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► **To cite this version:**

Charlotte Bouzbib, Philippe Cluzel, Philippe Sultanik, Brigitte Bernard-Chabert, Julien Massard, et al.. Prognosis of patients undergoing salvage TIPS is still poor in the preemptive TIPS era. *Clinics and Research in Hepatology and Gastroenterology*, 2021, 45 (6), pp.101593. 10.1016/j.clinre.2020.101593 . hal-04542044

HAL Id: hal-04542044

<https://hal.sorbonne-universite.fr/hal-04542044>

Submitted on 11 Apr 2024

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Title: Prognosis of patients undergoing salvage TIPS is still poor in the preemptive TIPS era

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Electronic word count: 3847

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All authors have approved the final article.

Funding or grant support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial disclosure: None

Tables: 4; **Figures:** 3

Supplementary Tables: 2; Supplementary Figures: 2

Abbreviations:

ALT = alanine aminotransferase

AST = aspartate aminotransferase

AVB = acute variceal bleeding

DBP = diastolic blood pressure

GGT = gamma-glutamyl transferase

HE = hepatic encephalopathy

INR = International Normalized Ratio

IU = international units

MELD = model for end-stage liver disease

NASH = non-alcoholic steato-hepatitis

NSBB = non-cardioselective beta-blockers

PT = prothrombin time

PTFE = polytetrafluoroethylene

SBP = systolic blood pressure

TIPS = transjugular intrahepatic portosystemic shunt

UGB = upper gastrointestinal bleeding

Abstract:

Background: Salvage transjugular intrahepatic portosystemic shunts (TIPS) are associated with poor prognosis, especially in patients with Child-Pugh C cirrhosis. Since preemptive TIPS improved prophylaxis of variceal bleeding in those patients, recourse to salvage TIPS may now affect patients with a better prognosis.

Aim: To assess the impact of the preemptive TIPS policy on outcomes after salvage TIPS placement.

Methods: We conducted a retrospective monocentric study on cirrhotic patients undergoing salvage TIPS with polytetrafluoroethylene-covered stents from 2002 to 2017 (period 1 until February 2011; period 2 after the preemptive TIPS policy in March 2011). The primary endpoint was one-year transplant-free survival.

Results: We included 106 patients (period 1/2=53/53 patients, male gender 82%, age 54±9 years, alcoholic cirrhosis 70%, Child-Pugh score B/C 94%). One-year transplant-free survival was 46.0% during period 1 compared to 40.2% during period 2 (p=0.65). Amongst 61 patients with history of variceal bleeding, 32 (52.5%) had an inadequate secondary prophylaxis, including 19 (59.4%) with a previous indication of preemptive TIPS. One-year transplant-free survival was 33.2% if inadequate secondary prophylaxis vs 65.2% if adequate (p=0.008). Independent factors associated with survival were a lower Child-Pugh or MELD score, infection, failure to control bleeding, and HE after TIPS.

Conclusion: Prognosis after salvage TIPS remained poor in our series. Optimizing secondary prophylaxis, including preemptive TIPS placement, should be the main concern to improve prognosis.

Keywords: (6/6)

Cirrhosis; portal hypertension; refractory variceal bleeding; TIPS; prophylaxis; Child-Pugh score

Introduction

Acute variceal bleeding (AVB) is one of the main complications of cirrhosis. The prognosis of AVB has been improved over the last decades thanks to a combination of medical therapy (vasoactive drugs and antibiotics) and endoscopic therapy (1), with 6-week survival reaching 85-90% in the last series (2-4). Nevertheless, 6-week mortality in patients with advanced liver disease, i.e., those displaying severe portal hypertension and/or liver failure, still reaches 25-75% (5-7) because of uncontrolled bleeding and/or early re-bleeding despite standard care. In those patients, transjugular intrahepatic portosystemic shunt (TIPS) placement (8) is used to significantly and rapidly decrease portal pressure (salvage TIPS procedure). Despite its very good control of bleeding, one-month mortality after salvage TIPS has been very high in previous series, ranging from 30% to 50% (7,9,10). More recently, TIPS placement has been suggested for the prevention of recurrent bleeding in high-risk patients after bleeding has been controlled (preemptive TIPS procedure) (8,11), i.e., at an early stage after bleeding to prevent re-bleeding and death in high-risk patients, defined for this purpose as patients displaying Child-Pugh B cirrhosis and active bleeding on endoscopy or Child-Pugh C10-13 cirrhosis (12,13). This therapeutic attitude has shown to drastically decrease re-bleeding and increase survival. Hence, the Baveno VI recommendations in 2015 stated that preemptive TIPS must be considered in high-risk cirrhotic patients with acute variceal bleeding (11).

One could expect that those recommendations would be followed up at an international level and that applying this policy would lead to a decrease in the prevalence of re-bleeding in high-risk patients, thus increasing the proportion of patients with a better prognosis amongst patients needing salvage TIPS, i.e., with

Child-Pugh A cirrhosis or Child-Pugh B cirrhosis but no active bleeding on endoscopy.

In our tertiary intensive care unit devoted to the management of the complications of cirrhosis, the procedures are written and regularly reviewed according to international guidelines. The preemptive TIPS policy started after the landmark trial on preemptive TIPS (12), i.e., in March 2011 (14). Moreover, the prothesis used for TIPS placement have all been polytetrafluoroethylene (PTFE)-covered since 2002, thus addressing the bias induced by the previous use of bare stents, which showed a lower efficacy in all settings because of stenosis and/or thrombosis (15-17). Yet, the outcomes of PTFE-covered stents have never been studied in the setting of salvage TIPS. This gave us the opportunity to compare, in a homogeneous series, the characteristics and outcomes of patients presenting with variceal bleeding and requiring the placement of salvage TIPS before and after implementing the preemptive TIPS policy.

More, some prognostic factors have previously been identified as pejorative in salvage TIPS settings (i.e., Child-Pugh C class (18-20), hyponatremia (18), renal failure (21-23), hyperbilirubinaemia (22-24), use of balloon tamponade (10) and association with aspiration pneumonia (25)), but they have turned out to be nonspecific (26) and cannot be considered accurate enough to define patients who may actually benefit from salvage TIPS. Nevertheless, if this procedure is considered as a last resort for patients with uncontrolled bleeding, its indication should be reconsidered if we presume its futility for a subgroup of patients, regarding the fact that it often requires the transfer of unstable patients to tertiary centres.

Thus, the aims of this study were, in a series of patients who underwent salvage TIPS with PTFE-covered stents in a tertiary-care centre: 1) to assess the impact of the preemptive TIPS policy on outcomes after salvage TIPS placement; 2) to identify prognostic factors after salvage TIPS with PTFE-covered stents.

Material and methods

Patients and methods

Patients

From January 2002 to December 2017, we retrospectively analysed patients who underwent salvage TIPS for uncontrolled variceal bleeding in our Intensive Care Unit in La Pitié-Salpêtrière Hospital, a tertiary centre in Paris, France. We prospectively followed a protocol for the management of patients with AVB, in accordance with the consecutive Baveno guidelines (27,28,8,11). We defined 2 periods according to the application of the preemptive TIPS policy in our centre: period 1, from January 2002 to February 2011 (before the preemptive TIPS policy), and period 2, from March 2011 to December 2017 (after the preemptive TIPS policy). The inclusion criteria were: patients with cirrhosis and uncontrolled variceal bleeding requiring salvage TIPS placement. The exclusion criteria were: TIPS placement failure, a previous TIPS placement, hepatocellular carcinoma out of the Milan criteria, a previous history of pulmonary hypertension, and severe multiorgan failure.

Diagnosis of cirrhosis was based on patients' history and clinical, biological, radiological and/or histological findings when available.

Methods

- Management of the bleeding episode

AVB was treated according to the Baveno III-VI guidelines (27,28,8,11), i.e., with vasoactive drugs (somatostatin, octreotide or terlipressin), antibiotics (third-

generation cephalosporins or quinolones) and endoscopic therapy (variceal band ligation in the case of esophageal varices or gastro-esophageal varices type 1; glue injection if gastro-esophageal varices type 2 or isolated gastric varices).

- *TIPS procedure*

The preemptive TIPS policy was strictly applied in our centre from March 2011 in patients with Child-Pugh B cirrhosis and active bleeding on endoscopy or in patients with Child-Pugh C10-13 cirrhosis. The classical contra-indications of preemptive TIPS were applied as previously described (12). Salvage TIPS was considered in case of failure to control bleeding or early re-bleeding according to the Baveno criteria. TIPS placement was then performed as soon as possible, within 6 hours following the diagnosis of uncontrolled bleeding. The TIPS procedure was performed as previously described in the interventional radiological unit of our centre, which is available twenty-four hours a day, seven days a week. Fifteen to 70 procedures have been performed there each year since 2005 (Supplementary Figure 1, data missing between 2002 and 2004). TIPS were inserted under general anaesthetic. PTFE-covered stents were used in all patients (Viatorr® TIPS endoprosthesis, Gore®) and were dilated until 8 or 10 mm to obtain a portal-pressure gradient below 10 mmHg. Vasoactive drugs were then discontinued if the portal-pressure gradient was lower than 10 mmHg but were continued if higher and then replaced by non-cardioselective beta-blockers (NSBB) when patients stabilized. TIPS patency was systematically assessed with an abdominal ultrasound on the next day. Further ultrasound controls or invasive measures of the portal-pressure gradient were performed if TIPS patency was uncertain, according to the physician's assessment.

Endpoints

The primary endpoint was one-year transplant-free survival according to period 1 or 2.

The secondary endpoints were six-week and one-year overall survival, control of bleeding and complications after TIPS placement.

Definitions

TIPS failure was defined by the impossibility of TIPS insertion due to anatomical issues.

According to the Baveno V definitions, failure to control bleeding was defined as clinically significant re-bleeding occurring within 5 days from the time of initial bleeding and early re-bleeding was considered if occurring between day 5 and day 42 from the time of initial bleeding (8).

Hypovolemic shock was defined as systolic blood pressure falls to 90 mmHg or less or mean blood pressure falls to 65 mmHg or less, and evidence of organ hypoperfusion such as oliguria or cold sweating with pale skin, including if vasoactive drugs were needed.

Survival was assessed from the time of salvage TIPS.

Hepatic encephalopathy (HE) was defined by neurological impairment, excluding the other obvious neurological diagnosis as metabolic disorders or intracerebral

haematoma. HE was considered to be a TIPS complication if it occurred within the days following the TIPS placement during hospitalization.

Primary prophylaxis of variceal bleeding was defined as adequate if patients with large varices without any previous history of bleeding were treated with either NSBB or iterative band ligation every 3-4 weeks until eradication. Patients without any previous diagnosis of cirrhosis or without any previous screening of varices were not considered as patients with adequate or inadequate prophylaxis.

Secondary prophylaxis of variceal bleeding was defined as adequate if patients with a previous history of variceal bleeding were treated with NSBB and iterative band ligation every 3-4 weeks until eradication in the absence of a previous indication of preemptive TIPS (i.e., TIPS within 72 hours after controlling bleeding in patients with Child-Pugh B cirrhosis and active bleeding on endoscopy or in patients with Child-Pugh C10-13 cirrhosis). In patients with a previous indication of preemptive TIPS, secondary prophylaxis was inadequate by definition.

Collection of data

Patients for whom TIPS was performed were selected thanks to our coding system (medicalization program of information system). We retrospectively collected data from the medical files of patients with refractory variceal bleeding requiring salvage TIPS. Routine biological data were collected at admission. Previous indication of preemptive TIPS was retrospectively assessed in the whole population (period 1 and period 2).

Patients were followed up for one year or until death or liver transplantation, whichever occurred earlier. Data collection ended in September 2018.

Statistical analysis

Statistical analysis was performed using the NCSS software. The results are presented as the mean \pm standard deviation. The variables for the aetiology and severity of cirrhosis and the severity of bleeding (all variables listed in Table 1) were considered as potential prognostic factors and were tested by univariate analysis with Student's t-test or Pearson's Chi-2 test when appropriate. If the variables were significantly correlated with the endpoints, they were analysed via multivariate logistic regression. Survival was analysed using the Kaplan-Meier method. Statistical significance was determined for p-values less than 0.05.

Results

Patients

From 2002 to 2017, 1175 bleeding episodes were managed in 1059 patients: 658 patients during period 1 and 401 patients during period 2. Overall, 111 salvage TIPS were indicated: TIPS failure occurred in 5 patients. We analysed data from 106 patients: 53 during period 1 and 53 during period 2. Three patients were lost to follow-up before six weeks and 15 before one year.

The patients' characteristics are described in Table 1. The MELD score was significantly higher during period 2 (21.8 ± 7.3 vs 18.6 ± 8.2 , $p=0.038$). Sixty-one patients (57.5%) had a previous history of AVB, with no difference between periods 1 and 2, but amongst them, only 41 patients (67.2%) were treated with NSBB, with a significantly lower proportion during period 2 (41.4% vs 90.6%, $p<0.001$). Over the two periods, cirrhosis was not previously described for 17 patients (16.0%), and 4 patients did not have a previous screening for gastro-esophageal varices despite a previous diagnosis of cirrhosis. Amongst patients with a previous diagnosis of cirrhosis and screening for varices, prophylaxis was inadequate for 36 patients (40.4%) (Supplementary Figure 2).

Alcohol-associated hepatitis was diagnosed in 19 patients (21.3%, data missing for 17 patients).

Proportion of patients requiring salvage TIPS according to period

Recourse to salvage TIPS was significantly more frequent during period 2 than during period 1: 53/658 patients (8.1%) needed salvage TIPS during period 1 vs 53/401 (13.2%) during period 2 ($p = 0.007$).

Transplant-free survival in the whole population

Ten patients were transplanted within one year after TIPS placement: 2 during period 1 and 8 during period 2. One-year transplant-free survival was 46.0% during period 1 ($n=26$) and 40.2% during period 2 ($n=20$) ($p=0.65$) (Figure 1). The Child-Pugh and MELD scores were associated with mortality or liver transplantation at one year: transplant-free survival was null for patients with a Child-Pugh score higher than or equal to 14 vs 60% for patients with lower score ($p<0.0001$), and it was significantly lower for patients with a MELD score strictly higher than 19 (16.1% vs 62.6%, $p<0.001$). Mortality or liver transplantation at one year were also associated with the severity of bleeding, no previous treatment with NSBB, failure to control bleeding with TIPS placement, infections and HE after TIPS placement in univariate analysis (Table 2). In multivariate analysis, factors associated with mortality or liver transplantation at one year were the Child-Pugh and MELD scores, failure to control bleeding with TIPS placement, HE and infections after TIPS placement (Table 3).

Regarding the indication of salvage TIPS, 55 patients (51.9%) required salvage TIPS because of a straightaway refractory bleeding and 51 (48.1%) because of an early re-bleeding. One-year transplant-free survival for those patients was 57.1% ($n=28$) and 59.5% ($n=25$) respectively ($p=0.98$).

Transplant-free survival in patients with an inadequate secondary prophylaxis

Over the two periods, 61 patients had a history of previous variceal bleeding, including 19 (33.3%) with a previous theoretical indication of preemptive TIPS (data missing for 4 patients). One-year transplant-free survival was significantly lower in patients with a previous indication of preemptive TIPS compared to patients without any indication of preemptive TIPS (30.1% vs 56.4%, $p=0.03$).

In the 38 patients with a previous episode of variceal bleeding but without any indication of preemptive TIPS, 13 (34.2%) did not receive an adequate secondary prophylaxis, particularly because of non-prescribed NSBB (Supplementary Figure 2). In the whole population of patients with a history of previous variceal bleeding, the secondary prophylaxis was more often inadequate during period 2 (85.2% vs 30.0% during period 1, $p<0.001$). One-year transplant-free survival was significantly lower in patients with an inadequate secondary prophylaxis compared to those with an adequate secondary prophylaxis (33.2% vs 65.2%, $p=0.008$) (Figure 2). Patients with an inadequate secondary prophylaxis had a significantly higher Child-Pugh score (11.6 ± 2.2 vs 8.2 ± 2.2 , $p<0.001$) and MELD score (22.8 ± 7.0 vs 14.3 ± 4.1 , $p<0.001$) at admission than those with an adequate prophylaxis. The factors associated in univariate analysis with mortality or liver transplantation at one year in patients with a history of previous variceal bleeding were inadequate secondary prophylaxis, the severity of cirrhosis, the severity of bleeding, failure to control bleeding with TIPS placement and infections and HE after TIPS (Supplementary Table 1). The size of this population was not big enough to perform a multivariate analysis.

Performance of models for the prediction of one-year transplant-free survival

Discrimination was studied by analysing the ROC curves. Figure 3A shows the ROC curve of the Child-Pugh score for predicting one-year transplant-free survival. The AUROC was 0.86 ± 0.04 . Figure 3B shows the ROC curve of the MELD score for predicting one-year transplant-free survival. The AUROC was 0.76 ± 0.07 .

Overall survival

Six-week and one-year survival were 61.9% (62 patients) and 55.4% (46 patients), respectively, without any difference between periods 1 and 2 (60.4 vs 63.7% (n=32 and 30 respectively), $p=0.91$, and 54.4 vs 56.8% (n=26 and 20 respectively), $p=0.99$, respectively).

Six-week survival was 5% for patients with a Child-Pugh score ≥ 14 vs 67.5% if lower ($p<0.001$).

One-year survival for patients with a straightaway refractory bleeding was 43.6% (n=24) and for patients with an early re-bleeding was 43.1% (n=22) ($p=0.78$).

Death mostly occurred within the days following TIPS placement: in-hospital mortality was 98% (n=39) amongst patients who died. Death was mostly due to multiorgan failure (64%, n=25), followed by refractory bleeding (28%, n=11) and cerebral oedema (8%, n=3), data missing for 2 patients. MELD score and severity of bleeding were significantly higher in patients who died.

The factors associated with six-week mortality in univariate analysis were the severity of cirrhosis, the severity of bleeding, no previous treatment with NSBB, failure to

control bleeding with TIPS placement, infections and HE after TIPS placement (Supplementary Table 2).

Other outcomes

Control of bleeding

UGB was refractory to TIPS placement in 21 patients (19.8%), with a significantly higher proportion during period 1 (28.3% vs 11.3%, $p=0.028$) (Table 4).

Complications after TIPS

Seventy patients (66.7%) presented with at least one complication after TIPS placement during hospitalization: HE in 61 patients, infections in 52 patients, and acute heart failure in 8 patients. Heart failure was significantly more frequent during period 1 (13.2% vs 2.0%, $p=0.031$), but there was no significant difference regarding HE and infections between periods 1 and 2 (Table 4).

Discussion

In the present series of 106 patients with cirrhosis and uncontrolled AVB requiring salvage TIPS placement, one-year transplant-free survival was not statistically different before and after the implementation of the preemptive TIPS policy.

To our knowledge, this series is the largest cohort of patients who underwent salvage TIPS using PTFE-covered stents. The strength of our study relies on the homogeneity of patients' management and the low proportion of patients who were lost to follow-up. Furthermore, TIPS was performed in a tertiary centre with TIPS expertise in which TIPS is available 24 hours a day and seven days a week, with more than 20 TIPS performed each year, which is known to reduce morbidity and mortality induced by TIPS placement (29,30).

We found that one-year transplant-free survival and 6-week survival were significantly associated with liver function according to Child-Pugh and MELD scores at admission, which is consistent with previous studies (18,19). We especially found that prognosis was very poor in patients with the most severe liver dysfunction (Child-Pugh score ≥ 14), with one-year transplant-free survival of 0%. This result strongly suggests that TIPS placement is futile if no liver transplantation is envisioned in those patients. Consequently, it seems reasonable to avoid transferring such a patient to a tertiary centre to perform a futile and invasive procedure, with significant material and human costs.

In addition, this is the first study, to our knowledge, that tried to assess the impact of the preemptive TIPS policy on the prognosis of patients requiring salvage TIPS placement. We found that prognosis was comparable, as overall survival and transplant-free survival were not statistically different between the 2 periods.

Nevertheless, we recognize that it is very hard to draw any conclusion regarding the impact of the preemptive TIPS policy, as we found that many patients had an inadequate secondary prophylaxis, especially during period 2. In particular, preemptive TIPS was not performed despite a previous indication in more than 30% of patients with history of AVB, and even more during period 2, while it might have avoided refractory bleeding if it had been performed. This finding is consistent with a previous multicentre study (31) showing that adherence to preemptive TIPS was very poor (6.8%) in academic and non-academic centres, mostly because physicians were reluctant to consider it despite several validation studies of preemptive TIPS on re-bleeding and survival (13,14,32,33). The discordance between the results of those studies and their application in real-life practice may be due to the debate regarding the criteria to define high-risk patients, especially concerning Child-Pugh B patients with active bleeding on endoscopy, which is a highly subjective criterion (34), not always associated neither with an improvement of prognosis with preemptive TIPS (33,35,36), nor with one-year transplant-free survival in our study. Moreover, there was a significantly higher rate of inadequate prescription of NSBB during period 2, particularly in the setting of secondary prophylaxis. Yet, there was no notion of intolerance to NSBB reported in the medical files for those patients, providing that data were collected retrospectively, nor was there any notion of considering TIPS as secondary prophylaxis before the uncontrolled variceal bleeding. More, we found that cirrhosis was more severe during period 2 (higher MELD score) and particularly in patients with an inadequate secondary prophylaxis. This finding is probably related to the conclusions of emergent studies that cast the benefit of beta-blockers into question in patients with severe cirrhosis (37-39) and could explain the low rate of adequate secondary prophylaxis in the latter years. This shows that there may be

confusion amongst physicians regarding the appropriate prophylaxis for large esophageal varices in decompensated cirrhosis, while the risk of AVB is the most important. As a consequence, we confirmed that prognosis was poorer in patients in whom the secondary prophylaxis was inadequate. Most importantly, we found that prevention of bleeding could have been better in at least 40 patients (37.7%) (36 with an inadequate primary or secondary prophylaxis, and 4 without any variceal screening despite a previous diagnosis of cirrhosis). One can hypothesize that some of them might not have undergone salvage TIPS if screening and prophylaxis of variceal bleeding had been adequate. We voluntarily considered secondary prophylaxis as inadequate if a patient had a previous indication of preemptive TIPS because it has been demonstrated that the use of preemptive TIPS significantly decreased the rate of re-bleeding and improved 6-week survival compared to prophylaxis combining NSBB and iterative band ligation in high-risk patients (13,14,32,33). Indeed, 6-week survival reached 92-97% in the main studies on preemptive TIPS (12,32,33), which is far better than that in an emergency context with salvage TIPS, leading us to presume that the use of preemptive TIPS would have considerably improved the prognosis of those patients if it had been applied. More, we found, as expected, that one-year transplant-free survival and 6-week survival were significantly associated with failure to control bleeding with TIPS placement, which underlines the importance to prevent bleeding, rather than to try to control it, which is often harder.

Of note, our study has some limitations. First, data were collected retrospectively, which may include some bias: we cannot exclude that the most severe patients were straightaway excluded from a salvage TIPS project, which may have resulted in an overestimation of the prognosis of patients with refractory AVB, but the rate of 6-

week survival in our study is consistent with data from the literature (7,9). Second, we compared two consecutive periods, but patients were not strictly comparable. Indeed, cirrhosis was more often due to excessive alcohol consumption and mixed causes and less often virus-related during period 2, probably because of the improvement in management of HCV with direct-acting antivirals for the last years and the increase of patients with non-alcoholic steato-hepatitis (NASH). More, MELD score was significantly higher during period 2, which may suggest a higher severity of the bleeding and then explain the higher proportion of patients requiring salvage TIPS during this period. This may be due by the fact that our study was conducted in a tertiary-centre, which manages the most severe patients who cannot be managed elsewhere, which intensified for the last years. Furthermore, the expertise of interventional radiologists for TIPS placement probably improved over time. This procedure has been performed increasingly more often each year over the past 15 years (from 15 a year to more than 70 a year for the last 6 years) (Supplementary Figure 1). This increase in the frequency of performance could have improved outcomes during period 2, which would be consistent with our finding that there were significantly less AVB refractory to TIPS placement and less heart failure during period 2 than during period 1, but this technique improvement did not result in improvement of survival. Third, regarding the fact that data were collected retrospectively, we did not have enough data to know if alcoholic patients remained abstinent during the study period, which may have impacted the one-year transplant-free survival. More, comorbidities were not taken into account for the long-term survival. Finally, as above-mentioned, the impact of the preemptive TIPS policy could not be correctly assessed in our study given its low application.

In conclusion, in our series of 106 patients with cirrhosis and refractory variceal bleeding undergoing salvage TIPS with PTFE-covered stents, we found that the prognosis of patients was still very poor during the preemptive TIPS era. We strongly suggest to pay more attention to improving the prophylaxis of AVB to avoid the recourse to salvage TIPS. Moreover, patients with a Child-Pugh score of C14-15 seem to be too severe to receive any benefit from salvage TIPS placement if no liver transplantation is envisioned. Thus, these criteria should lead to reconsideration of the indication for this invasive procedure.

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Tables

Table 1. Patients' characteristics

Variables	All patients (n=106)	Period 1 (n=53)	Period 2 (n=53)	p-value
Age (years)	54.0 ± 9.1	52.9 ± 9.3	55.0 ± 8.8	0.24
Male gender n (%)	87 (82.1%)	41 (77.4%)	46 (86.8%)	0.21
Cirrhosis				
Aetiology n (%)				0.01
Alcoholic	74 (69.8%)	34 (64.2%)	40 (75.4%)	
Hepatitis B/C virus	12 (11.3%)	10 (18.8%)	2 (3.8%)	
NASH	7 (6.7%)	6 (11.3%)	1 (1.9%)	
Other	1 (0.9%)	0 (0%)	1 (1.9%)	
Mixed	12 (11.3%)	3 (5.7%)	9 (17.0%)	
Previously unknown cirrhosis n (%) †	17 (16.0%)	9 (17.0%)	8 (15.1%)	0.79
Previously diagnosed cirrhosis				
Previous history of AVB n (%)	61 (57.5%)	32 (60.4%)	29 (54.7%)	0.55
Previous screening of gastro-esophageal varices for primary prophylaxis n (%) †	20 (80.0%)	8 (80.0%)	12 (80.0%)	1.00
Previous indication for primary prophylaxis n (%)	17 (85.0%)	7 (87.5%)	10 (83.3%)	0.80

Treatment with NSBB before admission n (%)	51 (48.1%)	35 (66.0%)	16 (30.2%)	<0.001
For primary prophylaxis	10 (58.8%)	6 (85.7%)	4 (40.0%)	0.25
For secondary prophylaxis	41 (67.2%)	29 (90.6%)	12 (41.4%)	<0.001
Endoscopic band ligation for primary prophylaxis n (%)	3 (17.6%)	0 (0%)	3 (30.0%)	0.11
Previous indication of preemptive TIPS n (%) †	19 (18.6%)	6 (11.8%)	13 (25.5%)	0.08
Severity at admission				
Child-Pugh class n (%) †				0.22
A	6 (5.7%)	5 (9.6%)	1 (1.9%)	
B	32 (30.5%)	16 (30.8%)	16 (30.2%)	
C	67 (63.8%)	31 (59.6%)	36 (67.9%)	
Child-Pugh score †	10.7 ± 2.6	10.3 ± 2.9	11.0 ± 2.3	0.22
MELD score †	20.2 ± 7.8	18.6 ± 8.2	21.8 ± 7.3	0.038
Ascites n (%) †	60 (60.6%)	32 (64.0%)	28 (57.1%)	0.49
HE n (%) †	52 (51.0%)	25 (48.1%)	27 (54.0%)	0.55
Haemodynamics at admission				
Cardiac frequency (bpm) ‡	95 ± 26	95 ± 24	95 ± 28	0.94
SBP (mmHg) †	110 ± 26	107 ± 28	113 ± 24	0.27
DBP (mmHg) †	61 ± 18	58 ± 19	63 ± 17	0.11
Hypovolemic shock at admission n (%) †	56 (53.9%)	31 (59.6%)	25 (48.1%)	0.24

Haemoglobin level (g.dL ⁻¹)	8.8 ± 2.0	8.2 ± 1.9	9.3 ± 2.0	0.003
Blood cell transfusion ‡				
Overall	11 ± 8	11 ± 9	11 ± 7	0.86
After TIPS placement	2 ± 4	2 ± 3	2 ± 4	0.33
Other biological findings at admission				
PT (%) †	44 ± 16	46 ± 19	41 ± 13	0.10
INR †	2.10 ± 1.00	1.95 ± 0.92	2.24 ± 1.07	0.14
Sodium level (mmol. L ⁻¹)	138 ± 6	138 ± 5	137 ± 6	0.52
Creatinine level (µmol.L ⁻¹)	104 ± 88	97 ± 79	110 ± 97	0.45
Albumin level (g. L ⁻¹) †	24.6 ± 5.8	25.0 ± 6.9	24.1 ± 4.6	0.44
ALT level (IU.L ⁻¹)	100 ± 214	97 ± 209	103 ± 219	0.89
AST level (IU.L ⁻¹)	206 ± 448	186 ± 458	225 ± 438	0.65
Bilirubin level (µmol.L ⁻¹)	88.4 ± 96.1	79.7 ± 81.8	97.1 ± 110.4	0.36
GGT level (IU.L ⁻¹)	108 ± 144	105 ± 162	111 ± 125	0.83
Lactate level (mmol.L ⁻¹) ‡	3.8 ± 3.4	3.6 ± 3.9	3.9 ± 3.3	0.89
Platelet count (G.L ⁻¹) ‡	91.7 ± 45.1	85.9 ± 43.7	97.5 ± 46.4	0.21
Characteristics of AVB				
Active bleeding on endoscopy n (%) †	77 (76.2%)	43 (84.3%)	34 (68.0%)	0.054

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, AVB = acute variceal bleeding, DBP = diastolic blood pressure, GGT = gamma-glutamyl transferase, HE = hepatic encephalopathy, INR = International Normalized Ratio, IU = international units, MELD = model for end-stage liver disease, NASH = non-alcoholic steato-hepatitis, NSBB = non-cardioselective beta-blockers, PT =

prothrombin time, SBP = systolic blood pressure, TIPS = transjugular intrahepatic portosystemic shunt

Data are expressed as the mean \pm SD or numbers (%)

† Data were not available for 7 patients or less

‡ Data were not available for less than 20 patients

Table 2. Factors associated with one-year transplant-free survival in univariate analysis §

Variables	Patients alive without liver transplantation at 1 year (n=38)	Patients dead or with liver transplantation at 1 year (n=53)	p-value
Age (years)	54.3 ± 8.9	54.2 ± 8.8	0.54
Male gender n (%)	30 (79.0%)	44 (83.0%)	0.62
Period 1 / 2 n (%)	23 (46.0%) / 15 (36.6%)	27 (54.0%) / 26 (63.4%)	0.36
Cirrhosis			
Cause n (%)			0.62
Alcoholic	27 (71.0%)	35 (66.0%)	
Hepatitis B/C virus	3 (7.9%)	9 (17.0%)	
NASH	3 (7.9%)	3 (5.7%)	
Other	0 (0%)	1 (1.9%)	
Mixed	5 (13.2%)	5 (9.4%)	
History of AVB n (%)	25 (65.8%)	26 (49.1%)	0.11
Previous indication of preemptive TIPS n (%) †	4 (11.4%)	12 (23.1%)	0.17
Treatment with NSBB before admission n (%)	25 (65.8%)	21 (39.6%)	0.014
Severity at admission			
Child-Pugh class n (%)			<0.001
A	6 (15.8%)	0 (0%)	

B	19 (50.0%)	8 (15.1%)	
C	13 (34.2%)	45 (84.9%)	
Child-Pugh score †	8.9 ± 2.3	12.1 ± 2.2	<0.001
MELD score	15.7 ± 5.1	23.8 ± 8.6	<0.001
Ascites at admission n (%) †	17 (47.2%)	39 (78.0%)	0.003
HE at admission n (%) †	8 (22.9%)	38 (71.7%)	<0.001
Haemodynamics at admission			
Cardiac frequency (bpm) †	85 ± 18	100 ± 30	0.004
SBP (mmHg) †	113 ± 24	104 ± 27	0.91
DBP (mmHg) †	64 ± 18	56 ± 18	0.97
Hypovolemic shock at admission n (%) †	17 (46.0%)	24 (64.2%)	0.09
Haemoglobin level (g.dL ⁻¹)	8.8 ± 1.9	8.6 ± 2.3	0.62
Units of blood transfused			
Overall †	8.6 ± 6.5	14.1 ± 8.7	0.001
After TIPS placement †	0.7 ± 1.6	3.1 ± 4.4	<0.001
Other biological findings at admission			
PT (%) †	54 ± 14	35 ± 16	<0.001
INR †	1.56 ± 0.35	2.57 ± 1.21	<0.001
Sodium level (mmol. L ⁻¹)	138 ± 4	136 ± 7	0.87
Creatinine level (µmol.L ⁻¹)	88 ± 101	113 ± 75	<0.001
Albumin level (g. L ⁻¹) †	26.7 ± 5.6	22.7 ± 5.4	0.005
ALT level (IU.L ⁻¹)	57 ± 107	125 ± 232	0.012

AST level (IU.L ⁻¹)	81 ± 141	288 ± 551	<0.001
Bilirubin level (µmol.L ⁻¹)	51.1 ± 41.7	118.7 ± 120.1	<0.001
GGT level (IU.L ⁻¹) †	104 ± 129	116 ± 170	0.40
Platelet count (G.L ⁻¹) †	81.3 ± 38.2	94.5 ± 50.8	0.16
Characteristics of UGB			
Active bleeding on endoscopy at admission n (%) †	30 (81.1%)	38 (76.0%)	0.57
Other outcomes			
Failure to control bleeding with TIPS placement n (%) †	1 (2.6%)	20 (37.7%)	<0.001
Complications after TIPS placement			
Early re-bleeding n (%) †	4 (10.5%)	10 (21.7%)	0.17
Intra-hepatic haematoma n (%) †	1 (2.7%)	4 (7.9%)	0.30
Infections n (%) †	11 (29.7%)	34 (66.7%)	<0.001
Heart failure n (%) †	4 (10.8%)	2 (3.9%)	0.20
TIPS thrombosis n (%) †	3 (8.1%)	0 (0%)	0.037
Post-TIPS HE n (%) †	10 (27.0%)	42 (80.8%)	<0.001

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, AVB = acute variceal bleeding, DBP = diastolic blood pressure, GGT = gamma-glutamyl transferase, HE = hepatic encephalopathy, INR = International Normalized

Ratio, IU = international units, MELD = model for end-stage liver disease, NASH = non-alcoholic steato-hepatitis, NSBB = non-cardioselective beta-blockers, PT = prothrombin time, SBP = systolic blood pressure, TIPS = transjugular intrahepatic portosystemic shunt, UGB = upper gastrointestinal bleeding

§ Analysis performed in 91 patients

Data are expressed as the mean \pm SD or numbers (%)

† Data were not available for 15 patients or less

Table 3. Factors associated with one-year transplant-free survival after salvage TIPS in multivariate analysis §

Model 1.

Variables	Odds-ratio	95% CI	p-value
MELD score	0.86	0.77-0.95	0.003
Treatment with NSBB before admission	0.55	0.13-2.35	0.42
Hypovolemic shock at admission	0.29	0.08-1.03	0.056
Failure to control bleeding	0.04	0.003-0.48	0.011
Infections after TIPS placement	0.12	0.03-0.50	0.004

Model 2.

Variables	Odds-ratio	95% CI	p-value
Child-Pugh score	0.54	0.34-0.86	0.004
Treatment with NSBB before admission	0.32	0.05-1.90	0.21
Hypovolemic shock at admission	0.33	0.07-1.51	0.15
Overall units of blood transfused	0.99	0.89-1.11	0.88
Failure to control bleeding	0.02	0.001-0.44	0.01
Infections after TIPS placement	0.28	0.05-1.57	0.15
HE after TIPS placement	0.19	0.04-0.95	0.04

Abbreviations: HE = hepatic encephalopathy, MELD = model for end-stage liver disease, NSBB = non-cardioselective beta-blockers, TIPS = transjugular intrahepatic portosystemic shunt

§ Analysis performed in 91 patients, including 46 with one-year transplant-free survival

Table 4. Outcomes after TIPS placement in univariate analysis: comparison of periods 1 and 2.

Variables (n (%))	All patients (n=106)	Period 1 (n=53)	Period 2 (n=53)	p-value
Failure to control bleeding	21 (19.8%)	15 (28.3%)	6 (11.3%)	0.028
Early recurrence of bleeding after TIPS placement †	16 (16.2%)	8 (17.0%)	8 (15.4%)	0.83
In-hospital mortality †	41 (39.4%)	22 (42.3%)	19 (36.5%)	0.55
In-hospital liver transplantation	10 (9.4%)	3 (5.7%)	7 (13.2%)	0.18
Complications after TIPS placement				
Any complications †	70 (66.7%)	34 (64.2%)	36 (69.2%)	0.58
Intra-hepatic haematoma †	6 (5.8%)	3 (5.8%)	3 (5.9%)	0.98
TIPS thrombosis †	3 (2.9%)	2 (3.8%)	1 (2.0%)	0.58
Infections †	52 (50.5%)	24 (46.2%)	28 (54.9%)	0.37
Heart failure †	8 (7.7%)	7 (13.2%)	1 (2.0%)	0.031
Hepatic encephalopathy †	61 (58.7%)	29 (54.7%)	32 (62.8%)	0.41

Data are expressed as numbers (%)

† Data were not available for 7 patients or less

Figure legends

Figure 1. One-year transplant-free survival during periods 1 and 2 (Kaplan-Meier analysis)

One-year transplant-free survival was not significantly different when comparing period 1 (red line) and period 2 (blue line) ($p=0.65$).

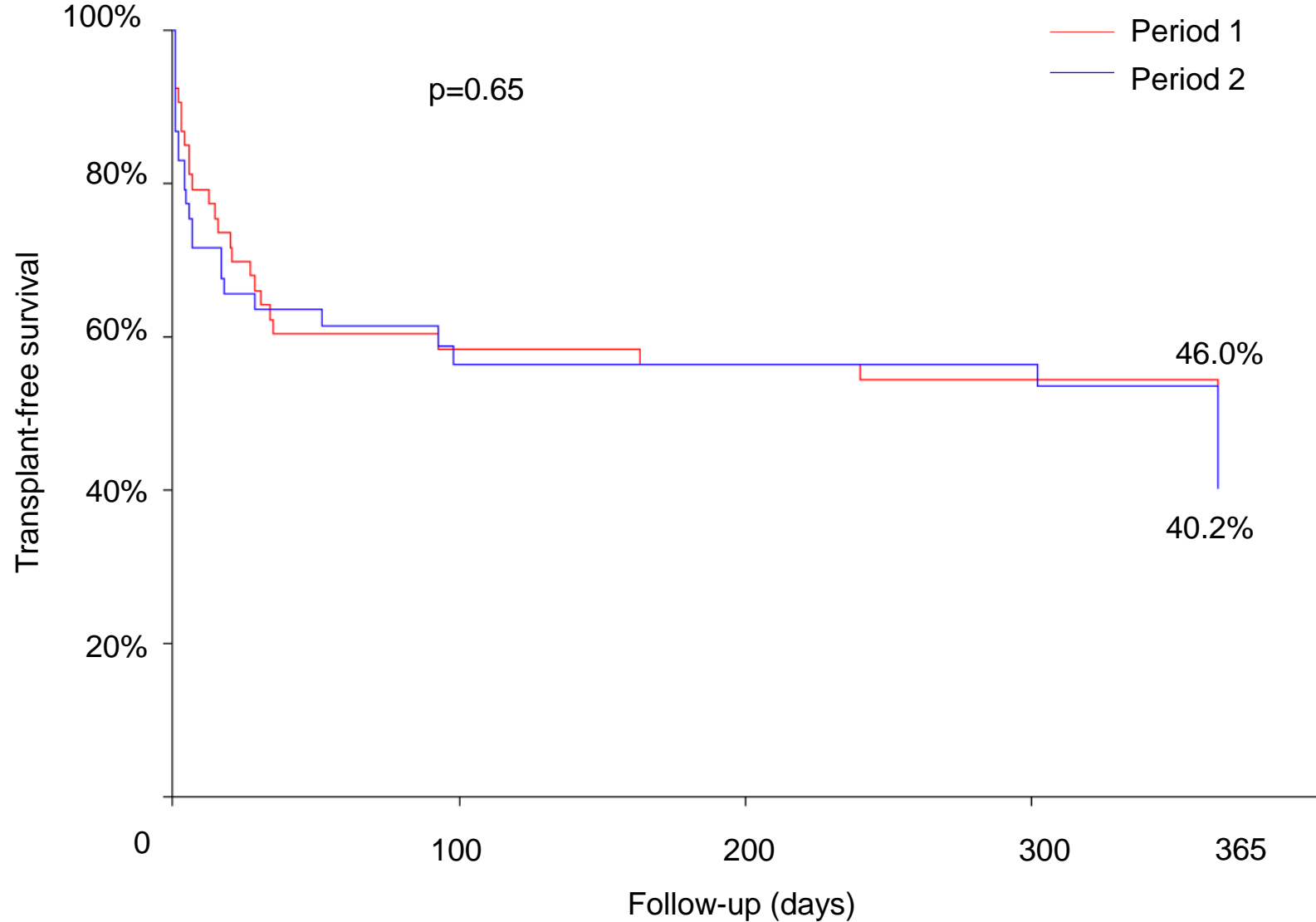
Figure 2. One-year transplant-free survival after salvage TIPS in patients with a history of previous variceal bleeding according to their secondary prophylaxis (Kaplan-Meier analysis)

Amongst patients with a history of variceal bleeding who underwent salvage TIPS, those with an adequate secondary prophylaxis (blue line), i.e., association of non-cardioselective beta-blockers and iterative band ligation when preemptive TIPS not indicated, had a significantly higher one-year transplant-free survival than those with an inadequate secondary prophylaxis (red line) ($p=0.008$) (data missing for 4 patients).

Figure 3. ROC curves of the Child-Pugh score (A) and the MELD score (B) for predicting one-year transplant-free survival after salvage TIPS in the entire population (periods 1 and 2)

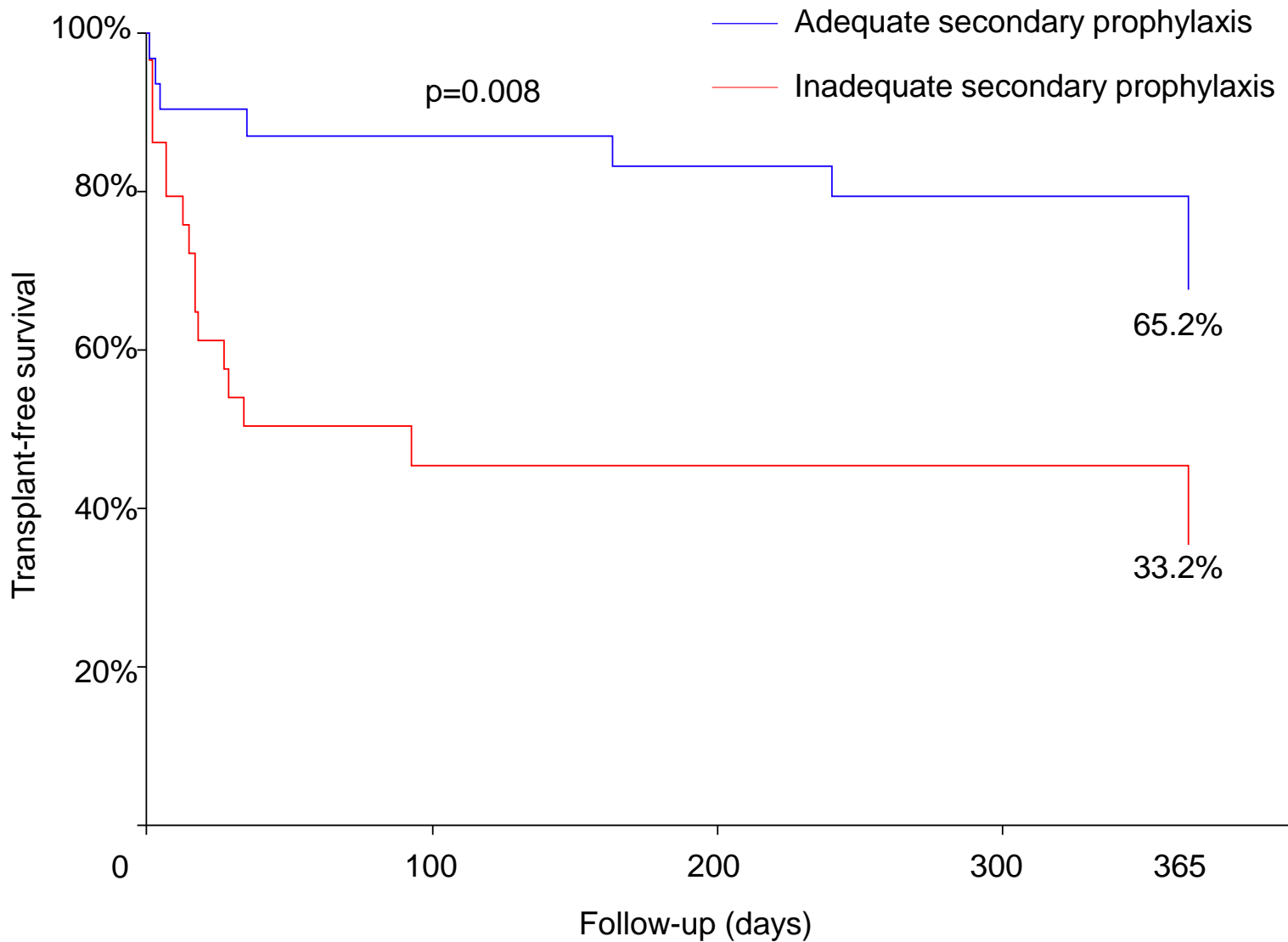
AUROC = 0.86 ± 0.04 for the Child-Pugh score; AUROC = 0.76 ± 0.07 for the MELD score.

Figure 1



Period 1	53	30	29	27	26
Period 2	53	23	23	22	20

Figure 2



Adequate secondary prophylaxis	25	21	20	18	17
Inadequate secondary prophylaxis	32	9	9	9	9

Figure 3

