ORIGINAL ARTICLE

Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: a multicentre observational study

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ABSTRACT

Objectives Early placement of transjugular intrahepatic portosystemic shunt (TIPS) has been shown to improve survival in high-risk patients (Child-Pugh B plus active bleeding at endoscopy or Child-Pugh C 10–13) with cirrhosis and acute variceal bleeding (AVB). However, early TIPS criteria may overestimate the mortality risk in a significant proportion of patients, and the survival benefit conferred by early TIPS in such patients has been questioned. Alternative criteria have been proposed to refine the criteria used to identify candidates for early TIPS. Nevertheless, the true survival benefit provided (or not) by early TIPS compared with standard treatment in the different risk categories has not been investigated in specifically designed comparative studies.

Design We collected data on 1425 consecutive patients with cirrhosis and AVB who were admitted to 12 university hospitals in China between December 2010 and June 2016. Of these, 206 patients received early TIPS, and 1219 patients received standard treatment. The Fine and Gray competing risk regression model was used to compare the outcomes between the two groups that were stratified based on the currently available risk stratification systems after adjusting for liver disease severity and other potential confounders.

Results Overall, early TIPS was associated with an 80% relative risk reduction (RRR) in mortality at 6 weeks (adjusted HR=0.20; 95% CI: 0.10 to 044; p<0.001) and 51% RRR at 1 year (adjusted HR=0.49, 95% CI: 0.32 to 0.73; p<0.001) compared with standard treatment. In stratification analyses, the RRRs in mortality did not significantly differ among the risk categories. However, the absolute risk reductions (ARRs) of mortality were more pronounced in high-risk patients. The ARRs at 6 weeks were −2.1%, −10.2% and −32.4% in Model for End-stage Liver Disease (MELD) ≤11, 12–18 and ≥19 patients and were −1.5%, −9.1% and −23.2% in Child-Pugh A, B and C patients, respectively (interaction tests, p<0.001 for both criteria). The ARRs for mortality at 1 year were −1.7%, −5.4% and −32.7% in MELD ≤11, 12–18 and ≥19 patients, respectively, and −3.6%, −5.2% and −20.3% in Child-Pugh A, B and C patients,

Significance of this study

What is already known on this subject?

- Compared with standard therapy, early (pre-emptive) covered transjugular intrahepatic portosystemic shunt (TIPS) (placed within 72 hours of admission) is associated with significantly lower treatment failure and mortality rates in selected high-risk patients.
- The use of Child-Pugh class B plus active bleeding at endoscopy as a criterion for selecting high-risk patients has been criticised.
- Several alternative risk stratification systems have been established to refine the criteria for identifying candidates for early TIPS. Nevertheless, the true survival benefit provided (or not) by early TIPS compared with standard treatment in the different risk categories has not been investigated in specifically designed comparative studies.

What are the new findings?

- Compared with standard therapy, early TIPS was associated with an improved survival in patients with cirrhosis and acute variceal bleeding, while high-risk patients benefited the most from early TIPS.
- Early TIPS was associated with an improved survival in patients with Model for End-stage Liver Disease (MELD) ≥19 or Child-Pugh C <14 cirrhosis but not in patients with MELD ≤11 or Child-Pugh A.
- In MELD 12–18 patients, early TIPS was associated with improved survival at 6 weeks. Nevertheless, this beneficial effect did not extend to 1 year.
- In Child-Pugh B patients, a survival benefit was observed in those with active bleeding but not in those without active bleeding. However, the evaluation of active bleeding was associated with high interobserver variability.

Significance of this study

How might it impact on clinical practice in the foreseeable future?

- Early use of TIPS is justified in MELD ≥19 or Child-Pugh C patients, but may not be necessary in MELD ≤11 or Child-Pugh A patients.
- In MELD 12–18 or Child-Pugh B patients, future studies addressing optimal selection criteria for early TIPS remain highly warranted.

respectively (interaction tests, p<0.001 for both criteria). After adjusting for liver disease severity and other potential confounders, a survival benefit was observed in MELD ≥19 or Child-Pugh C patients but not in MELD ≤11 or Child-Pugh A patients. In MELD 12–18 patients, a survival benefit was observed within 6 weeks but not at 1 year. In Child-Pugh B patients, a survival benefit was observed in those with active bleeding but not those without active bleeding. However, the evaluation of active bleeding was associated with a high interobserver variability. Furthermore, early TIPS was associated with a significantly reduced incidence of failure to control bleeding or rebleeding and new or worsening ascites, without increasing the risk of overt hepatic encephalopathy.

Conclusions Early TIPS was associated with improved survival in patients with MELD ≥19 or Child-Pugh C cirrhosis but not in patients with MELD ≤11 or Child-Pugh A cirrhosis. For MELD 12–18 or Child-Pugh B patients, future studies addressing optimal selection criteria for early TIPS remain highly warranted.

INTRODUCTION

Acute variceal bleeding (AVB) is a major complication of portal hypertension and represents a leading cause of death in patients with cirrhosis.[1 2] The current standard of care for AVB is a combination of vasoactive drugs, prophylactic antibiotics and endoscopic variceal ligation.[3–5] However, despite standard treatment, the 6-week mortality of patients with AVB remains high (15%–20%).[6–10] Because of the significant heterogeneity in prognosis for these patients, risk stratification and adapting the different available treatments according to the expected risk constitutes a rational therapeutic approach.[3–5] This approach is particularly relevant since it was demonstrated that early placement (within 72 hours of admission) of transjugular intrahepatic portosystemic shunt (TIPS) as a preventive therapy prior to recurrent bleeding can improve survival in patients with AVB who are at high risk of treatment failure.[11 12]

However, several observational studies including only 'high-risk' patients (Child-Pugh C up to 13 points or Child-Pugh B and active bleeding at initial endoscopy) did not confirm the effect of early TIPS on survival.[13–15] In contrast, a US nationwide database study that included unselected patients with AVB and decompensated cirrhosis showed that early TIPS was associated with significant reductions in rebleeding and mortality,[16] questioning whether the survival benefit of early TIPS is restricted to a specific subset or whether it can be extended to all patients with cirrhosis and AVB.[17 18] Moreover, the criterion of Child-Pugh class B plus active bleeding at endoscopy has been criticised for possibly overestimating the risk of death. Child-Pugh B patients treated with standard of care have been shown to have a significantly better outcome than Child-Pugh C patients, regardless of the presence of active bleeding at endoscopy.[7 19 20]

In recent years, several alternative risk stratification systems have been established to refine the criteria for identifying candidates for early TIPS.[7 19–22] Nevertheless, the true survival benefit provided (or not) by early TIPS compared with standard treatment in the different risk categories has not been investigated in specifically designed comparative studies. Thus, the answers to the following questions are still unclear: (1) does early TIPS improve survival? (2) do the effects of early TIPS on the outcomes vary depending on patient characteristics? (3) which criteria can optimise the early use of TIPS?

Therefore, we performed this large, multicentre, observational study to assess the effects of early TIPS (compared with standard treatment) on the mortality, failure to control acute bleeding or rebleeding, new or worsening ascites and overt hepatic encephalopathy (OHE) among patients with cirrhosis and AVB who were stratified by current available risk stratification systems.

PATIENTS AND METHODS

Study design

We retrospectively extracted the data from the electronic charts and prospective database of consecutive patients with cirrhosis who were admitted for AVB at 12 tertiary academic hospitals in China from December 2010 to June 2016. All participating centres have a gastroenterology/liver unit and highly experienced clinicians performing TIPS. Only centres with a prospective register of all patients with cirrhosis and AVB were eligible for the current study. Written informed consent was obtained for every procedure from all patients before starting treatments according to the institutional guidelines.

Inclusion criteria for the study were a diagnosis of cirrhosis (based on clinical signs, laboratory and imaging tests or liver biopsy) and a first admission for AVB confirmed by emergency endoscopy according to Baveno V definitions.[23] Exclusion criteria were same as those in the early TIPS trial[11]: Child-Pugh score >13 points, age >75 years, hepatocellular carcinoma that did not meet the Milano criteria, a creatinine level ≥3 mg/dL (265 μmol/L), bleeding from isolated gastric or ectopic varices, complete portal vein thrombosis, recurrent hepatic encephalopathy and heart failure. Patients were grouped according to whether they received early TIPS (defined by placement within 72 hours of admission prior to recurrent bleeding, the early TIPS group) or not (the medical group). Of note, patients receiving a rescue TIPS that was placed after a failure to control bleeding despite the use of a combination of intensive pharmacological and endoscopic treatment were classified as medical group.

The primary end point of the study was all-cause mortality. The secondary end points were failure to control acute bleeding or rebleeding (defined according to the Baveno V consensus),[23] new or worsening ascites (new-onset or sustained ascites up to a volume requiring paracentesis despite diuretic use) and the development of OHE (diagnosed and graded according to the West-Haven criteria).[24]

Therapeutic interventions

Patients were managed according to the Baveno V consensus workshops and American Association for the Study of Liver Diseases guidelines.[23 25] The decision to institute therapeutic modifications, especially regarding placement of early TIPS, was based on individual centre policy and the judgement of local physicians according to their clinical assessment of the patients. In general, the physicians were prone to place early TIPS in patients with ascites on admission, active bleeding at initial endoscopy and with a Child-Pugh C <14 points.

Briefly, after admission, patients were treated with vasoactive drugs (octreotide, somatostatin or terlipressin), endoscopic band ligation (sclerotherapy if technically difficult or not feasible) performed within 12 hours of admission, and prophylactic antibiotics. For patients receiving early TIPS, TIPS was performed according to the standard technique with vasoactive drugs administered until the procedure. An 8 or 10 mm polytetrafluoroethylen (PTFE)-covered stent was used based on the discretion of the local physicians. TIPS revision with angioplasty or another stent placement was performed when there was clinical re-emergence of complications associated with portal hypertension or evidence of dysfunction on Doppler ultrasonography. For patients in whom early TIPS was not performed, treatment with vasoactive drugs was continued for up to 5 days. On day 6, β-blockers combined with endoscopic band ligation (EBL) were initiated when applicable in 2-week to 4-week intervals for the prophylaxis of variceal rebleeding. Further variceal ligation sessions were conducted if varices reappeared. A rescue TIPS was performed when bleeding or rebleeding could not be controlled.

All patients were followed in the outpatient clinic at 1, 3 and 6 months and every 6 months thereafter. Medical history, physical examination, biochemistry, haematological tests, abdominal ultrasound and antiviral treatment were recorded. The follow-up time was defined as the intervals from admission to death, liver transplantation, the last visit or the end of the study (31 September 2017).

Stratification systems

We evaluated the impact of early TIPS versus standard therapy on the outcomes by stratifying patients based on the following classification rules: Model for End-Stage Liver Disease (MELD) 11–19 criteria (low risk/intermediate risk/high risk: MELD ≤11/12–18/≥19),[21] Child-Pugh class (low risk/intermediate risk/high risk: Child-Pugh A/B/C),[20 22] early TIPS criteria (low risk: Child-Pugh A plus Child-Pugh B without active bleeding, high risk: Child-Pugh B with active bleeding plus Child-Pugh C ≤13 points)[11] and Child-Pugh C-C1 criteria (low risk: Child-Pugh A/B plus Child-Pugh C with creatinine level <1 mg/dL; high risk: Child-Pugh C with creatinine ≥1 mg/dL).[7]

Statistical analysis

Quantitative variables were expressed as mean±SD and compared using Student's t-test or Mann-Whitney U test. Qualitative variables were presented as frequency (percentages) and compared by means of the X^2 test. Cumulative incidences of failure to control bleeding or rebleeding, new or worsening ascites and OHE were estimated in a competing risks setting, where the death or liver transplantation competed with the event of interest. When the cumulative mortality rate was estimated, liver transplantation was taken into account as a competing risk.

The non-linear relationships between the MELD/Child-Pugh score and the risk of the evaluated outcomes were visualised using restricted cubic splines by entering the MELD/Child-Pugh score as a continuous variable into the logistic regression analysis. To explore the adjusted effect of the treatment group on the evaluated outcomes, we conducted two analyses with competing risk regression models. First, a multivariate model included the treatment group, the MELD/Child-Pugh score and other potential confounders. A potential confounder was considered if a variable was significantly associated with the outcome in a univariate analysis at a level of 10% or if, when added to the models, a variable changed the matched HR by at least 10%. Within each stratum, the components (ascites, encephalopathy, bilirubin, international normalised ratio (INR), albumin and creatinine) instead of the coarse MELD/Child-Pugh score were included in the models to allow fine-tuning of the models. A second multivariate model included the treatment group and a propensity score (detailed in online supplementary materials and methods). To rule out the effect that antiviral treatment might have in our findings, we also adjusted for the virologic response (HBV-DNA or HCV-RNA could not be detectable) that was encoded as a time-dependent covariate. The Wald test was used to assess the homogeneity of the effect of early TIPS across different strata. We tested the interaction between treatment and risk categories on both multiplicative (HR) and additive (absolute difference) scales.[26]

For all analyses, the percentages of missing values of covariates were lower than 6%. We imputed missing data of the covariates by using multiple imputations.[27] Five datasets were created and analysed together (detailed in online supplementary materials and methods). To verify the robustness of our results, two different sensitivity analyses with case-wise deletion of missing values and propensity score matching were performed. Statistical significance was established at $p<0.05$ (two-sided). All analyses were conducted using SPSS V.19.0 (IBM, Somers, New York, USA) and R V.3.4.1 (http://www.R-project.org/) with the add-on packages *Hmisc*, *rms* and *cmprsk*.

RESULTS

Of the 2055 consecutive patients with cirrhosis and AVB admitted to the 12 participating hospitals during the study period, a total of 1425 patients were eligible for the study. The disposition of the patients is shown as a flow chart in online supplementary figure 1. Of the eligible patients, 1219 patients (85.5%) received standard therapy (medical group), and 206 (14.5%) received early TIPS (the early TIPS group). The baseline characteristics of the patients are summarised in table 1. As might be expected by indication bias, patients in the early TIPS group had more severe liver disease, reflected by higher MELD and Child-Pugh scores. The early TIPS group also had a higher proportion of patients with active bleeding at initial endoscopy, lower haemoglobin and a lower likelihood of receiving EVL therapy. The baseline characteristics of patients according to early TIPS criteria are shown in online supplementary table 1.

In the early TIPS group, TIPS was performed within a mean 20.2±15.1 hours from admission; 8 and 10 mm diameter stents were used in 174 (84.5%) and 32 (15.5%) patients, respectively. The mean portacaval pressure gradient (PPG) dropped from 25.4±4.7 to 8.7±3.8 mm Hg ($p<0.001$). In the medical group, 853 patients (70.0%) received propranolol, and 141 patients (11.6%) received nadolol. For the remaining 225 (18.4%) patients, non-selective β-blockers were not initiated because of early death (n=57), receiving rescue TIPS (n=104), non-compliance (n=38) and unknown reasons (n=26). Variceal eradication was achieved in 658 patients after a mean of 2.0±1.2 EBL sessions. All 733 patients with detectable HBV-DNA/HCV-RNA received antiviral treatment, and a virologic response was achieved in 690 (94.1%) patients on follow-up (77 in the early TIPS group and 613 in the medical group).

The mean (±SD) follow-up period was 22.9±16.3 months in the early TIPS group and 23.4±18.2 months in the medical group. Sixty-four (4.5%) patients (8 in the early TIPS group and 56 in medical group) were lost to follow-up after a median follow-up of 13.2 months (range: 0.3–16 months).

Table 1 Baseline characteristics of patients*

Characteristics	Early TIPS group (n=206)	Medical group (n=1219)	P values
Age (years)	54.1±11.6	52.0±15.6	0.023
Male, n (%)	129 (62.6)	855 (70.2)	0.030
Aetiology of cirrhosis, n (%)			0.077
Chronic HBV infection	117 (56.8)	677 (55.5)	
Chronic HCV infection	16 (7.8)	66 (5.4)	
Alcohol	14 (6.8)	123 (10.1)	
Others	20 (9.7)	121 (9.9)	
Miscellaneous	35 (17)	164 (13.5)	
Cryptogenic	4 (1.9)	68 (5.6)	
HBV-DNA detectable, n (%)	83 (40.3)	602 (49.4)	0.016
HCV-RNA detectable, n (%)	7 (3.4)	41 (3.4)	0.980
MELD score* (points)	13.1±4.0	11.8±3.8	<0.001
MELD score*, n (%)			<0.001
≤11	74 (35.9)	665 (54.6)	
12–18	110 (53.4)	438 (35.9)	
≥19	18 (8.7)	77 (6.3)	
Missing data	4 (1.9)	39 (3.2)	
MELD-Na score* (points)	14.3±5.3	12.6±5.3	<0.001
Child-Pugh score (points)	7.9±1.7	7.1±1.5	<0.001
Child-Pugh class, n (%)			<0.001
A (5–6)	40 (19.4)	455 (37.3)	
B (7–9)	131 (63.6)	654 (53.7)	
C (10–13)	33 (16.0)	88 (7.2)	
Missing data	2 (1.0)	22 (1.8)	
Interval from start of bleeding to admission (hours)	21±16	20±18	0.904
Active bleeding at endoscopy, n (%)	74 (35.9)	310 (25.4)	0.002
Location of varices at index gastroscopy, n (%)			0.161
Oesophageal varices only	129 (62.6)	824 (67.6)	
Oesophageal and gastric varices	77 (37.4)	395 (32.4)	
Size of varices (large), n (%)	186 (90.3)	1126 (93.1)	0.146
Previous variceal bleeding, n (%)	109 (52.9)	608 (49.9)	0.420
Previous treatment with β-blockers, n (%)	13 (6.3)	90 (7.4)	0.582
Encephalopathy, n (%)	13 (6.3)	52 (4.3)	0.193
Ascites, n (%)			<0.001
Mild	86 (41.7)	342 (28.1)	
Moderate	37 (18.0)	150 (12.3)	
Massive	14 (6.8)	42 (3.4)	
Haemoglobin (g/dL)	7.6±2.0	8.0±2.3	0.030
International normalised ratio	1.55±0.43	1.37±0.32	<0.001
Bilirubin (mg/dL)	1.74±1.64	1.61±1.62	0.304
Albumin (g/L)	28.7±5.3	30.0±5.7	0.003
Creatinine (mg/dL)	0.85±0.28	0.88±0.41	0.408
Creatinine ≥1 mg/dL, n (%)	53 (26.0)	271 (22.6)	0.284
Platelet count ($\times 10^9$/L)	80.6±123.4	86.1±108.3	0.506
Sodium (mmol/L)	138.9±4.9	138.9±9.5	0.947
Commodities†, n (%)	57 (27.7)	324 (26.6)	0.744
Portal vein thrombosis, n (%)	30 (14.6)	151 (12.4)	0.386
Hepatocellular carcinoma, n (%)	7 (3.4)	38 (3.1)	0.831
Heart rate at admission (beats/min)	84±15	84±16	0.763
Systolic blood pressure at admission (mm Hg)	112.3±15.7	112.5±16.8	0.878
Diastolic blood pressure at admission (mm Hg)	67.1±10.9	67.1±11.2	0.990
Infection at admission, n (%)	19 (9.2)	89 (7.3)	0.203
Shock at admission‡, n (%)	36 (17.5)	211 (17.3)	0.953
Patients transfused, n (%)	116 (56.3)	656 (53.8)	0.506
Blood transfusion within 24 hours (units of packed red cells)	3.5±3.1	3.4±3.5	0.695
Plasma expanders within 24 hours (mL)	3310±538	2803±944	0.454
Antibiotherapy, n (%)	178 (86.4)	990 (81.2)	0.073
Initial endoscopic treatment, n (%)			
Endoscopic band ligation	178 (86.4)	1093 (89.9)	0.001

Continued

Table 1 Continued

Characteristics	Early TIPS group (n=206)	Medical group (n=1219)	P values
Endoscopic sclerotherapy	18 (8.7)	126 (10.1)	
None§	10 (4.9)	0 (0)	
Initial pharmacological therapy, n (%)			
Octreotide	166 (80.6)	990 (81.2)	0.542
Somatostatin	35 (17.0)	184 (15.1)	
Terlipressin	5 (2.4)	45 (3.7)	

Data presented as mean±SD or number of patients (percentage) where appropriate.
*Some data were missing for some patients. The number of patients missing data never exceeded 82 (5.8%).
†Commodities include hypertension, coronary artery disease and diabetes.
‡Hypovolemic shock was defined as systolic blood pressure <100 mm Hg and heart rate >100 bpm.
§In 10 patients without active bleeding at diagnostic endoscopy under vasoactive therapy, physicians decided to place directly early TIPS, without performing endoscopic treatment.
MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

Mortality

Overall, 133 patients (9.3%) died within 6 weeks, and 240 patients (16.8%) died within 1 year. The causes of death are summarised in table 2. Compared with the medical group, the cumulative incidences of death were significantly lower in the early TIPS group at 6 weeks (3.6% vs 10.6%, p=0.002) but not at 1 year (14.1% vs 17.3%, p=0.218, online supplementary figure 2). However, after adjusting for potential confounders, the risk of death with early TIPS was reduced by 80% at 6 weeks (adjusted HR=0.20; 95% CI: 0.10 to 044; p<0.001) and 51% at 1 year (adjusted HR=0.49, 95% CI: 0.32 to 0.73; p<0.001) (table 3). As shown in figures 1-2, this protective effect was consistent in all risk spectrums, but the absolute risk reduction was more pronounced in patients with high-risk profiles. This finding was confirmed by the analyses of the treatment effect in subgroups of patients according to the risk category of four classification rules (table 4, figures 3-4 and online supplementary figure 3).

Specifically, according to MELD 11–19 rules, the early TIPS group had a significantly lower cumulative incidence of death in the MELD ≥19 category (5.6% vs 38.0% at 6 weeks; p=0.011; 16.7% vs 49.4% at 1 year, p=0.008) but not MELD ≤11 category (2.8% vs 4.8% at 6 weeks, p=0.393; 7.4% vs 10.0% at 1 year, p=0.362) compared with the medical group. In MELD 12–18 category, a significantly lower cumulative incidence of death in the early TIPS group was only observed at 6 weeks (3.8% vs 14.2%, p=0.004) but not at 1 year (17.8% vs 23.1%; p=0.239, figure 3A). This pattern persisted after adjusting for potential confounders, with the adjusted HRs (95% CI) being 0.33 (0.08 to 1.42), 0.17 (0.06 to 0.49), 0.07 (0.01 to 0.51) in MELD ≤11/12–18/≥19 category at 6 weeks, respectively, and 0.52 (0.22 to 1.23), 0.71 (0.44 to 1.15), 0.18 (0.05 to 0.58) at 1 year, respectively (table 4). These results were confirmed by the analysis after adjusting for propensity scores (figure 4). Although the relative risk reduction in mortality was homogeneous (p>0.1 for the interaction), the absolute risk reduction with early TIPS was greater in the MELD ≥19 category (−32.4% at 6 weeks and −32.7% at 1 year) than MELD 12–18 (−10.2% at 6 weeks and −5.4% at 1 year) and MELD ≤11 categories (−2.1% at 6 weeks and −1.7% at 1 year), with p<0.001 for the interaction test (figure 4).

Similar patterns emerged when patients were stratified according to their Child-Pugh class. In Child-Pugh C class patients, the cumulative incidences of death were significantly lower in the early TIPS group at 6 weeks (6.1% vs 29.3%, p=0.002) as well as at 1 year (24.2% vs 44.6%, p=0.021). In

Table 2 Summary of outcome measurements

Outcome	Early TIPS (n=206)			Medical (n=1219)		
	5 days	6 weeks	1 year	5 days	6 weeks	1 year
Mortality, n (%)	1 (0.5)	7 (3.4)	29 (14.1)	57 (4.7)	126 (10.3)	211 (17.3)
Cause of death, n (%)						
Liver failure	1 (0.5)	4 (1.9)	16 (7.8)	14 (1.1)	36 (3.0)	73 (6.0)
GI bleeding	0 (0)	0 (0)	1 (0.5)	31 (2.5)	63 (5.2)	83 (6.8)
Sepsis/pneumonia	0 (0)	1 (0.5)	1 (0.5)	3 (0.2)	5 (0.4)	8 (0.7)
Multiorgan failure	0 (0)	0 (0)	2 (1)	1 (0.1)	5 (0.4)	10 (0.8)
Hepatocellular carcinoma	0 (0)	0 (0)	4 (1.9)	0 (0)	0 (0)	4 (0.3)
Unrelated with liver disease	0 (0)	1 (0.5)	3 (1.5)	4 (0.3)	11 (0.9)	23 (1.9)
Unknown	0 (0)	1 (0.5)	2 (1.0)	4 (0.3)	6 (0.5)	10 (0.8)
Liver transplantation, n (%)	0 (0)	2 (1.0)	15 (7.3)	0 (0)	21 (1.7)	78 (7.2)
Failure to control bleeding or rebleeding, n (%)	4 (1.9)	12 (5.8)	22 (10.7)	219 (18.0)	343 (28.1)	490 (40.2)
Failure to control bleeding	0 (0)	0 (0)	0 (0)	96 (7.9)	96 (7.9)	96 (7.9)
Rebleeding from any source	4 (1.9)	12 (5.8)	22 (10.7)	123 (10.1)	247 (20.2)	394 (32.3)
Overt hepatic encephalopathy, n (%)	12 (5.8)	53 (25.7)	77 (37.4)	63 (5.2)	249 (20.4)	333 (27.3)
More than one episode	6 (2.9)	24 (11.7)	31 (15.0)	36 (3.0)	122 (10.0)	151 (12.4)
Grade 3–4	5 (2.4)	22 (10.7)	35 (17.0)	26 (2.1)	98 (8.0)	125 (10.3)
New or worsening ascites, n (%)	0 (0)	3 (1.5)	9 (4.4)	4 (0.3)	37 (3.0)	116 (9.5)
Spontaneous bacterial peritonitis, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0.6)	31 (2.5)

Data presented as number of patients (percentage).
TIPS, transjugular intrahepatic portosystemic shunt.

Table 3 Univariate and multivariate analysis of factors associated with 6-week and 1-year mortality in the entire cohort (n=1425)

	Univariate analysis		Multivariate analysis (model 1)		Multivariate analysis (model 2)	
Variables	**HR (95% CI)**	**P values**	**HR (95% CI)**	**P values**	**HR (95% CI)**	**P values**
Mortality within 6 weeks						
Treatment (early TIPS vs medical)*†	0.27 (0.12 to 0.62)	0.002	0.20 (0.10 to 044)	<0.001	0.18 (0.08 to 0.39)	<0.001
Age (per year increase)*†	1.02 (1.01 to 1.04)	0.003	1.02 (1.01 to 1.03)	0.017	1.02 (1.01 to 1.03)	0.023
HBV-DNA or HCV-RNA detectable (yes vs no)*†	2.18 (1.51 to 3.15)	<0.001	1.72 (1.17 to 2.53)	0.006	1.99 (1.36 to 2.91)	<0.001
Ascites (yes vs no)*	1.31 (1.09 to 1.58)	0.003				
Hepatic encephalopathy (yes vs no)*	2.14 (0.94 to 4.85)	0.069				
Serum albumin (per g/L increase)*	0.91 (0.88 to 0.94)	<0.001	0.94 (0.91 to 0.97)	<0.001		
Serum total bilirubin (per mg/dL increase)	1.13 (1.08 to 1.19)	<0.001				
INR (per unit increase)	3.43 (2.64 to 4.47)	<0.001				
Creatinine (per mg/dL increase)†	1.72 (1.42 to 2.08)	<0.001			1.39 (1.26 to 2.01)	<0.001
MELD score (per point increase)*	1.17 (1.13 to 1.20)	<0.001	1.14 (1.11 to 1.18)	<0.001		
Child-Pugh score (per point increase)†	1.46 (1.33 to 1.61)	<0.001			1.48 (1.34 to 1.64)	<0.001
Active bleeding at endoscopy (yes vs no)*†	2.86 (2.03 to 4.02)	<0.001	2.61 (1.84 to 3.69)	<0.001	2.75 (1.95 to 3.89)	<0.001
Shock at admission (yes vs no)*†	2.23 (1.54 to 3.23)	<0.001				
Infection at admission (yes vs no)*†	3.21 (1.02 to 10.07)	0.046			3.38 (1.07 to 10.65)	0.037
Commodities‡ (yes vs no)*†	1.37 (0.95 to 1.96)	0.092				
HCC at admission (yes vs no)*†	2.49 (1.27 to 1.90)	0.008				
Mortality with 1 year						
Treatment (early TIPS vs medical)*†	0.78 (0.53 to 1.16)	0.191	0.49 (0.32 to 0.73)	<0.001	0.46 (0.31 to 0.69)	<0.001
Age (per year increase)*†	1.03 (1.01 to 1.04)	<0.001	1.02 (1.01 to 1.03)	<0.001	1.02 (1.01 to 1.03)	<0.001
HBV-DNA or HCV-RNA detectable (yes vs no)*†	2.01 (1.54 to 2.63)	<0.001	1.73 (1.31 to 2.29)	<0.001	1.73 (1.31 to 2.29)	<0.001
Ascites (yes vs no)*	1.44 (1.26 to 1.64)	<0.001	1.25 (1.09 to 1.43)	0.001		
Hepatic encephalopathy (yes vs no)*	2.58 (1.44 to 4.61)	0.001	1.72 (1.12 to 2.64)	0.013		
Serum albumin (per g/L increase)*	0.92 (0.90 to 0.94)	<0.001	0.95 (0.93 to 0.97)	<0.001		
Serum total bilirubin (per mg/dL increase)	1.14 (1.10 to 1.19)	<0.001				
INR (per unit increase)	3.47 (2.78 to 4.34)	<0.001				
Creatinine (per mg/dL increase)†	1.62 (1.38 to 1.90)	<0.001			1.51 (1.25 to 1.82)	<0.001
MELD score (per point increase)*	1.16 (1.13 to 1.19)	<0.001	1.12 (1.10 to 1.15)	<0.001		
Child-Pugh score (per point increase)†	1.45 (1.35 to 1.56)	<0.001			1.47 (1.36 to 1.59)	<0.001
Active bleeding at endoscopy (yes vs no)*†	1.80 (1.39 to 2.34)	<0.001	1.69 (1.30 to 2.20)	<0.001	1.73 (1.33 to 2.26)	<0.001
Shock at admission (yes vs no)*†	1.74 (1.30 to 2.33)	<0.001				
Infection at admission (yes vs no)*†	3.10 (1.28 to 3.52)	0.012	3.12 (1.28 to 7.60)	0.011	3.36 (1.38 to 8.16)	0.007
Commodities‡ (yes vs no)*†	1.45 (1.11 to 1.89)	0.007				
HCC at admission (yes vs no)*†	1.77 (0.99 to 3.16)	0.054				

Only variables with a p value <0.1 in the univariate analysis are shown. Variables selected into the univariate analysis were treatment, gender, age, aetiology of cirrhosis, HBV-DNA or HCV-RNA detectable, Child-Pugh score, MELD score, interval from start of bleeding to admission, location of varices at index gastroscopy, grade of oesophageal varices, ascites, hepatic encephalopathy, previous bleeding, treatment with β-blockers at admission, haemoglobin, serum albumin, serum total bilirubin, INR, serum creatinine, commodities, portal vein thrombosis, hepatocellular carcinoma, heart rate at admission, infection at admission, shock at admission, transfusion requirement, antibiotherapy, initial endoscopic treatment and initial pharmacological therapy.
*Variables introduced in model 1.
†Variables introduced in model 2.
‡Commodities include hypertension, coronary artery disease and diabetes.
§Hypovolemic shock was defined as systolic blood pressure <100 mm Hg and heart rate >100 bpm.
HCC; hepatocellular carcinoma; INR, international normalised ratio; MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

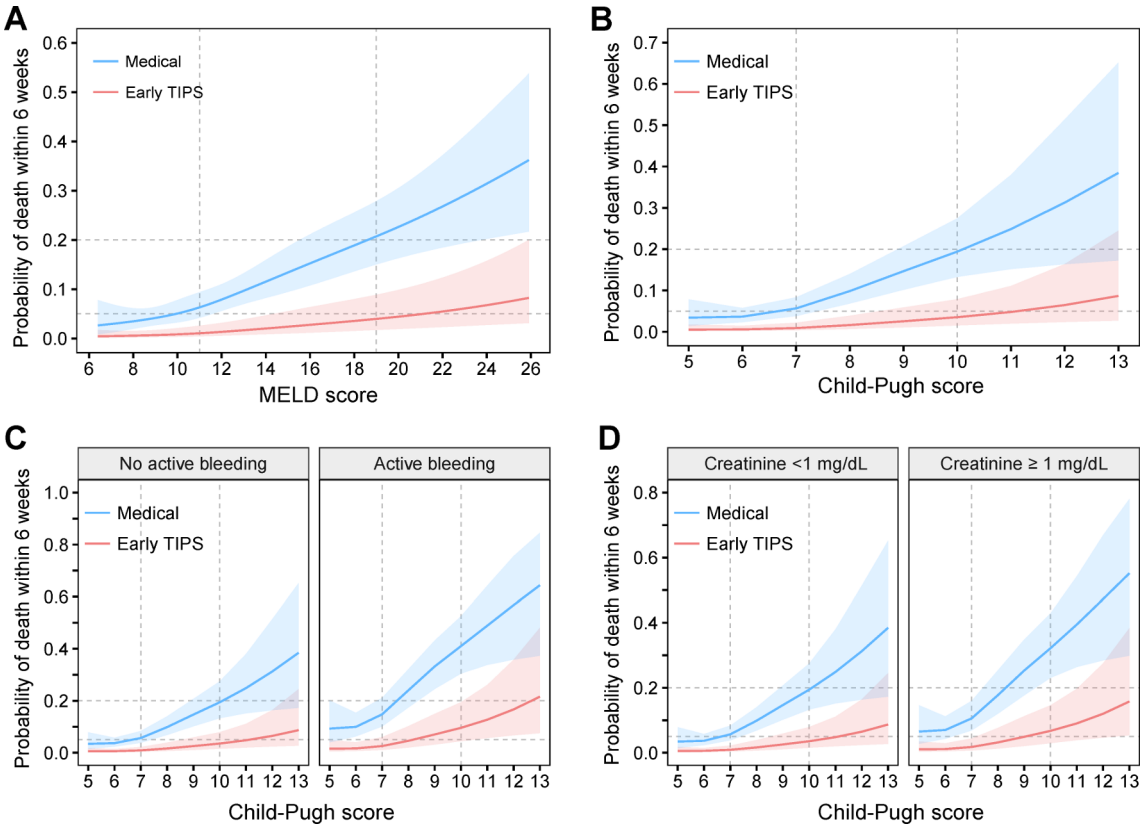

Figure 1 Adjusted 6-week mortality stratified by different risk categories and treatment groups. Probability of death within 6 weeks according to (A) MELD score or (B) Child-Pugh score or (C) Child-Pugh score stratified by active bleeding or (D) Child-Pugh score stratified by creatinine level and the treatment group. Restricted cubic splines were generated using logistic regression models adjusted for (A) age, HBV-DNA or HCV-RNA detectable, albumin and active bleeding at endoscopy; (B) age, HBV-DNA or HCV-RNA detectable, creatinine, infection at admission and active bleeding at endoscopy; (C) age, HBV-DNA or HCV-RNA detectable, creatinine and infection at admission; (D) age, HBV-DNA or HCV-RNA detectable, infection at admission and active bleeding at endoscopy. The colour ribbons indicate 95% CIs. MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

Child-Pugh B class patients, the cumulative incidences of death were significantly lower in the early TIPS group at 6 weeks (3.1% vs 12.2%, p=0.002) but not at 1 year (17.5% vs 19.7%, p=0.160). In Child-Pugh A class, the cumulative incidences of death were not significantly different between the groups at 6 weeks (2.4% vs 3.9%, p=0. 604) as well as at 1 year (4.8% vs 8.4%, p=0.382, figure 3B). This pattern was not altered after adjusting for potential confounders (table 4 or the propensity score (figure 4). Again, although the relative risk reduction was homogeneous (p>0.1 for the interaction tests), the absolute mortality reduction with early TIPS was greater in Child-Pugh C class (−23.2% at 6 weeks and −20.3% at 1 year) than Child-Pugh B (−9.1% at 6 weeks and −5.2% at 1 year) and Child-Pugh A classes (−1.5% at 6 weeks and −3.6% at 1 year). This was also confirmed by significant tests of interaction (p<0.001 for the interaction tests, figure 4).

Per the early TIPS criteria, significantly lower cumulative incidences of death in the early TIPS group were observed in the high-risk category (7.1% vs 25.4% at 6 weeks, p<0.001 and 17.4% vs 23.2% at 1 year, P=0.005) but not in the low-risk category (2.5% vs 5.8% at 6 weeks, p=0.131 and 17.4% vs 23.2% at 1 year, p=0.717, figure 3C). Similar results were observed after adjusting for potential confounders (table 4), and the analysis adjusting for the propensity score (figure 4). Furthermore, the absolute risk reduction decreased from −20.7% in the high-risk category to −3.3% in the low-risk category at 6 weeks and from −15.8% to −0.8% at 1 year (p<0.001 for the interaction test).

Per Child-Pugh C-C1 criteria, the early TIPS group had significantly lower cumulative incidences of death at 6 weeks in the low-risk category (3.1% vs 9.0%, p=0.005) and in the high-risk category (7.1% vs 48.5%, p=0.008). However, when follow-up extended to 1 year, significantly lower cumulative incidences of death in the early TIPS group was only in the high-risk category (28.6% vs 54.5%, p=0.046) but not the low-risk category (13.0% vs 16.3%, p=0.241; figure 3D). After adjusting for potential confounders, the pattern persisted at 6 weeks, while early TIPS was associated with a significantly reduced risk of death in the low-risk but not the high-risk category at 1 year (table 4). Similar results were observed after adjusting for the propensity score (figure 4). Nevertheless, the absolute risk reduction was more pronounced in the high-risk compared with the low-risk category both at 6 weeks and 1 year (p<0.001 for the interaction test).

We also evaluated the impact of early TIPS on mortality in Child-Pugh B patients with and without active bleeding. As shown in figure 5A, a lower cumulative incidence of death in the early TIPS group was only observed in those with active bleeding (2.0% vs 23.6% at 6 weeks, p=0.012 and 9.4% vs 27.7% at 1 year, p=0.014) but not in those without active bleeding (3.9% vs 7.6% at 6 weeks, p=0.214 and 17.9% vs 16.5% at 1 year, p=0.938). A similar pattern emerged after adjusting for potential confounders (table 4) or the propensity score (figure 5B). However, the proportion of patients with active bleeding varied greatly among the centres, ranging from 15.2% to 53.6% (p<0.001, online supplementary figure 4).

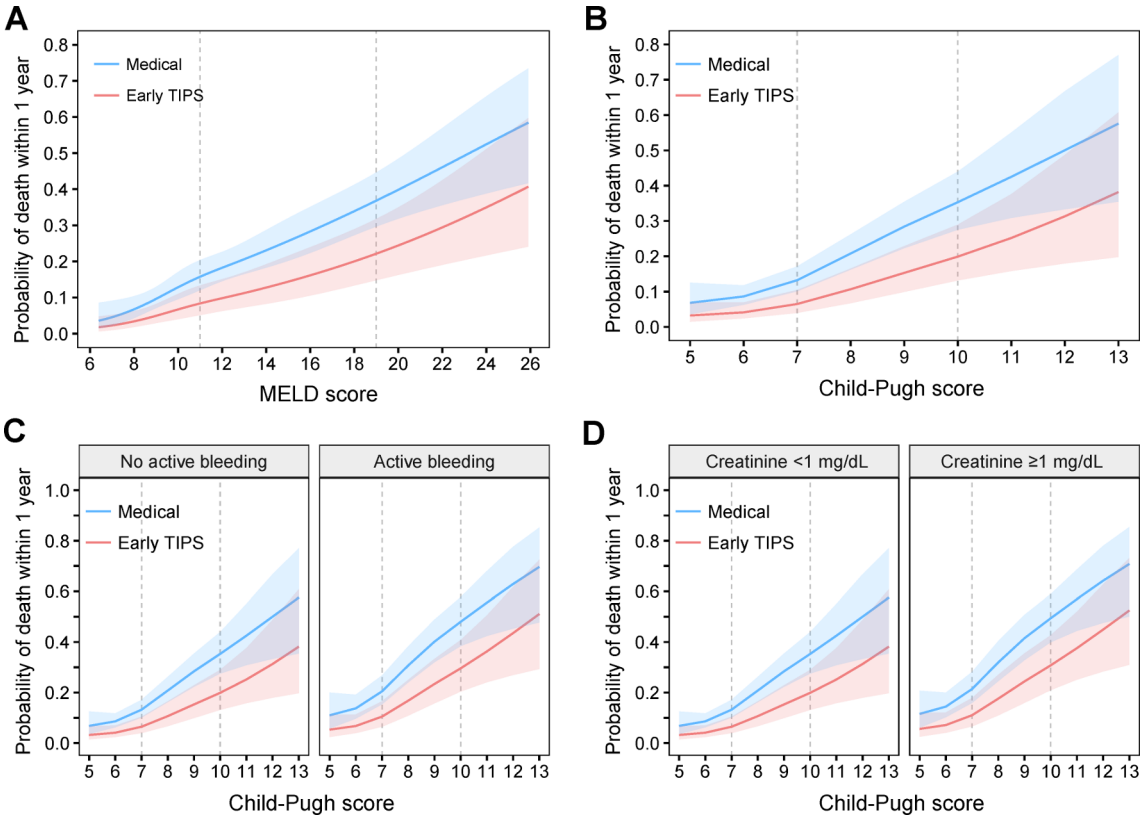

Figure 2 Adjusted 1-year mortality stratified by different risk categories and treatment groups. Probability of death within 1 year according to (A) MELD score or (B) Child-Pugh score or (C) Child-Pugh score stratified by active bleeding or (D) Child-Pugh score stratified by creatinine level and the treatment group. Restricted cubic splines were generated using logistic regression models adjusted for (A) age, HBV-DNA or HCV-RNA detectable, ascites, hepatic encephalopathy, albumin, infection at admission and active bleeding at endoscopy; (B) age, HBV-DNA or HCV-RNA detectable, creatinine, infection at admission and active bleeding at endoscopy; (C) age, HBV-DNA or HCV-RNA detectable, creatinine and infection at admission; (D) age, HBV-DNA or HCV-RNA detectable, infection at admission and active bleeding at endoscopy. The colour ribbons indicate 95% CIs. MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

Failure to control bleeding or rebleeding

During follow-up, 22 patients (10.7%) in the early TIPS group vs 490 patients (40.7%) in the medical group had failure to control bleeding or rebleeding (p<0.001, table 2). One hundred and four patients (8.5%) in the medical group received TIPS as rescue therapy. As shown in online supplementary table 2, patients receiving rescue TIPS had more severe liver disease and a higher rate of mortality than those not receiving TIPS or receiving early TIPS. Overall, the cumulative incidence of failure to control bleeding or rebleeding was lower in the early TIPS group at 6 weeks (5.8% vs 28.1%, p<0.001) as well as at 1 year (10.7% vs 40.1%, p<0.001) compared with the medical group (see online supplementary figure 5). This pattern was not altered after adjusting for potential confounders (see online supplementary table 3) and, more importantly, was homogeneous across the entire risk spectrum in any of the four classification rules (see online supplementary figures 6-9 and online supplementary table 4).

New or worsening ascites

The cumulative incidence of new or worsening ascites requiring paracentesis was not different between the groups at 6 weeks (1.6% vs 3.5%, p=0.213). However, it was significantly decreased in the early TIPS group at 1 year (5.2% vs 11.9%, p=0.021) compared with the medical group (see online supplementary figure 10). This pattern persisted after adjusting for potential confounders (see online supplementary table 5). In the stratification analysis, the absolute risk reduction of new or worsening ascites with early TIPS was more pronounced in the higher risk patients (see online supplementary figures 11-13 and online supplementary table 6).

Overt hepatic encephalopathy

No significant differences in the cumulative incidence of OHE at 6 weeks (early TIPS, 25.7% vs medical, 20.4%; p=0.41) and 1 year (37.4% vs 27.3%, p=0.57, online supplementary figure 14) were observed between the two treatment groups. These results were not altered after adjusting for the potential confounders (see online supplementary table 7) and, more importantly, consistent across the risk strata in any of the four classification rules (see online supplementary figures 15-18 and online supplementary table 8).

Sensitivity analysis

Similar results were obtained when analyses were performed after adjusting for virologic response (data not shown), deletion of missing values (see online supplementary table 9) and using propensity score matching (see online supplementary table 10).

DISCUSSION

In this multicentre observational study, by using comparative effectiveness methods, we showed that early TIPS was associated with an improved survival, decreased failure to control bleeding or rebleeding, new or worsening ascites, without increasing the

Table 4 Impact of early -TIPS (vs standard treatment) on 6-week and 1-year mortality according to different risk classification rules

		Univariate models Unadjusted estimates			Multivariate models Adjusted for the baseline predictive variables			
Risk classification	**No. of patients (%)**	**HR (95% CI)**	**P values**	**P for interaction**	**HR (95% CI)**	**P values**	**P for interaction**	**Variables adjusted for***
6-Week Mortality								
MELD 11–19				0.183			0.272	
≤11	756 (53.1)	0.54 (0.13 to 2.27)	0.402		0.33 (0.08 to 1.42)	0.332		Active bleeding, INR, ascites, albumin
12–18	572 (40.1)	0.25 (0.09 to 0.69)	0.007		0.17 (0.06 to 0.49)	0.001		Age, active bleeding, PLT, INR, creatinine, albumin
≥19	97 (6.8)	0.11 (0.02 to 0.84)	0.033		0.07 (0.01 to 0.51)	0.009		Age, INR, HCC
Child-Pugh class				0.384†			0.407†	
A	504 (35.4)	0.59 (0.08 to 4.43)	0.608		0.45 (0.06 to 3.44)	0.440		Age, active bleeding, INR, albumin, creatinine
B	796 (55.9)	0.24 (0.09 to 0.66)	0.006	0.036‡	0.21 (0.08 to 0.59)	0.003	0.014‡	Age, active bleeding, INR, albumin, creatinine, HBV-DNA or HCV-RNA detectable
Without active bleeding	552 (69.3)	0.47 (0.15 to 1.54)	0.214		0.32 (0.10 to 1.06)	0.062		Age, INR, PLT
With active bleeding	244 (30.7)	0.08 (0.01 to 0.58)	0.012		0.10 (0.01 to 0.73)	0023		Age, INR, PLT, albumin
C	125 (8.8)	0.18 (0.04 to 0.74)	0.017		0.16 (0.04 to 0.69)	0.014		Albumin, creatinine, infection at admission
Early TIPS§				0.233			0.259	
Low risk	1056 (74.1)	0.42 (0.13 to 1.35)	0.144		0.33 (0.10 to 1.07)	0.066		Albumin, INR, creatinine, HBV-DNA or HCV-RNA detectable
High risk	369 (25.9)	0.17 (0.06 to 0.46)	<0.001		0.15 (0.05 to 0.40)	<0.001		Age, INR, albumin, creatinine
Child-Pugh C-C1¶				0.288			0.234	
Low risk	1378 (96.7)	0.33 (0.15 to 0.75)	0.008		0.18 (0.08 to 0.42)	<0.001		Age, active bleeding, INR, albumin, HBV-DNA or HCV-RNA detectable
High risk	47 (3.3)	0.11 (0.01 to 0.81)	0.031		0.10 (0.01 to 0.79)	0.029		Age, INR, albumin
1-Year Mortality								
MELD 11–19				0.062			0.155	
≤11	756 (53.1)	0.82 (0.35 to 1.89)	0.637		0.52 (0.22 to 1.23)	0.134		Age, active bleeding, ascites, INR, albumin, bilirubin
12–18	572 (40.1)	0.75 (0.47 to 1.21)	0.241		0.71 (0.44 to 1.15)	0.168		Age, active bleeding, albumin, HBV-DNA or HCV-RNA detectable
≥19	97 (6.8)	0.23 (0.07 to 0.75)	0.015		0.18 (0.05 to 0.58)	0.004		Age, INR, HCC
Child-Pugh class				0.428†			0.491†	
A	504 (35.4)	0.54 (0.13 to 2.22)	0.390		0.51 (0.12 to 2.10)	0.347		Active bleeding, ascites, albumin, bilirubin, creatinine
B	796 (55.9)	0.71 (0.44 to 1.15)	0.163	0.041‡	0.65 (0.40 to 1.05)	0.075	0.029‡	Age, active bleeding, albumin, HBV-DNA or HCV-RNA detectable, INR, creatinine
Without active bleeding	552 (69.3)	1.02 (0.58 to 1.81)	0.938		0.64 (0.35 to 1.15)	0.137		Age, INR, PLT
With active bleeding	244 (30.7)	0.34 (0.13 to 0.84)	0.020		0.35 (0.14 to 0.87)	0.024		Age, INR, PLT, HBV-DNA or HCV-RNA detectable
C	125 (8.8)	0.42 (0.20 to 0.90)	0.025		0.37 (0.16 to 0.82)	0.015		Age, INR, creatinine
Early TIPS§				0.089			0.122	
Low risk	1056 (74.1)	0.90 (0.52 to 1.57)	0.718		0.62 (0.35 to 1.09)	0.097		Age, ascites, albumin, bilirubin, creatinine, HBV-DNA or HCV-RNA detectable
High risk	369 (25.9)	0.47 (0.27 to 0.80)	0.006		0.40 (0.63 to 0.70)	0.001		Age, INR, albumin, creatinine, HCC
Child-Pugh C-C1¶				0.138			0.212	
Low risk	1378 (96.7)	0.47 (0.31 to 0.73)	0.001		0.55 (0.36 to 0.83)	0.005		Age, active bleeding, ascites, albumin, bilirubin, HBV-DNA or HCV-RNA detectable
High risk	47 (3.3)	0.35 (0.12 to 1.04)	0.059		0.33 (0.11 to 0.99)	0.049		Age, INR, albumin

HR for the effect of early TIPS vs medical treatment (as reference).
*We adjusted these variables on the basis of their associations with the outcomes of interest or a change in effect estimates of >10%.
†P value for the interaction between treatment effect and Child-Pugh class in the entire cohort.
‡P value for the interaction between treatment effect and active bleeding in the Child-Pugh B class.
§Early TIPS criteria: low risk: Child-Pugh A and Child-Pugh B without active bleeding at initial endoscopy; high risk: Child-Pugh B with active bleeding at endoscopy and Child-Pugh class C <14.
¶Child-Pugh C-C1 criteria: low risk: Child-Pugh class A or B and Child-Pugh C with creatinine <1 mg/dL; high risk: Child-Pugh C with creatinine ≥1 mg/dL.
HCC, hepatocellular carcinoma; INR, international normalised ratio; MELD, Model for End-Stage Liver Disease; PLT, platelet count; TIPS, transjugular intrahepatic portosystemic shunt.

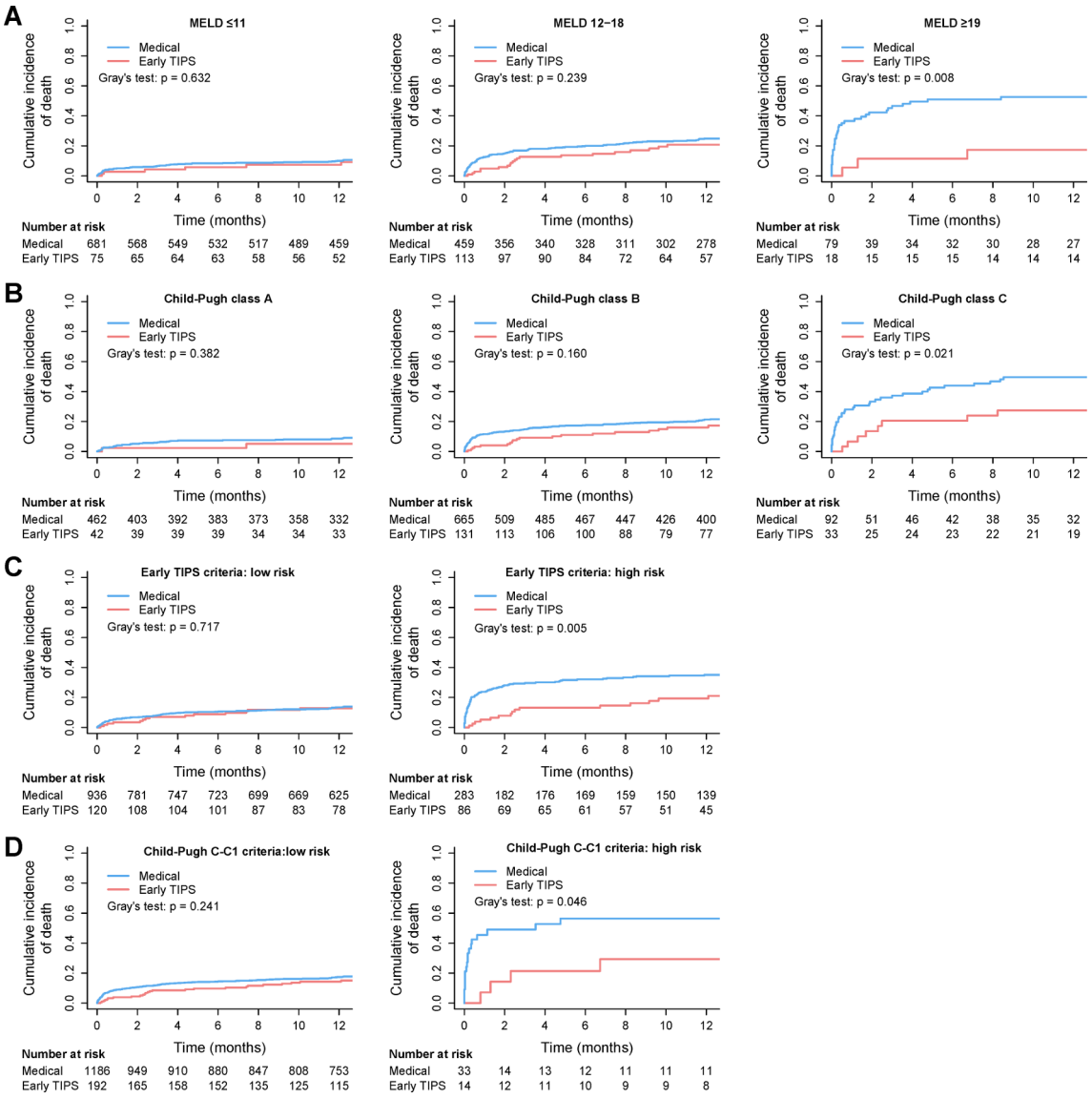

Figure 3 Cumulative incidence of death at 1 year in the early TIPS group vs medical group stratified according to (A) MELD 11–19 rules, (B) Child-Pugh class, (C) early TIPS criteria and (D Child-Pugh C-C1 criteria based on competing risk approach (the Fine and Gray method) with liver transplantation being the competing events. Early TIPS criteria: low risk: Child-Pugh A and Child-Pugh B without active bleeding at initial endoscopy; high risk: Child-Pugh B with active bleeding at endoscopy and Child-Pugh class C <14. Child-Pugh C-C1 criteria: low risk: Child-Pugh class A or B and Child-Pugh C with creatinine <1 mg/dL; high risk: Child-Pugh C with creatinine ≥1 mg/dL. MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

risk of developing OHE in patients with cirrhosis and AVB. Remarkably, in contrast to a consistent relative and absolute effect on the failure to control bleeding or rebleeding and OHE across the risk strata, the absolute risk reduction in mortality as well as new or worsening ascites with early TIPS were strongly associated with the patients' baseline risks. Patients with a high risk of treatment failure or mortality benefited the most from early TIPS.

The landmark early TIPS study by García-Pagán *et al*[11] opened the way to individualised care for patients with cirrhosis and AVB. Since then, a series of validation studies has been published.[13–15 28] Compared with the latter, the strengths of our study include: (1) unselected patients with various risks of mortality rather than a singular focus on high-risk patients; (2) a large sample size, extended observation period and comprehensive outcomes analyses; (3) for the first time, an evaluation of the applicability of MELD 11–19 and Child-Pugh C-C1 criteria in early TIPS patients and (4) a novel finding that patients with a higher MELD score benefit the most from TIPS, which contrasts with many studies that evaluated upper MELD cut-offs to exclude TIPS patients.

The overall 6-week mortality in the medical group was 10.6% in our cohort. This value is in the low range of the 6-week mortality reported in most recent studies.[19–21] However, the 6-week mortality in each risk category is comparable with those reported in previous studies. Indeed, by showing a 6-week mortality rate of 3.9%, 12.2%, 29.3% in Child-Pugh A/B/C and 4.8%, 13.7%, 38.0% in the MELD ≤11, 12 to 18, and ≥19 categories in patients receiving standard treatment, our data confirm that using either Child-Pugh class (A/B/C) or the risk equivalent of MELD score with a threshold of 11 and 19 is useful for identifying patients with a high, intermediate and low mortality risk (>20%, 20% to 5% and <5%, respectively).[20 21] Therefore, the lower 6-week mortality in our cohort could be explained by

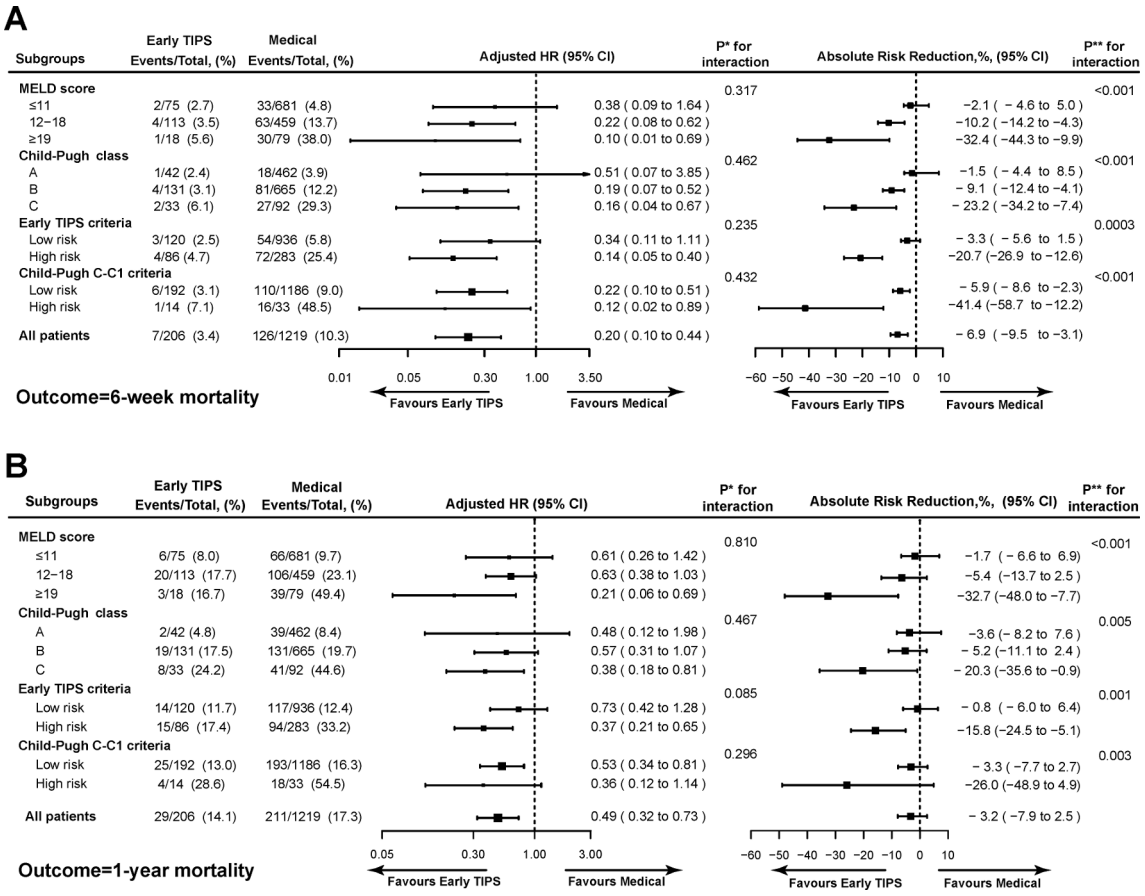

Figure 4 Event rate, adjusted HRs and the absolute risk reduction for the (A) 6-week and (B) 1-year mortality by risk categories and treatment groups. Early TIPS criteria: low risk: Child-Pugh A and Child-Pugh B without active bleeding at initial endoscopy; high risk: Child-Pugh B with active bleeding at endoscopy and Child-Pugh class C <14. Child-Pugh C-C1 criteria: low risk: Child-Pugh class A or B and Child-Pugh C with creatinine <1 mg/dL; high risk: Child-Pugh C with creatinine ≥1 mg/dL. In the forest plot, the adjust HRs and absolute risk reduction for the early group compared with the medical group are shown, with the size of each black square proportioned to the number of patients in the subgroup and the horizontal lines indicating 95% CIs. Adjusted HRs indicate the effect of early TIPS vs medical treatment (as reference) on the mortality adjusted for propensity score. *P for interaction between treatment and risk categories on the HR scale. **P for interaction between treatment and risk categories on the absolute risk reduction scale. MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

the lower proportion of patients with Child-Pugh C cirrhosis. Moreover, our data showed that active bleeding was associated with an increased risk of mortality, either in the entire population or in the subgroup of Child-Pugh B cirrhosis. This conflicts with the findings of two recent studies that active bleeding at initial endoscopy did not confer additional risk to Child-Pugh B patients.[19 20] Nevertheless, our finding is in agreement with several earlier studies showing that active bleeding bears a significant prognostic weight in variceal bleeding.[6 29] These conflicting results may provide further confirmation that active bleeding is not a reliable prognostic indicator in this setting. Indeed, as illustrated by our and other studies, active bleeding is evaluated in a heterogeneous fashion in different centres.[19 30]

When our entire cohort of 1425 patients is considered, early TIPS was associated with a relative 80% reduction in death at 6 weeks and a 51% reduction at 1 year, a result that is consistent with the findings of a recent large USA study.[16] Notably, this beneficial effect on survival was observed even though rescue TIPS was used in patients in whom medical treatment failed. In addition, we found that the survival benefit provided by early TIPS was modified by the baseline risk profile. Although not entirely understood, early TIPS may improve survival in patients with cirrhosis and AVB as a result of both haemodynamic (reduction in portal pressure) and non-haemodynamic effects (decreasing gut bacterial translocation and systemic inflammation that may further aggravate organ dysfunction and precipitate the onset of acute-on-chronic liver failure).[31–34] This phenomenon has been demonstrated by data showing that a great reduction in portal pressure following TIPS led to normalisation of the intestinal permeability evaluated by sugar probes[35] and a decrease in markers of systemic inflammation and bacterial translocation (endotoxin and tumour necrosis factor receptor, chemokines such as C-X-C motif ligand 9).[36 37] Since portal hypertension and bacterial translocation worsen as cirrhosis progresses,[38] it may explain why the survival benefit of early TIPS increases with increasing severity of liver disease, which is associated with the risk of death. However, there was no interaction between the risk categories and the survival benefit of early TIPS in the relative HR scales, suggesting that the survival benefit from early TIPS extends through the entire risk spectrum. It should still be noted that patients with Child-Pugh score >13 were excluded in our and other early TIPS studies.[11 13–15 28] Currently, the cut-off Child-Pugh/MELD score up to which early TIPS can be performed safely remains unknown. Therefore, further studies are warranted to assess whether there is a ceiling of severity at which early TIPS fails to improve outcomes.

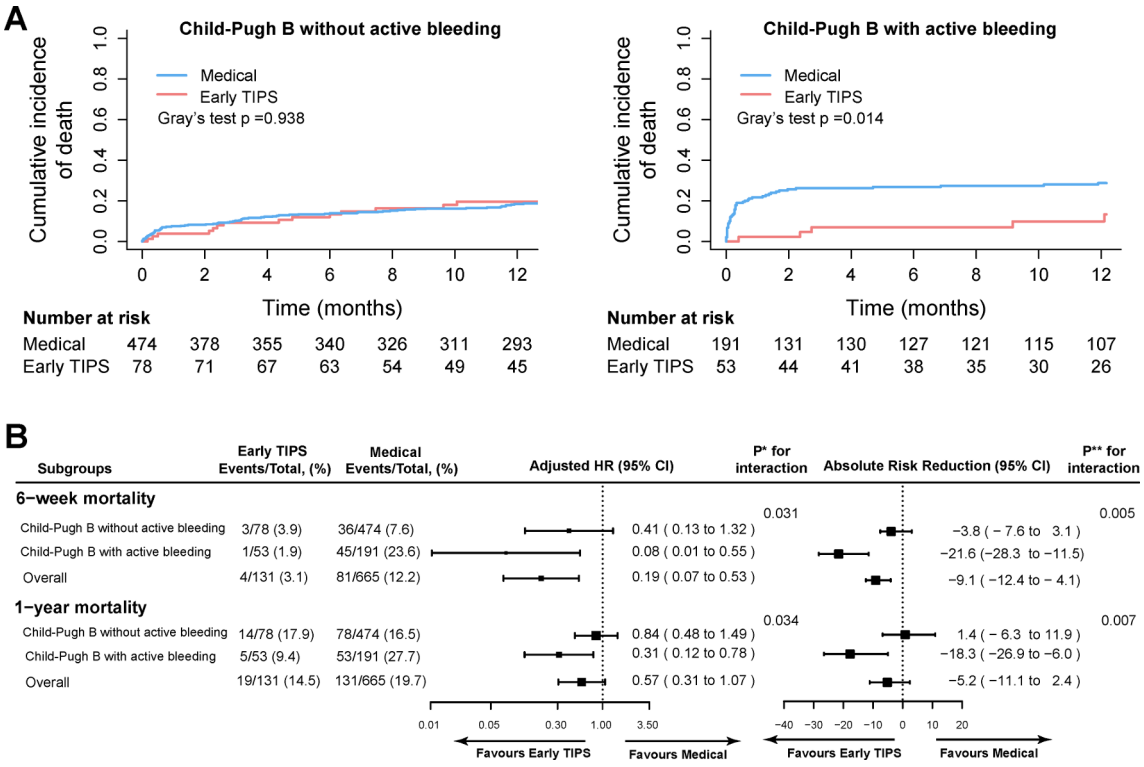

Figure 5 Effect of early TIPS vs standard therapy on the mortality stratified by active bleeding in Child-Pugh B patients. (A) Cumulative incidence of death in early TIPS group vs medical group stratified by presence of active bleeding at index endoscopy. (B) Event rate, adjusted HRs and the absolute risk reduction for the 6-week and 1-year mortality by active bleeding and treatment groups (early TIPS vs medical). Adjusted HRs indicate the effect of early TIPS vs medical treatment (as reference) on the mortality adjusted for propensity scores. *P for interaction between treatment and active bleeding on the HR scale. **P for interaction between treatment and active bleeding on the absolute risk reduction scale. TIPS, transjugular intrahepatic portosystemic shunt.

In MELD ≤11 or Child-Pugh A patients, the risk of mortality with standard treatment was already low. Consequently, although the adjusted HR for mortality showed a strong signal for benefit of 0.38 (95% CI 0.09 to 1.64), 0.51 (95% CI 0.07 to 3.85), respectively at 6 weeks, and 0.61 (95% CI 0.26 to 1.42), 0.48 (95% CI 0.12 to 1.98), respectively at 1 year, the differences did not reach significance. In addition, the absolute risk reductions (−1.7% to −3.6%) were negligible, and the number needed to treat (NNT) to prevent 1 death was 28–59 patients. In contrast, early TIPS was associated with a marked reduction in 6-week and 1-year mortality in MELD ≥19 or Child-Pugh C <14 patients, from 38.0% to 5.6% and 29.3% to 6.1%, respectively at 6 weeks, from 49.4% to 16.7% and 44.6% to 24.2%, respectively at 1 year. The NNT to prevent one death was as low as three to five patients, suggesting that early TIPS treatment is likely to be most cost-effective in this subpopulation. These findings strongly support the recommendation of the most recent European Association for the Study of the Liver (EASL) clinical practice guidelines that early pre-emptive covered TIPS can be recommended in patients with Child-Pugh class C with a score <14.[39]

In MELD 12–18 or Child-Pugh B patients, early TIPS was associated with an improved survival at 6 weeks. Nevertheless, this beneficial effect did not extend to 1 year. It is possible that as time progresses, the positive effects of early TIPS in preventing further decompensation by controlling bleeding, treating ascites and preventing bacterial translocation is counterbalanced by the adverse effect of deteriorating liver function. Indeed, in patients with MELD 12–18 or Child-Pugh B cirrhosis, early TIPS did not confer a significant benefit in reducing the 1-year incidence of new or worsening ascites requiring paracentesis. Furthermore, our data demonstrated that early TIPS improved survival among Child-Pugh B patients with active bleeding. This finding is at odds with a recent large observational study by Hernández-Gea *et al*[28] that failed to show a survival benefit in this subgroup of patients. However, with only 19 patients with Child-Pugh class B and active bleeding in their study, the sample may not have been large enough with sufficient statistical power to detect a difference. As discussed above, active bleeding is also hampered by subjectivity. Therefore, it is still necessary to establish an objective and accurate prognostic prediction in this setting.

In keeping with previous studies,[11 13 14 28] early TIPS was not associated with an increase in the development of OHE. More importantly, this observation was homogeneous across the entire risk spectrum. In view of the comparable OHE rate, early TIPS may have no disadvantage irrespective of the stratification category. Thus, one could speculate that while stratification and selective treatment of patients is an option, it is not mandatory. Surely, before jumping to this conclusion, prospective large randomised or observational studies are needed.

Our study has several limitations. First, selection and indication bias are inherent in any non-randomised observational study. Second, although we performed a multivariate regression and propensity score analysis to adjust for potential confounders, unidentified biases may have acted in favour of the medical group. Third, in terms of the end point of new or worsening ascites, only those requiring paracentesis not all grades of ascites were evaluated, because the data regarding

ultrasound surveillance of variations in the amount of ascites were not available in all patients. This may have led to an underestimation of the benefits of early TIPS. Fourth, since most study patients had HBV-related liver cirrhosis, the results should be interpreted cautiously for patients with other types of chronic liver disease. Fifth, because the shortage of available donor organs limits the potential number of organ transplantations in China,[40] the liver transplantation rate in our cohort was very low.

In conclusion, by presenting the risk-stratified effects of early TIPS on outcomes in patients with cirrhosis and AVB, our study supports the early use of TIPS in MELD ≥19 or Child-Pugh C patients who have a high risk of death with standard treatment but benefit the most from early TIPS. However, TIPS may not be necessary in MELD ≤11 or Child-Pugh A patients considering their low risk of death with standard treatment and the small benefit associated with TIPS. Although early TIPS may be a valuable option for MELD 12–18 or Child-Pugh B patients, further studies are needed. Considering the retrospective nature of our study, these results should be interpreted with caution and are needed to be confirmed in future large prospective studies.

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