the per-protocol population (appendix p 5).

Univariate analysis and multivariate Cox proportional hazard model showed that MELD score was an independent predictor of all-cause mortality or transplantation, whereas early TIPS treatment was the sole protective factor (table 3). The introduction of HBV aetiology or HBV DNA detectable at baseline in the final model did not affect our findings. Finally, the effect of early TIPS was homogeneous across the Child-Pugh/MELD score spectrum (appendix p 6) and most of the prespecified and post-hoc subgroups (appendix pp 7–8). There were no significant interactions in any of the subgroups (p>0·10 for all comparisons).

11 (13%) patients in the early TIPS group experienced failure to control bleeding or rebleeding (table 2); the case of failure to control bleeding was the patient who died before TIPS replacement. The remaining ten patients experienced rebleeding. Of these patients, six underwent TIPS revision and remained free from rebleeding thereafter; four patients received medical and endoscopic treatment for the management of rebleeding (two died of further bleeding and two required later shunt revision for stent stenosis associated with rebleeding). 17 (38%) patients in the control group experienced failure to control bleeding or rebleeding (table 2). Seven of these patients required rescue TIPS (three of whom died due to liver failure or multiorgan failure); six patients achieved haemostasis by further endoscopic treatment, while the remaining four patients died because of massive bleeding or bleeding-related complications.

The actuarial probability of remaining free from uncontrolled bleeding or rebleeding was higher in the early TIPS group than in the control group at 1 year (89% [95% CI 82–96] *vs* 66% [50–80]; ARD 23% [95% CI 8–38]; p=0·001 for ARD) and at 2 years (86% [79–94] *vs* 57% [44–76]; ARD 29% [13–44]; p<0·0001 for ARD; figure 2B). The HR for failure to control bleeding or rebleeding was 0·26 (95% CI 0·12–0·55; p<0·0001). Similar results were obtained using competing risk analysis (appendix p 4) and in the per-protocol population (appendix p 5). Univariate and multivariable analyses confirmed that the independent protective role of early TIPS against failure to control bleeding or rebleeding (table 3). The effect of early TIPS was consistent across most of the prespecified and post-hoc subgroups (appendix pp 7–8).

14 (17%) patients in the early TIPS group and 20 (44%) in the control group had new or worsening ascites (table 2). Four patients in the control group received TIPS placement due to refractory ascites. The actuarial probability of remaining free from new or worsening ascites was higher in the early TIPS group than in the control group at 1 year (89% [95% CI 82–96] *vs* 57% [44–74]; ARD 32% [95% CI 15–47]; p<0·0001 for ARD) and at 2 years (81% [95% CI 73–91] *vs* 54% [41–72]; ARD 27% [11–44]; p<0·0001 for ARD; figure 2C). The HR for new or worsening ascites was 0·28 (95% CI 0·14–0·55; p<0·0001). Similar patterns were observed using competing risk analysis (appendix p 4) and in the per-protocol population (appendix p 5). Univariate and multivariable Cox proportional hazard model showed that treatment and age were significantly associated with new or worsening ascites (table 3). The observed effect of early TIPS was consistent across most of the prespecified and post-hoc subgroups (appendix pp 7–8).

29 (35%) patients in the early TIPS group and 16 (36%) in the control group developed at least one episode of overt hepatic encephalopathy during follow-up (table 2). In the control group, the patients who required TIPS placement due to further bleeding or refractory ascites had a high rate of overt hepatic encephalopathy than did those who did not change therapy (eight [73%] of 11 patients *vs* eight [24%] of 34; p=0·009). No significant differences in the actuarial probability of remaining free from overt hepatic encephalopathy were observed between the groups at 1 year (68% [95% CI 59 to 79] in the early TIPS group *vs* 64% [51 to 81] in the control

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Death or liver transplantation				
Treatment (early TIPS *vs* control)*	0·50 (0·25–0·98)	0·04	0·44 (0·22–0·88)	0·02
Child-Pugh score (per point increase)	1·32 (1·03–1·70)	0·03	..	..
MELD score (per point increase)*	1·11 (1·02–1·21)	0·02	1·13 (1·03–1·23)	0·01
Serum total bilirubin (per mg/dL increase)	1·25 (0·98–1·60)	0·07	..	..
Creatinine (per mg/dL increase)	1·76 (1·01–3·04)	0·05	..	..
Failure to control bleeding or rebleeding				
Treatment (early TIPS *vs* control)*	0·26 (0·12–0·55)	<0·0001	0·25 (0·12–0·54)	<0·0001
Previous bleeding (yes *vs* no)*	1·88 (0·90–3·95)	0·09	..	..
New or worsening ascites				
Treatment (early TIPS *vs* control)*	0·28 (0·14–0·55)	<0·0001	0·25 (0·13–0·50)	<0·0001
Age (per year increase)*	0·968 (0·939–0·997)	0·03	0·960 (0·929–0·992)	0·02
Overt hepatic encephalopathy				
Child-Pugh score (per point increase)	1·27 (1·01–1·59)	0·04	..	..
MELD score (≥19 *vs* <19)	1·98 (1·13–3·45)	0·02	..	..
Ascites (yes *vs* no)*	1·27 (0·96–1·68)	0·09	..	..
Serum total bilirubin (per mg/dL increase)*	1·34 (1·10–1·63)	0·003	1·30 (1·08–1·58)	0·01

Only variables with a p value <0·1 in the univariate analysis are shown. Variables included into the univariate analysis were treatment (early TIPS *vs* control), sex, age, aetiology of cirrhosis, detectable HBV DNA, Child-Pugh score, MELD score, location of varices at index endoscopy, size of oesophageal varices, ascites, hepatic encephalopathy, white blood cell, haemoglobin, platelet, serum albumin, serum total bilirubin, INR, serum creatinine, comorbidities, portal vein thrombosis, body-mass index, heart rate at admission, transfusion requirement, initial endoscopic treatment, and initial pharmacological therapy. MELD=Model for End-Stage Liver Disease. TIPS=transjugular intrahepatic portosystemic shunt. *Variables introduced in multivariable analysis.

Table 3: **Univariate and multivariate analysis**

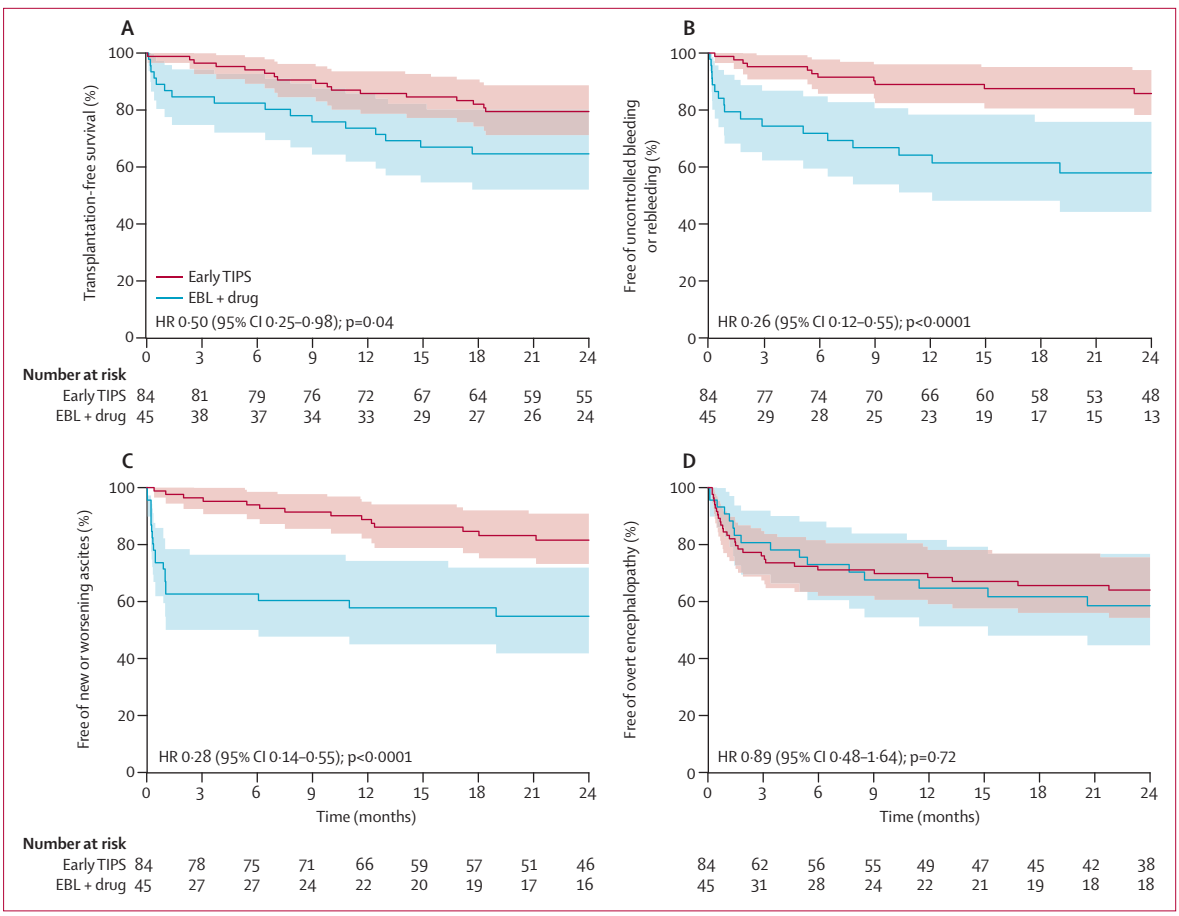

Figure 2: **Kaplan-Meier curves in the intention-to-treat population**
Transplantation-free survival (A); survival free from failure to control bleeding or rebleeding (B); survival free from new or worsening ascites (C); survival free from overt hepatic encephalopathy (D). EBL=endoscopic band ligation. TIPS=transjugular intrahepatic portosystemic shunt.

group; ARD 4% [95% CI –13 to 19]; p=0·82 for ARD) and at 2 years (63% [54 to 75] *vs* 58% [44 to 76]; ARD 5% [–12 to 21]; p=0·71 for ARD; figure 2D). The HR for overt hepatic encephalopathy was 0·89 (95% CI 0·48 to 1·64; p=0·72). Overt hepatic encephalopathy did not significantly differ between groups in competing risk analysis (appendix p 4) and in the per-protocol populations (appendix p 5). Univariate and multivariable analysis showed that bilirubin level was the only independent predictor of overt hepatic encephalopathy (table 3).

There were no significant differences between groups in the incidence of hepatic hydrothorax, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatocellular carcinoma (table 3). There were no significant differences between groups in the number of patients who experienced other serious adverse events or non-serious adverse events (table 4, appendix p 10). A slight increase of both median bilirubin concentrations and median international normalised ratio at 1 and 3 months was observed in the TIPS group but this reduced after 6 months (appendix p 11). Albumin and sodium concentrations were improved in both groups during the study period, while median creatinine concentrations did not change significantly (appendix p 11). Median MELD scores were significantly higher at 1 and 3 months in the TIPS group than in the control group but the differences disappeared after 6 months (appendix p 11).

Discussion

Despite current guidelines, implementation of early TIPS has not been widely accepted in daily clinical practice. As shown in two recent real-world multicentre studies,[17,30] only 7–13% of patients meeting high-risk criteria received early TIPS, mainly due to a lack of confidence in the current data regarding an effect on survival and the lack of availability of the technique.[14,31] In our randomised trial, we found that early use of TIPS in patients with advanced cirrhosis and acute variceal bleeding reduced the risk of transplantation or death compared with standard treatment. At 1 year, early TIPS was associated with an absolute risk reduction of 13% (95% CI 2–28), equivalent to treating

eight patients to prevent one death or transplantation. This effect was probably related to better control of factors contributing to death, such as failure to control bleeding or rebleeding or new or worsening ascites, without increasing the frequency and severity of overt hepatic encephalopathy and other adverse events. This study provides direct evidence and greater confidence in the recommendations of current guidelines that early TIPS should be performed in high-risk patients without contraindications.[2–5]

This is the second randomised trial evaluating the role of early TIPS in the management of acute variceal bleeding in which patient selection was based on clinical parameters. Compared with the previous trial,[13] the strengths of our study include: the use of a survival-based primary endpoint; a larger sample size and broader population (including patients with Child-Pugh class B or C regardless of presence of active bleeding at initial endoscopy); consideration of the effect of aetiological therapy on the outcomes; and the use of multivariate and subgroup analyses that permitted adjustment for potential confounding factors.

The mean portacaval pressure gradient dropped from 24·4 (SD 4·8) to 8·3 (2·4) mm Hg after placement of an 8 mm stent in the early TIPS group and the median heart rate fell from 77 to 58 beats per minute with a median dose of 60 mg propranolol in the control group. These reductions of portacaval pressure gradient and heart rate were greater than in European studies with the same TIPS stent or similar dose of propranolol, but are comparable with those from studies with Chinese patients.[13,23,24,32–34] The discrepancy might be related to differences in ethnicity. Nevertheless, differences in the timing of portacaval pressure gradient measurement after TIPS placement between studies cannot be excluded.[23,35]

1-year transplantation-free survival in our study was 73% in the control group and 86% in the early TIPS group, both of which seem higher than reported in other studies.[13,15–17,30] However, observed survival rates in the high-risk category (Child-Pugh B with active bleeding or Child-Pugh C [score 10–13]) were comparable with those reported in previous studies (appendix p 13). Therefore, the higher survival rates in our patients might be due to the inclusion of patients with Child-Pugh B cirrhosis without active bleeding, who had a lower risk of death than those with Child-Pugh B plus active bleeding or Child-Pugh C cirrhosis. The smaller proportion of patients with Child-Pugh C cirrhosis compared with European studies[13,15–17,30] might be related to the different aetiology of cirrhosis. Pre-TIPS portacaval pressure gradient in our patients was higher than in European studies, although liver function was better (appendix p 14). Patients with viral hepatitis-related cirrhosis may have higher portal pressure than do patients with alcohol-related cirrhosis with comparable liver function. It has been shown that the presence of a non-alcohol-related cause of cirrhosis (compared with alcohol-related cirrhosis) was a strong predictive factor of treatment failure in patients with acute variceal bleeding treated with pharmacological and endoscopic therapy, independent of Child-Pugh class.[36] Nevertheless, the results of our study are consistent with earlier European trials,[12,13] suggesting the findings may have global relevance.

Several observational studies have suggested that early TIPS is not associated with a survival benefit.[15–17] Nevertheless, these studies were non-randomised and most were retrospective in nature. Thus, there is potential for selection bias and unidentified confounders, which may have favoured medical treatment. Furthermore, the majority of patients in the study by Rudler and colleagues[15] had Child–Pugh C disease (including some with a score ≥14); the perceived benefit from early TIPS in such a population is perhaps outweighed by poor survival related to very advanced disease.

	Early TIPS group (n=84)	Control group (n=45)	ARD (95% CI)*	p value
Complications of portal hypertension	40 (48%)	27 (60%)	–12% (–29 to 56)	0·18
Hepatocellular carcinoma	4 (5%)	1 (2%)	3% (–4 to 9)	0·68
Hepatic hydrothorax	2 (2%)	1 (2%)	0% (–5 to 6)	0·96
Hepatic encephalopathy	29 (35%)	16 (36%)	–1% (–18 to 16)	1·00
Spontaneous bacterial peritonitis	1 (1%)	3 (7%)	–6% (–13 to 2)	0·12
Hepatorenal syndrome	4 (5%)	6 (13%)	–8% (–19 to 2)	0·10
Other serious adverse events	10 (12%)	11 (24%)	–12% (–28 to 1)	0·07
Peptic ulcer/gastritis	5 (6%)	2 (4%)	2% (–6 to 9)	1·00
Urinary retention	1 (1%)	0 (0%)	1% (–1 to 4)	1·00
Sepsis/systemic infection	1 (1%)	0 (0%)	1% (–1 to 4)	1·00
Deep venous thrombosis	1 (1%)	1 (2%)	–1% (–6 to 4)	1·00
Oesophageal stenosis	0 (0%)	1 (2%)	–2% (–7 to 2)	1·00
Pneumonia	2 (2%)	3 (7%)	–4% (–12 to 4)	0·34
Portal vein thrombosis	0 (0%)	2 (4%)	–4% (–10 to 2)	0·12
Bleeding from banding ulcer	0 (0%)	2 (4%)	–4% (–10 to 2)	0·12
Non-serious adverse events	21 (25%)	19 (42%)	–17% (–34 to 0)	0·05
Severe itching	2 (2%)	0 (0%)	2% (–1 to 6)	0·54
Peripheral oedema	3 (4%)	1 (2%)	2% (–5 to 7)	1·00
Diarrhoea	3 (4%)	1 (2%)	2% (–5 to 7)	1·00
Rash	1 (1%)	0 (0%)	1% (–1 to 4)	1·00
Abdominal pain	2 (2%)	1 (2%)	0% (–5 to 6)	1·00
Dizziness	2 (2%)	1 (2%)	0% (–5 to 6)	1·00
Dysphagia	1 (1%)	1 (2%)	-1% (–6 to 6)	1·00
Nausea	3 (4%)	3 (7%)	-3% (–11 to 5)	0·42
Abdominal distension	0 (0%)	2 (4%)	–4% (–10 to 2)	0·12
Chest pain (after EBL)	0 (0%)	2 (4%)	–4% (–10 to 2)	0.12
Fatigue	3 (4%)	4 (9%)	–5% (–15 to 4)	0·24
Fever	1 (1%)	3 (7%)	–6% (–13 to 2)	0·12

Data are n (%) or % (95% CI). ARD=absolute risk difference. EBL=endoscopic band ligation. TIPS=transjugular intrahepatic portosystemic shunt. *Calculated according to event rates in each treatment group.

Table 4: **Adverse events**

Although early TIPS improves survival in the acute bleeding phase, it does not seem to have such an effect in the setting of prevention of rebleeding, even in patients with advanced cirrhosis and using covered TIPS.[24,27,28,32–34] The difference in outcomes between early and late (prophylactic) TIPS studies suggest a crucial role for timing of the intervention.[37] If performed within 72 h after bleeding, TIPS has a substantial survival benefit in patients with high risk of early rebleeding. If performed beyond the acute bleeding phase (after 5 days) and patients are haemodynamically stabilised, the advantage of TIPS disappears and TIPS has no effect on mortality. This fact was reflected in the different causes of death in early and late (prophylactic) TIPS studies. In studies examining early TIPS, patients under standard treatment predominantly died from early variceal rebleeding, which was successfully prevented by TIPS.[12,13,15–17,20,30] By contrast, in studies of late TIPS, patients under standard treatment rarely died from rebleeding. Despite a significantly higher rebleeding rate in patients under standard treatment, deaths due to rebleeding were comparable with those undergoing TIPS. Liver failure followed by infection were the most prominent causes of death in patients either undergoing standard treatment or TIPS in the studies of late TIPS.[24,32,34,37] A recent meta-analysis showed that TIPS placed within 5 days after index bleeding is also associated with improved 1-year survival compared with medical treatment for secondary prophylaxis of bleeding without significantly increasing the incidence of hepatic encephalopathy.[38] However, the latency time (4–5 days), which may be associated with survival benefits, remains to be defined.

Whether early TIPS can be equally recommended in Child-Pugh B and C patients remains an open issue. Traditionally, patients with Child-Pugh B cirrhosis, especially those without active bleeding at index endoscopy, were not considered to be candidates for early TIPS because they are not at high risk for failure to control bleeding.[39,40] However, the key criteria for selecting candidates for early TIPS might be whether an individual can benefit from early TIPS rather than whether they have a high risk of failure to control bleeding with standard treatment.[18,19] Our results indicate that there was no interaction between risk categories and treatment group, suggesting that the survival benefit of early TIPS extends across the whole risk spectrum. However, one should also note that our trial is not adequately powered to detect subgroup effects. Although subgroup analyses did not show a significant difference between treatment groups in patients with Child-Pugh B disease, the HR for mortality was suggestive of benefit associated with early TIPS. Furthermore, better control of further rebleeding and ascites without increasing the risk or severity of overt hepatic encephalopathy could also justify the early use of TIPS in this subgroup of patients.

No difference in overt hepatic encephalopathy was observed between groups, which is in keeping with previous early TIPS studies.[13,15,16,24,30] Our results showed that almost a quarter of patients in the control group required TIPS placement, and that these patients had a high rate of overt hepatic encephalopathy. Thus, it is possible that this crossover might have decreased the difference between groups by exposing patients in the control group to the risk of TIPS-induced overt hepatic encephalopathy.

Another important finding of our study was that liver function immediately improved in the control group after the acute bleeding phase. In the early TIPS group, liver function initially deteriorated but subsequently rapidly improved. This finding confirms previous assumptions[18,19] that acute bleeding might cause an acute but transient deterioration that upgrades a patient's Child-Pugh score, but which does not reliably reflect baseline liver function. This may account, at least in part, for the comparable 2-year survival rates between patients with Child-Pugh B and C cirrhosis receiving early TIPS (80–86%) and patients with Child-Pugh A and B treated electively (76–85%).[13,23,24,30,32,34] This could also explain why patients with MELD score of 18 points or more are regarded as contraindications for elective TIPS while they are suitable for early TIPS in the acute bleeding setting.

Our study has several limitations. First, this study was conducted in a tertiary hospital by experienced practitioners. Therefore, the findings need to be validated in other clinical settings. Second, as most patients had HBV-related liver cirrhosis, no definitive conclusions can be drawn for patients with other chronic liver diseases. Third, patients with Child-Pugh A cirrhosis and Child-Pugh score of 14–15 points were excluded from the study. Whether these patients could benefit from early TIPS merits additional investigation. Finally, due to shortage of available donor organs and transplant policies in China, the rate of liver transplantation in our study was lower than we had expected.

In conclusion, among patients with advanced cirrhosis and acute variceal bleeding, early TIPS is superior to drugs plus endoscopic treatment in improving transplantation-free survival, reducing further bleeding and new or worsening ascites without increasing the risk of overt hepatic encephalopathy. Our results favour the early use of TIPS in patients with advanced cirrhosis and acute variceal bleeding. Future studies addressing whether early TIPS can be equally recommended in Child-Pugh B and C patients are warranted.

Contributors

ZYa, YL, and GH conceived and designed the study. KL, CH, ZW, WG, WB, HZ, HX, LY, JW, TL, XY, TY, BL, XL, JY, NH, YZ, JN, ZYi, and GH enrolled and treated patients. YL, ZYa, LL, KL, CH, ZW, WG, WB, HZ, HX, LY, JW, TL, HC, QW, XY, TY, EW, DX, BL, XL, JY, NH, YZ, JN, ZYi, and GH acquired data. YL, ZY, LL, JX, HC, and GH analysed and

interpreted the data. YL drafted the manuscript. ZYa, ZYi, GH, and DF critically revised the manuscript. YL, ZYa, JX, and HC did the statistical analysis. KW and DF provided administrative and material support.

Declaration of interests

We declare no competing interests.

Data sharing

The study protocol, statistical analysis plan, and deidentified participant data can be made available upon request for non-commercial purposes and after approval of a study proposal through a signed data access agreement. Proposals should be directed to hangh@fmmu.edu.cn.

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