Heliyon 10 (2024) e25824

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

The time window for pre-emptive transjugular intrahepatic portosystemic shunt could be extended to 5 days

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ARTICLE INFO

Keywords:
Pre-emptive TIPS
Time window
Acute variceal bleeding
Sarcopenia
Prognosis

ABSTRACT

As recommended by Baveno VII consensus, the utilization of pre-emptive transjugular intrahepatic portosystemic shunt (pTIPS) has been considered as standard therapeutic approach for the management of acute variceal bleeding (AVB) associated with cirrhosis., but the 72-h window for pTIPS is too narrow. This study aimed to compare the clinical outcomes between patients who received <72 h pTIPS and 72 h-5d pTIPS. In this study, a total of 63 cirrhotic patients with AVB who underwent pTIPS between October 2016 and December 2021 were included in this retrospective study. They were divided into <72 h group (n = 32) and 72 h-5d group (n = 31), based on the timing of the intervention. The Kaplan-Meier curves demonstrated that there were no significant differences in the cumulative incidence of death (22.3% ± 7.4% vs. 19.9% ± 7.3%, log-rank P = 0.849), variceal rebleeding (9.7% ± 5.3% vs. 17.8% ± 7.3%, log-rank P = 0.406), OHE (28.5% ± 8.0% vs. 23.9% ± 8.0%, log-rank P = 0.641) and shunt dysfunction (8.6% ± 6.0% vs. 17.4% ± 8.1%, log-rank P = 0.328) between <72 h and 72 h-5d groups. In the total cohort, sarcopenia was identified as an independent risk factor for mortality (HR = 11.268, 95% CI = 1.435–88.462, P = 0.021) and OHE(HR = 12.504, 95% CI = 1.598–97.814, P = 0.016). In conclusion, the clinical outcomes of cirrhotic patients with AVB who underwent pTIPS within the 72-h to 5-day window were found to be comparable to those treated within the 72-h window.

Abbreviations: AVB, acute variceal bleeding; NSBB, non-selective beta-blockers; TIPS, transjugular intrahepatic portosystemic shunt; PPG, portal pressure gradient; pTIPS, pre-emptive TIPS; PTFE, polytetrafluoroethylene; RCT, randomized clinical trials; OHE, overt hepatic encephalopathy; MELD, model for end-stage liver disease; FIPS, Freiburg index of post-TIPS survival; L3 SMI, skeletal muscle index at the L3 vertebra; HR, hazard ratio; CI, confidence interval; TBIL, total bilirubin; ALB, albumin; AST, aspartate aminotransferase; HVPG, hepatic venous pressure gradient.

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https://doi.org/10.1016/j.heliyon.2024.e25824
Received 7 November 2023; Received in revised form 26 January 2024; Accepted 2 February 2024
Available online 3 February 2024

1. Introduction

Acute variceal bleeding (AVB) is a prevalent and life-threatening complication in cirrhotic patients with portal hypertension, resulting in short-term mortality ranging from 20% to 30% [1,2]. The principal goal of AVB management is to effectively control bleeding, prevent rebleeding, and reduce mortality. Currently, the prevailing treatments for AVB encompass endoscopic therapy, non-selective beta-blockers (NSBBs) and transjugular intrahepatic portosystemic shunt (TIPS) [3].

TIPS is a technique that could rapidly reduce the portal pressure gradient (PPG) by creating an artificial shunt between the portal vein branches and the systemic circulation within the liver parenchyma, thereby effectively controlling variceal bleeding and preventing rebleeding [4]. According to the Baveno VII consensus, it is recommended that patients presenting with oesophageal varices and type 1/2 gastro-oesophageal varices should undergo pre-emptive transjugular intrahepatic portosystemic shunt (pTIPS) using polytetrafluoroethylene (PTFE) covered stents within 72 h if they meet the following criteria: Child-Pugh class C $<$ 14 or Child-Pugh class B $>$ 7, active bleeding is observed during endoscopy, or hepatic venous pressure gradient (HVPG) exceeds 20 mmHg at the time of bleeding [5]. Several meta-analyses of randomized clinical trials (RCTs) have confirmed the significant advantages of pTIPS over conventional endoscopy plus NSBBs for the treatment of AVB [6,7] Currently, pTIPS has gained considerable recognition among clinicians and is extensively employed in the management of AVB [8].

However, pTIPS is recommended to be performed within 72 h, but this time window is too narrow, which might limit the widespread use of pTIPS in clinical practice due to pre-TIPS tests cannot be completed within a limited time in some patients with AVB. In fact, pTIPS was performed in many patients with AVB outside the 72-h window in clinical practice [9]. Unfortunately, there is insufficient evidence to determine whether pTIPS placement beyond the 72-h window is still beneficial, as mentioned by Baveno VII consensus [5]. To this end, comprehensive and representative data on the efficacy and safety of pTIPS outside 72-h window are needed but currently limited.

When patients have recovered from an episode of AVB, this clinical setting was defined as secondary prophylaxis of variceal bleeding, which should start from day 6 of the index variceal episode as described in Baveno V consensus [10]. Consequently, this study aimed to compared the clinical outcomes of patients receiving $<$72 h pTIPS and 72 h-5d pTIPS, and further analyzed the factors associated with the prognosis of patients treated by pTIPS.

2. Materials and methods

The study protocol was approved by the Institutional Review Board of Wuhan Union Hospital (approval number: UHCT-IEC-SOP-016-03-01) in accordance with the declaration of Helsinki.

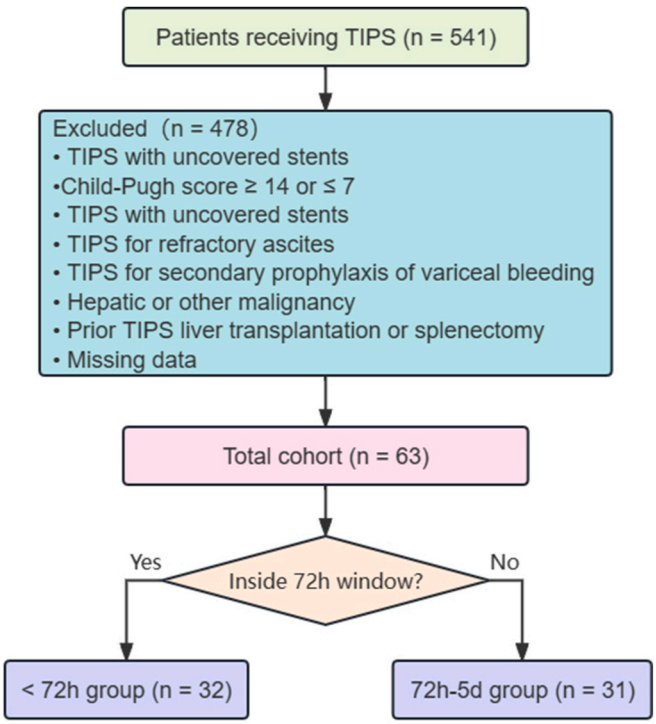

Fig. 1. Study design and flowchart.

2.1. Patients and methods

This retrospective study included 541 cirrhotic patients with variceal bleeding who underwent TIPS between October 2016 and December 2021.

The inclusion criteria for this study were as follows: (1) cirrhosis-related variceal bleeding diagnosed by clinical signs, laboratory examinations, endoscopy, imaging, or liver biopsy; (2) pTIPS for variceal bleeding. Exclusion criteria were as follows: (1) age <14 or >75 years; (2) Child-Pugh score ≥ 14 or ≤ 7; (3) TIPS with uncovered stents; (4) TIPS for refractory ascites; (5) TIPS for secondary prophylaxis of variceal bleeding; (6) missing data; (7) hepatic or other malignancy; (8) prior TIPS liver transplantation or splenectomy.

A total of 478 patients were excluded, and 63 patients were finally included in the total cohort. Patients were divided into <72 h group (n = 32) and 72 h-5d group (n = 31) according to the pTIPS procedure inside or outside the 72-h window (Fig. 1).

2.2. TIPS procedure

TIPS procedures were conducted in adherence to professional practice guidelines [11,12], and a previous study described the specific steps [13]. In brief, a transjugular hepatic access device (Rups-100; Cook Medical) was inserted via the right internal jugular vein into the hepatic vein. Subsequently, a hydrophilic guide wire and catheter were slowly introduced into the splenic or superior mesenteric vein upon puncturing the portal vein, portography was then performed to assess portal venous patency. Following the dilation of the liver parenchymal tract using a balloon catheter, an 8-mm bare metal stent (E-Luminexx or Lifestent; Bard Inc, Tempe, AZ) combined with an 8-mm ePTFE-covered stent (Fluency; Bard Inc. or Viabahn; Gore Inc.) was implanted between the hepatic vein and portal vein, followed by the dilation of the stent. PPG was measured in each patient before and after TIPS placement and post-TIPS PPG should be reduced to <12 mmHg or by $\geq 20\%$ of baseline [12].

2.3. Assessment of sarcopenia

The CT images that were stored electronically were utilized for the purpose of quantifying the skeletal muscle at the L3 vertebra. As previously described, skeletal muscle area (SMA) was identified and measured by applying Hounsfield unit (HU) thresholds of -29 to $+150$, and cross-sectional areas (cm^2) were automatically computed by summing tissue pixels and multiplying by pixel surface area. Images were analyzed by two trained observers using Slice-Omatic software, version 4.3 (Tomovision, Montreal, QC, Canada). Subsequently, the SMA was standardized to the individual's height in order to determine skeletal muscle index (SMI, cm^2/m^2) [13]. According to the Japan Society of Hepatology guidelines for sarcopenia in liver disease, sarcopenia was defined as L3 SMI <42 cm^2/m^2 for men and <38 cm^2/m^2 for women [14].

2.4. Follow-up, clinical outcomes and definitions

In this study, the primary endpoint was death, and the secondary endpoints were variceal rebleeding, overt hepatic encephalopathy (OHE) and shunt dysfunction. The follow-up period was determined from the date of TIPS procedure, which served as the starting point for monitoring. And all patients were followed until death, or for a duration exceeding one year.

Variceal rebleeding was defined in accordance with the Baveno VII consensus [5], while HE was diagnosed and graded according to the West-Haven criteria, with grade 2 and above being classified as OHE [15].

The findings of Doppler ultrasonography (maximal shunt flow velocity of ≤ 50 or ≥ 250 cm/s) as well as clinical findings (variceal rebleeding) were suggestive of shunt dysfunction, intrajugular venography was performed if shunt dysfunction was suspected. Once the shunt dysfunction was confirmed, TIPS revision was recommended, involving procedures such as thrombus aspiration, balloon angioplasty or stent implantation within the existing stent [12,16].

The model for end-stage liver disease (MELD), MELD-Na and Freiburg index of post-TIPS survival (FIPS) scores were calculated according to the corresponding criteria [17–19].

2.5. Statistical analysis

Considering the retrospective design of our study, no sample size calculation was made.

All statistical analyses were performed using R software (version 4.2.1) or IBM SPSS (version 22.0). Continuous variables were expressed as mean $\pm$ standard deviation and compared using Students *t*-test. Categorical variables were expressed as frequencies (percentages) and compared using chi-square or Fisher's exact test. Time-to-event endpoints including death, variceal rebleeding, OHE and shunt dysfunction were estimated using Kaplan-Meier method and the differences were compared by log-rank tests. Univariable and multivariable Cox regression models were used to determine the independent risk factors for mortality and OHE. All variables with $P < 0.10$ in the univariable analysis were included in multivariable Cox regression models, and the hazard ratio (HR) and 95% confidence interval (CI) were calculated and reported. All P values were bilateral, and $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics of patients in the <72 h group and 72 h-5d groups are presented in Table 1. The mean age for the two groups were 56.6 ± 12.7 and 56.4 ± 10.3 years (P = 0.953), respectively. The predominant etiology in both groups was hepatitis B cirrhosis, accounting for 59.4% and 71.0% (P = 0.698), respectively. In addition, the laboratory parameters, prognostic scores, and imaging indexes of the two groups demonstrated comparability.

The median follow-up for this study was 49 (range 17–79) months.

3.2. Perioperative complications and PPG

TIPS was successfully created in all patients, and no fatal complications associated with the procedure, such as biliary bleeding, intrahepatic bleeding, or hemoperitoneum, were observed within 24 h of TIPS placement.

The mean hospitalization time of the <72 h group and 72 h-5d groups were 8.2 ± 3.2 days and 10.4 ± 3.7 days (P = 0.017), respectively. During hospitalization, all patients included in this study received blood transfusions and none required transfer to the intensive care unit.

There was no significant difference in baseline PPG between the two groups ($P = 0.249$), and the post-TIPS PPG reached the target value in both groups. After TIPS placement, the mean PPG in the <72 h group decreased significantly from 26.1 ± 4.1 mmHg to 10.8 ± 3.3 mmHg ($P < 0.001$), and from 24.7 ± 4.6 mmHg to 9.5 ± 2.6 mmHg in 72 h-5d group (P < 0.001). Additionally, no difference was found in post-TIPS PPG of the two groups ($P = 0.120$) (Fig. 2).

3.3. Clinical outcomes

After TIPS implantation, 7(21.9%) and 6(19.4%) patients in <72 h and 72 h-5d groups died during the follow-up period, and the specific causes of death were shown in Table 2. Additionally, in <72 h and 72 h-5d groups, variceal rebleeding occurred in 3 (9.4%) and 5(16.1%) patients, OHE in 7 (28.1%) and 7 (22.6%) patients, and shunt dysfunction in 2 (6.3%) and 4 (12.9%) patients,

Table 1
Baseline characteristics of the patients included in this study.

Variables	All patients (n = 63)	<72 h group (n = 32)	72 h-5 d group (n = 31)	*P* values
Demographic Characteristics				
Age, years	56.5 ± 11.5	56.6 ± 12.7	56.4 ± 10.3	0.953
Gender, male	36 (57.1)	20 (62.5)	16 (51.6)	0.450
Body weight, kg	61.2 ± 10.2	60.3 ± 9.7	61.9 ± 10.9	0.574
Height, m	1.66 ± 0.07	1.66 ± 0.07	1.65 ± 0.08	0.578
BMI, kg/m^2	22.4 ± 3.2	22.0 ± 2.9	22.8 ± 3.5	0.393
History of endoscopic treatment	36 (57.1)	17 (53.1)	19 (61.3)	0.613
Etiology				0.698
HBV	41 (65.1)	19 (59.4)	22 (71.0)	
HCV	9 (14.3)	6 (18.8)	3 (9.7)	
Alcohol	3 (4.8)	2 (6.2)	1 (3.2)	
Others	10 (15.9)	5 (15.6)	5 (16.1)	
Laboratory Parameters				
TBIL, mg/mL	1.45 ± 0.87	1.47 ± 0.70	1.43 ± 1.02	0.852
ALB, g/L	27.7 ± 4.5	28.5 ± 4.7	26.9 ± 4.2	0.145
ALT, U/L	28.0 (18.0–39.0)	28.0 (18.3–37.8)	28.0 (16.0–47.0)	0.965
AST, U/L	37.0 (27.0–55.0)	37.05 (31.0–48.3)	37.0 (27.0–59.0)	0.986
Creatinine, mg/mL	0.78 ± 0.42	0.79 ± 0.43	0.76 ± 0.41	0.783
INR	1.45 ± 0.24	1.47 ± 0.26	1.43 ± 0.22	0.527
Platelet count, $10^9/L$	71.0 (52.0–108.0)	78.0 (58.0–108.0)	62.0 (48.0–98.0)	0.147
Child-Pugh score	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	0.891
MELD score	12.3 ± 3.1	12.6 ± 3.0	12.0 ± 3.2	0.782
MELD-Na score	12.7 ± 3.5	13.1 ± 3.5	12.2 ± 3.4	0.869
FIPS score	−0.95 ± 0.92	−0.94 ± 0.99	−0.96 ± 0.86	0.952
Radiographic Analysis				
Ascites	51 (81.0)	26 (81.3)	25 (80.6)	1.000
PVT	13 (20.6)	5 (15.6)	8 (25.8)	0.365
SPSS	7 (11.1)	2 (6.3)	5 (16.1)	0.257
L3-SMI, cm^2/m^2	43.6 ± 9.6	42.4 ± 8.5	44.7 ± 10.6	0.372
Sarcopenia	31 (49.2)	17 (53.1)	14 (45.2)	0.617

Data presented as mean ± SD or number of patients (%) or median (IQR) where appropriate.
Abbreviation: HBV, hepatitis B virus; HCV, hepatitis C virus; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; FIPS, Freiburg index of post-TIPS survival; PVT, portal vein thrombosis; SPSS, spontaneous portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt; PPG, portal pressure gradient.

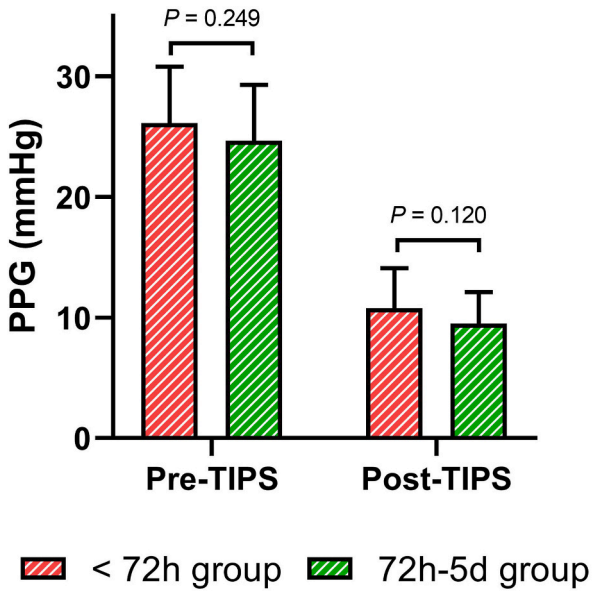

Fig. 2. The changes of portal pressure gradient (PPG) in <72 h and 72 h-5d groups.

Table 2
Causes of death in <72 h and 72 h-5 d groups.

Cause	<72 h group (n = 32)	72 h-5d group (n = 31)	Total (n = 63)
Liver failure	4 (12.5)	3 (9.7)	7 (11.1)
Variceal rebleeding	2 (6.3)	2 (6.5)	4 (6.3)
Renal failure	1 (3.1)	1 (3.2)	2 (3.2)
Total	7 (21.9)	6 (19.4)	13 (20.6)

Data presented as number of patients (%).

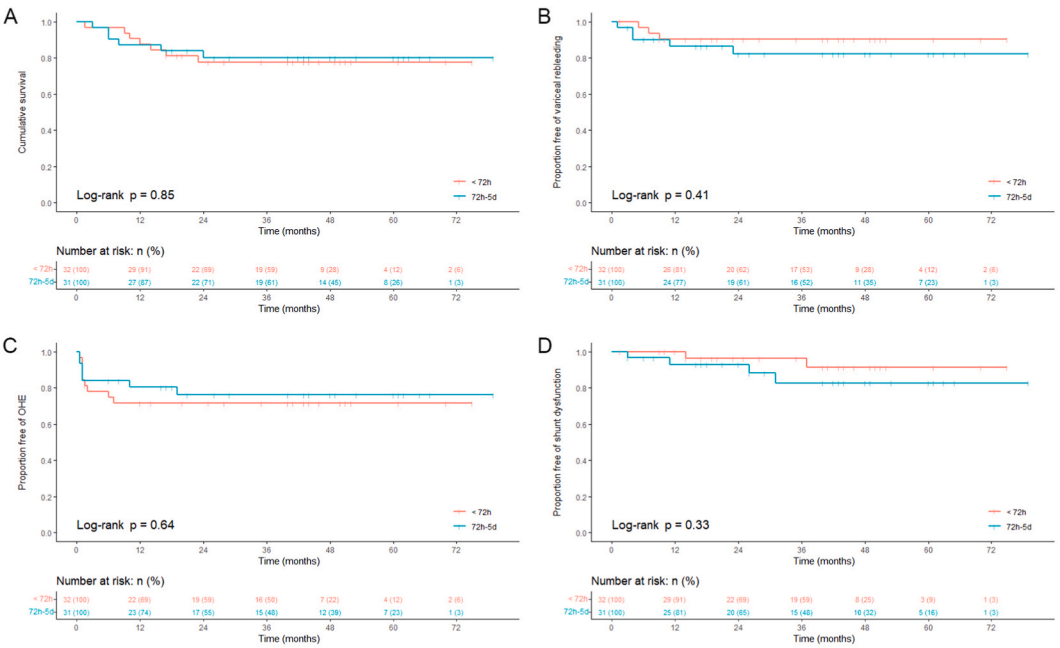

Fig. 3. Kaplan-Meier curves for survival (A), overt hepatic encephalopathy (OHE) (B), variceal rebleeding (C) and shunt dysfunction (D) in <72 h and 72 h-5d groups.

respectively.

The Kaplan-Meier curves indicated no significant difference in the cumulative incidence of death (Fig. 3A), variceal rebleeding (Fig. 3B), OHE (Fig. 3C) and shunt dysfunction (Fig. 3D) between <72 h and 72 h-5d groups. Specific results were as follows: death, 22.3% ± 7.4% vs. 19.9% ± 7.3% (log-rank P = 0.849); variceal rebleeding, 9.7% ± 5.3% vs. 17.8% ± 7.3% (log-rank P = 0.406); OHE, 28.5% ± 8.0% vs. 23.9% ± 8.0% (log-rank P = 0.641); and shunt dysfunction, 8.6% ± 6.0% vs. 17.4% ± 8.1% (log-rank P = 0.328).

Further, the occurrence of clinical events at different time periods after TIPS placement was demonstrated in detail in Table 3. The results showed that there were no significant differences between the two groups in the incidence of death, variceal rebleeding, OHE, shunt dysfunction and liver transplantation at 0–6, 6–12, 12–36, and 36–60 months post-TIPS.

3.4. Prognostic factors for mortality and OHE

All 63 patients were included in the total cohort. Subsequently, the risk factors for mortality and OHE in cirrhotic patients treated with pTIPS were analyzed.

Univariable Cox regression analysis revealed significant associations between mortality and age, total bilirubin (TBIL), creatinine, sarcopenia, Child-Pugh score, MELD score, MELD-Na score and FIPS score were significantly associated with mortality. Furthermore, age, TBIL, creatinine and sarcopenia were included in the multivariable Cox regression model, and the results showed that TBIL (HR = 1.597, 95% CI = 1.008–2.532, P = 0.046) and sarcopenia (HR = 11.268, 95% CI = 1.435–88.462, P = 0.021) were identified as the independent risk factors for mortality (Table 4).

As for OHE, age, TBIL, albumin (ALB), aspartate aminotransferase (AST), sarcopenia, Child-Pugh score, MELD score and MELD-Na score were potential risk factors for OHE. Subsequently, age, TBIL, ALB, AST and sarcopenia were included in the multivariable Cox regression model, which showed that the independent risk factors for OHE were age (HR = 1.075, 95% CI = 1.012–1.142, P = 0.019) and sarcopenia (HR = 12.504, 95% CI = 1.598–97.814, P = 0.016) (Table 5).

It is worth mentioning that univariate and multivariate regression analysis showed that >72 h were not an independent risk factor for mortality and OHE.

4. Discussion

In this study, we compared the clinical outcomes in patients treated with pTIPS inside and outside the 72-h window. The results indicated that there were no significant differences observedin the cumulative incidence of death, variceal rebleeding, OHE and shunt dysfunction during longer follow-up periods between the two groups. These findings suggests that pTIPS remains effective in treating cirrhosis-associated AVB even if performed outside the 72-h window without causing additional complications. Therefore, it may be advisable to extend the time window for pTIPS to 5 days for patients with AVB resulting from cirrhosis, as the current 72-h window may not be feasible for many patients to receive prompt treatments.

As early as the 1990s, Jalan R et al. introduced the concept of preventive insertion of TIPS (pre-emptive TIPS, within 72 h) as a strategy for management of AVB, and they conducted an RCT comparing pTIPS to variceal band ligation for the treatment of variceal

Table 3
The occurrence of clinical events at different time period after TIPS placement in <72 h and 72 h-5 d groups.

Outcomes	<72 h group (n = 32)	72 h-5 d group (n = 31)	*P* values
Death			0.510
0–6 months	1	3	
6–12 months	3	1	
12–36 months	3	2	
36–60 months	0	0	
Variceal rebleeding			0.679
0–6 months	1	3	
6–12 months	2	1	
12–36 months	0	1	
36–60 months	0	0	
OHE			0.700
0–6 months	8	5	
6–12 months	1	1	
12–36 months	0	1	
36–60 months	0	0	
Shunt dysfunction			0.682
0–6 months	0	1	
6–12 months	0	1	
12–36 months	1	1	
36–60 months	1	1	
Liver transplantation			0.613
0–6 months	0	0	
6–12 months	0	0	
12–36 months	0	0	
36–60 months	1	2	

Table 4
Univariable and multivariable analysis of factors associated with post-TIPS mortality.

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	*P* value
Age, years	1.067	1.017–1.118	0.008	1.057	0.993–1.125	0.080
Gender, male	1.759	0.542–5.731	0.347	–	–	–
BMI, kg/m2	0.924	0.727–1.174	0.518	–	–	–
TBIL, mg/mL	1.482	0.963–2.279	0.073	1.597	1.008–2.532	0.046
ALB, g/L	0.929	0.822–1.049	0.232	–	–	–
ALT, U/L	0.993	0.969–1.016	0.538	–	–	–
AST, U/L	1.007	0.991–1.023	0.415	–	–	–
Creatinine, mg/mL	3.046	1.488–6.232	0.002	2.010	0.926–4.363	0.077
INR	4.026	0.746–21.720	0.105	–	–	–
Platelet count, 109/L	0.987	0.970–1.004	0.136	–	–	–
Child-Pugh score	1.526	1.070–2.178	0.020	–	–	–
MELD score	1.272	1.103–1.467	<0.001	–	–	–
MELD-Na score	1.235	1.092–1.398	<0.001	–	–	–
FIPS score	2.800	1.462–5.360	0.002	–	–	–
Ascites	2.995	0.389–23.030	0.292	–	–	–
PVT	2.435	0.796–7.445	0.119	–	–	–
Pre-TIPS PPG, mmHg	1.001	0.884–1.134	0.982	–	–	–
Sarcopenia	15.650	2.031–120.5	0.008	11.268	1.435–88.462	0.021
72 h-5 d group	0.902	0.303–2.685	0.853	–	–	–

Abbreviation: TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; FIPS, Freiburg index of post-TIPS survival; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; PPG, portal pressure gradient.

Table 5
Univariable and multivariable analysis of factors associated with post-TIPS OHE.

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	*P* value
Age, years	1.049	1.006–1.094	0.027	1.075	1.012–1.142	0.019
Gender, male	0.748	0.281–1.994	0.562	–	–	–
BMI, kg/m2	1.003	0.859–1.241	0.732	–	–	–
TBIL, mg/mL	2.064	1.336–3.187	0.001	1.523	0.845–2.745	0.161
ALB, g/L	0.851	0.761–0.951	0.004	1.006	0.858–1.179	0.942
ALT, U/L	1.004	0.991–1.016	0.425	–	–	–
AST, U/L	1.018	1.005–1.031	0.005	1.000	0.981–1.019	0.986
Creatinine, mg/mL	0.482	0.079–2.961	0.431	–	–	–
INR	3.350	0.719–15.610	0.124	–	–	–
Platelet count, 109/L	0.997	0.985–1.009	0.587	–	–	–
Child-Pugh score	1.691	1.248–2.290	0.001	–	–	–
MELD score	1.146	0.999–1.314	0.051	–	–	–
MELD-Na score	1.153	1.026–1.296	0.018	–	–	–
FIPS score	1.275	0.737–2.275	0.385	–	–	–
Ascites	1.793	0.408–7.893	0.440	–	–	–
PVT	2.435	0.796–7.445	0.119	–	–	–
Pre-TIPS PPG, mmHg	0.982	0.879–1.099	0.756	–	–	–
Sarcopenia	3.425	1.272–9.220	0.015	12.504	1.598–97.814	0.016
72 h-5 d group	0.793	0.295–2.130	0.645	–	–	–

Abbreviation: TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; FIPS, Freiburg index of post-TIPS survival; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; PPG, portal pressure gradient.

bleeding [20][[]. Although the aforementioned study demonstrated a reduction in rebleeding risk with pTIPS, it did not result in a significant improvement in survival. Thereafter, researchers have progressively directed their attention towards the significance of risk stratification in the context of pTIPS for patients with AVB. In the RCT conducted by Monescillo et al. hepatic venous pressure gradient (HVPG) was used as a high-risk selection criterion, the results first proved that pTIPS could significantly improve the survival of high-risk patients with AVB (HVPG $\geq$20 mmHg) [21]. Nevertheless, the practical application of HVPG measurement is not straightforward in clinical settings, and the utilization of PTFF-covered stents was not widely advocated during the aforementioned trial. Consequently, the role of pTIPS remained underappreciated until 2010.

In 2010, a landmark RCT conducted by García-Pagán et al. was pivotal in redefining the role of pTIPS in the management of AVB with the utilization of a simpler risk stratification method (Child-Pugh score and endoscopic findings) for patient selection, which showed that pTIPS could significantly reduce the risk of rebleeding and improve patient survival [22]. The reliability of this result has

been further validated by multiple high-quality studies since then [23–25], and pTIPS has thus been recommended by clinical practice guidelines as the first-line treatment option for high-risk patients with AVB [5,26].

However, the time window for pTIPS procedure is limited to 72 h. This implies that the patients must be promptly transported from their residences to the hospital and undergo all essential clinical evaluations, laboratory tests, endoscopy and enhanced CT scans within this 72-h period following the onset of bleeding. Unfortunately, this narrow time window poses challenges for certain patients, particularly those residing in remote areas. Thus, as mentioned in the Baveno VII consensus, it is necessary to assess whether pTIPS performed outside the 72-h window is still effective and safe [5]. Dunne P et al. compared the clinical outcomes of early pTIPS (<72 h) and late pTIPS (72h-28 days) and similar short- and long-term survival benefits between the two groups were found [27]. The same results were observed in our study, but unlike the study conducted by Dunne P et al., we defined the time window for late pTIPS as 72 h-5d because the time frame for AVB is 5 d as defined by the Baveno consensus [10]. Strictly speaking, a TIPS performed over 5 days from the start of AVB cannot be defined as pTIPS, but rather TIPS for secondary prophylaxis of variceal bleeding. Our study showed that the risk of death, variceal rebleeding, OHE and shunt dysfunction were not significantly higher in patients who received pTIPS at 72 h-5d from AVB than in those <72 h. This suggests that for patients with AVB who are unable to receive pTIPS within 72 h, even a further delay of 2 days would not have an impact on the outcome. The time window for pTIPS could be extended to 5 days.

In addition, it is worth mentioning that a prognostic analysis was conducted on the total cohort, revealing sarcopenia as an independent risk factor for mortality and OHE in cirrhotic patients with AVB who underwent pTIPS treatment. In recent years, sarcopenia has gained significant attention within the field of cirrhosis, with numerous studies demonstrating its independent association with the poor prognosis in cirrhotic patients treated with TIPS [13,28] However, a study conducted by Benmassaoud et al. showed that sarcopenia was not associated with poor prognosis in patients with refractory ascites who underwent TIPS treatment [29], which indicates that the prognostic value of sarcopenia varies in different indications for TIPS. For patients who underwent TIPS, it is necessary to analyze the correlation between sarcopenia and prognosis separately according to different indications. In this study, we found that sarcopenia has an important prognostic value in cirrhotic patients with AVB treated by pTIPS, suggesting that clinicians need to pay attention to the nutritional status of these patients.

We acknowledge the following limitations in the study. First, the retrospective design might lead to selection bias. Secondly, the sample size is too small. In future studies, it is necessary to design RCT to validate our results.

In conclusion, the clinical outcomes of cirrhotic patients with AVB who underwent pTIPS within the 72-h to 5-day window were found to be comparable to those treated within the 72-h window. In addition, sarcopenia is independently associated with mortality and OHE in AVB patients treated with pTIPS.

Funding

This work was funded by National Natural Science Foundation of China (82102168).

Ethical approval

The study protocol was approved by the Institutional Review Board of Wuhan Union Hospital in accordance with the declaration of Helsinki.

Informed consent

N/A.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Xiangjun Dong: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Jiacheng Liu:** Writing – original draft, Software, Resources, Methodology, Formal analysis, Data curation. **Yaowei Bai:** Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Xiaoming Liu:** Software, Methodology, Formal analysis. **Jinqiang Ma:** Software, Formal analysis, Data curation. **Binqian Zhou:** Software, Data curation. **Yanqiao Ren:** Writing – review & editing, Visualization, Software, Project administration, Data curation, Conceptualization. **Chuansheng Zheng:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We want to express our gratitude to Chuang Sun for statistical analysis.

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