Preemptive-TIPS Improves Outcome in High-Risk Variceal Bleeding: An Observational Study

Virginia Hernández-Gea, Bogdan Procopet, Álvaro Giráldez, Lucio Amiratno, Candid Villanueva, Dominique Thabut, Luis Ibañez-Samaniego, Gilberto Silva-Junior, Javier Martinez, Joan Genéca, Christophe Bureau, Jonel Trebicka, Elba Llop, Wim Laleman, Jose Maria Palazon, Jose Castellote, Susana Rodrigues, Lise L. Gluud, Carlos Noronha Ferreira, Rafael Barcelo, Nuria Cañete, Manuel Rodriguez, Arnulf Ferlitsch, Jose Luis Mundi, Henning Gronbaek, Manuel Hernández-Guerra, Romano Sassatelli, Alessandra Dell’Era, Marco Senzolo, Juan G. Abraldes, Manuel Romero-Gómez, Alexander Zipprich, Meritxell Casas, Helena Masnou, Massimo Primignani, Aleksander Krąg, Frederik Nevens, Jose Luis Calleja, Christian Jansen, Marie Angele Robic, Irene Conejo, Maria-Vega Catalina, Agustin Albillos, Marika Rudler, Edilmar Alvarenga, Maria Anna Guardascione, Marcel Tantau, Jaime Bosch, Ferran Torres, and Juan Carlos Garcia-Pagán for the International Variceal Bleeding Observational Study Group and Baveno Cooperation

Patients admitted with acute variceal bleeding (AVB) and Child-Pugh C score (CP-C) or Child-Pugh B plus active bleeding at endoscopy (CP-B+AB) are at high risk for treatment failure, rebleeding, and mortality. A preemptive transjugular intrahepatic portosystemic shunt (p-TIPS) has been shown to improve survival in these patients, but its use in clinical practice has been challenged and not routinely incorporated. The present study aimed to further validate the role of preemptive TIPS in a large number of high-risk patients. This multicenter, international, observational study included 671 patients from 34 centers admitted for AVB and high risk of treatment failure. Patients were managed according to current guidelines, and use of drugs and endoscopic therapy (D+E) or p-TIPS was based on individual center policy. p-TIPS in the setting of AVB is associated with a lower mortality in CP-C patients compared with D+E (1 year mortality 22% vs. 47% in D+E group; P = 0.002). Mortality rate in CP-B+AB patients was low, and p-TIPS did not improve it. In CP-C and CP-B+AB patients, p-TIPS reduced treatment failure and rebleeding (1-year cumulative incidence function probability of remaining free of the composite endpoint: 92% vs. 74% in the D+E group; P = 0.017) and development of de novo or worsening of previous ascites without increasing rates of hepatic encephalopathy. Conclusion: p-TIPS must be the treatment of choice in CP-C patients with AVB. Because of the strong benefit in preventing further bleeding and ascites, p-TIPS could be a good treatment strategy for CP-B+AB patients. (Hepatology 2019;69:282-293).

Acute variceal bleeding (AVB) remains the most severe and life-threatening complication of portal hypertension in patients with cirrhosis. In recent decades, a better understanding of AVB pathophysiology has led to a significant improvement in its management and a reduction in mortality rates. However, despite applying the gold-standard therapy, 10% to 15% of patients with AVB experience...
treatment failure, 21% rebleed, and 24% die during the first 6 weeks.\(^{(4)}\) Moreover, there is a subgroup of patients with AVB with worse prognosis in which rebleeding is as high as 50% during the first year and mortality reaches 40%.\(^{(2)}\) Numerous efforts have been conducted to identify factors associated with this

**ARTICLE INFORMATION:**

From the 1 Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic-Institut d’Investigacions Biomèdiques August Pi i Sunyer, IMIDIM, University of Barcelona, Barcelona, Spain; 2Centro de Investigación Biomédica Red de enfermedades hepáticas y digestivas, Madrid, Spain; 3Regional Institute of Gastroenterology and Hepatology “Octavian Fodor”, Hepatology Department and “Iuliu Hatieganu” University of Medicine and Pharmacy, 3rd Medical Clinic, Cluj-Napoca, Romania; 4Clinical Management Unit of Digestive Diseases, University Hospital Virgen del Rocío, Sevilla, Spain; 5Gastroenterology Unit, Ospedale A Cardarelli, Naples, Italy; 6Servei de Patologia Digestiva, Hospital de la Santa Creu i Sant Pau and CIBEREd, Barcelona, Spain; 7Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Paris, France; 8Servicio de Medicina de Aparato Digestivo Gregorio Marañón, Hospital General Universitario Gregorio Marañón, ISGGM, CIBEREd, Barcelona, Spain; 9Department of Gastroenterology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCS), University of Alcalá, CIBEREd, Madrid, Spain; 10Liver Unit, Hospital Universitari Vall d’Hebron, Vall d’Hebron Institute of Research (VHIR), Universitat Autònoma de Barcelona and CIBEREd, Barcelona, Spain; 11Department of Hepato-Gastroenterology, Purpan Hospital, CHU Toulouse, INSERM U858, University of Toulouse, France; 12Department of Internal Medicine I, University of Bonn, Bonn, Germany; 13European Foundation for the Study of Chronic Liver Failure (EF-CLIF), Barcelona, Spain; 14Institute for Bioengineering of Catalonia, Barcelona, Spain; 15Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark; 16Liver Unit, Hospital U, Puerta de Hierro. Universidad Autónoma de Madrid, CIBEREd, Madrid, Spain; 17Department of Liver and Biliopancreatic Disorders, University of Leuven, Leuven, Belgium; 18Liver General Universitario de Alicante, Alicante, Spain; 19Gastroenterology Department, Hepatology Unit, Hospital Universitario de Bellvitge, IDIBELL, Universitat de Barcelona, Barcelona, Spain; 20Gastroenterology and Hepatology Department, Centro Hospitalar São João, Porto, Portugal; 21Gastronutri, Medical Division, University Hospital of Hvidovre, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; 22Serviço de Gastroenterologia e Hepatologia, Hospital de Santa Maria - Centro Hospitalar Lisboa Norte, Lisboa, Portugal; 23Medical Statistics Core Facility, Institut d’Investigacions Biomèdiques August Pi i Sunyer, Hospital Clinic Barcelona, Barcelona, Spain; 24Liver Section, Gastroenterology Department, Hospital del Mar, Universitat Autònoma de Barcelona, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain; 25Department of Gastroenterology, Hospital Central de Asturias, Oviedo, Spain; 26Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria; 27Department of Gastroenterology, University Hospital San Cecilio, Granada, Spain; 28Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; 29Gastroenterology Department, University Hospital of the Canary Islands, La Laguna, Tenerife, Spain; 30Unit of Gastroenterology and Digestive Endoscopy, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy; 31Gastroenterology Unit, ASST Fatebenefratelli Sacco, Department of Clinical and Biomedical Sciences, University of the Studies of Milan, Milan, Italy; 32Multivisceral Transplant Unit, Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University Hospital of Padua, Padua, Italy; 33Cirrhosis Care Clinic, Division of Gastroenterology (Liver Unit), CEGIR, University of Alberta, Edmonton, Canada; 34Unidad de Hepatología, Hospital Universitario de Valme, CIBEREd, Sevilla, Spain; 35First Department of Internal Medicine, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; 36Hepatology Unit, Digestive Disease Department Hospital de Sabadell, Universitat Autònoma de Barcelona, Sabadell, Spain; 37Hospital Universitari Germans Trias i Pujol, Universitat Autònoma Barcelona, Badalona, Spain; 38Division of Gastroenterology and Hepatology, IRCCS Ca’ Granda Maggiore Hospital Foundation, University of Milan, Milan, Italy; 39Swiss Liver Centre, Inselspital, Bern University, Bern, Switzerland; 40Biostatistics Unit, Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain;

**ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:**

Virginia Hernández-Gea, M.D., Ph.D.  
Barcelona Hepatic Hemodynamic Laboratory  
Liver Unit, Hospital Clinic  
Villarroel 170, Barcelona 08036, Spain  
E-mail: vihernandez@clinic.cat

Juan Carlos García-Pagán, M.D., Ph.D.  
Barcelona Hepatic Hemodynamic Laboratory  
Liver Unit, Hospital Clinic  
Villarroel 170, Barcelona 08036, Spain  
E-mail: jcgarcia@clinic.cat

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poor outcome that may help to select patients who might benefit from a more aggressive management. The Child-Pugh (CP) classification, aspartate aminotransferase levels, shock on admission, presence of portal vein thrombosis, presence of hepatocellular carcinoma, active bleeding at endoscopy on admission, hepatic venous pressure gradient ≥20 mmHg, and a MELD-based score have been identified as predictors of poor outcome in patients with cirrhosis and AVB.[3-9] Several studies of this subgroup of high-risk patients have shown that placement of a transjugular intrahepatic portosystemic shunt (TIPS) within 72 hours of admission, before uncontrolled bleeding or rebleeding occurs (called early or preemptive TIPS [p-TIPS]) is effective in preventing treatment failure and rebleeding[2,9-11] without increasing either hepatic encephalopathy (HE) or other adverse events. In addition, some of these of these studies (two randomized controlled trials and one observational) also demonstrated that the p-TIPS strategy increases survival.[2,10] Despite all this evidence and probably due to the relatively small number of patients included in all these studies, implementation of p-TIPS in real-life clinical practice has been defied. Indeed, a recently published paper[12] evaluated real-life results in 58 centers in France (including academic and nonacademic centers), and only 6.7% of the high-risk patients included were treated with p-TIPS, underscoring the lack of physician adherence in a real-life setting.

We aimed to conduct a large, multicenter, international observational study in patients with cirrhosis and high-risk AVB admitted to several centers worldwide, with the main aim of corroborating if the use of p-TIPS improves the outcome of these patients and therefore should be more rigorously included in clinical practice.

Patients and Methods

STUDY DESIGN AND PATIENTS

We performed a multicenter, international, observational study in 33 referral centers in Europe and 1 center in Canada, between October 2011 and May 2015. All 34 centers collected data prospectively from all patients with cirrhosis admitted for AVB from October 2013 to May 2015. In addition, patients who were prospectively registered since October 2011 in 19 of the 34 centers that already had preexisting databases/registers of all patients with AVB admitted to their hospitals were also included. All patients were managed according to current guidelines (Baveno V consensus and American Association for the Study of Liver Diseases [AASLD] guidelines). All consecutive patients admitted to the participating centers with a portal hypertension related bleeding were included in the database of the study regardless the severity of the hemorrhage and/or the presence of high-risk criteria. Patients were asked to sign an informed consent to be registered and for the use of their clinical data. A total of 2,138 patients were consecutively registered in the database. For this study, from the whole sample registered, only data from high-risk patients were analyzed. Although Model for End-Stage Liver Disease (MELD) score has been appointed as a prognostic factor in the setting of AVB,[8] we started the study before the publication of the paper demonstrating the value of the modified MELD. Moreover, centers performing p-TIPS selected high-risk patients based on Child–Pugh C score (CP-C) < 14 points and Child–Pugh B plus active bleeding (CP-B+AB) at initial endoscopy. Only 45 patients from all the participating centers did not give informed consent to use their clinical data and therefore were not registered in the database.

Exclusion criteria were age older than 75 years, pregnancy, hepatocellular carcinoma outside the Milan criteria, a creatinine level greater than 3 mg per deciliter (265 μmol per liter), a Child–Pugh score above 13 points, active sepsis, heart failure, and total portal-vein thrombosis. Due to the observational nature of the study, the decision to place p-TIPS or use drug plus endoscopic therapy in patients with high-risk AVB was based on the internal hospital policy and the treating physician’s opinion regardless of our study. Only nine centers from the 34 participating had incorporated p-TIPS in their daily clinical management algorithm; four of them were also involved in the previous trials[2,10] and five incorporated the p-strategy once the current study had already begun (Supporting Table S1).

All patients were initially treated with standard-of-care treatment (vasoactive drugs, antibiotics, and endoscopic treatment). Afterwards, patients continued on vasoactive drugs until a polytetrafluoroethylene (PTFE)-covered TIPS was performed within 72 hours after diagnostic endoscopy (p-TIPS group)
and/or were kept on vasoactive drugs (D+E group) until secondary prophylaxis was started, and PTFE-TIPS was only used as a rescue treatment.

The primary end point of the study was survival at 6 weeks and 1 year.

Secondary endpoints were (1) the composite end-point of failure to control acute bleeding (up to day 5), early rebleeding (from day 5 to day 42), and late rebleeding (from day 42); (2) onset or worsening of ascites (defined as need of large-volume paracentesis or permanent/significant increase in diuretic dose without complete ascites disappearance); and (3) development of HE. HE was diagnosed following the AASLD and the European Association for the Study of the Liver Practice Guidelines. Only clinical HE was considered for the study, and HE grades I through IV were defined according to the severity of manifestations. Ascites and ascites-related complications (spontaneous bacterial peritonitis and hepatorenal syndrome) were defined and graded according to the AASLD Practice Guidelines.

Patients were followed up to 12 months or until death or liver transplantation, and clinical information during this period was used for the analysis.

DATA COLLECTION

The ethics committees of all participating hospitals approved the study protocol. All data were gathered in the context of standard practice from the clinical records of the patients, and encrypted, collected, and managed using REDCap electronic data capture tools hosted at Hospital Santa Creu i Sant Pau (Barcelona). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

A steering committee was created to regularly monitor data to detect inconsistencies or errors; when found, queries requiring resolution by the local investigators were sent to each center. All reported clinical variables were finally validated by the steering committee before the statistical analysis of the data.

STATISTICAL ANALYSIS

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for reporting observational studies. Data were described as frequencies and percentages, means and standard deviation (SD), or median and inter-quartile range, as appropriate. Baseline characteristics were compared using Fisher’s exact test for categorical variables, t-test for Gaussian continuous variables, and the Mann-Whitney for ordinal and non-Gaussian continuous variables. Survival was estimated using the cumulative incidence function with orthotopic liver transplant (OLT) as a competing risk. The risk (hazard ratio and 95% CI) of death was evaluated using a competitive risk Cox model. The secondary time-to-event variables were evaluated likewise, but with both death and OLT as competing risks. Adjusted models were built using propensity scores (PS; i.e., the predicted probability of p-TIPS or the reason for p-TIPS placement) given a set of baseline covariates. All reported analyses for time-to-event variables are based on competitive risk models, and all the inferential analyses are PS adjusted unless otherwise specified.

All the analyses were performed using SAS software (version 9.2; SAS Institute Inc., Cary, NC) or Statistical Package for Social Sciences (version 19.0; SPSS, Chicago, IL), and a level of significance was established at the two-sided 5% level.

Results

From October 2013 to May 2015, the 34 centers participating in the observational study prospectively collected data from 1,334 patients with cirrhosis admitted for AVB. Further, an additional 804 patients prospectively registered from October 2011 to September 2013 in the 19 of these centers with pre-existing prospective database/registers were also included. Thus, a total of 2,138 patients with AVB were registered in the REDCap database, and 927 (43%) of them met the defined high-risk criteria (CP-C and CP-B+AB). As shown in Supporting Figure S1, 256 patients had one or more exclusion criteria. Consequently, 671 patients were included in the main analysis (434 CP-C and 237 CP-B+AB); 605 patients (90%) belonged to the D+E group and 66 (10%) to the p-TIPS group. There were no major
Two hundred eleven (31.4%) patients in the whole cohort were lost during the 1-year follow up; 89 (37.6%) in the CP-B+AB group and 122 (28.1%) in the CP-C group. At 42 days, 78 patients (11.6%) were lost to follow up; 21 patients (8.8%) in the CP-B+AB group and 53 patients (12.2%) in the CP-C group.

**SURVIVAL**

P-TIPS markedly improved survival in the whole cohort of high-risk patients admitted with AVB. Survival at 6 weeks was 92% versus 77%; at 1 year, survival was 78% versus 62% (P = 0.014; Fig. 1A). To assess whether CP-C and CP-B+AB patients equally benefitted from the p-TIPS placement, we evaluated both subgroups separately. CP-C patients treated with p-TIPS had a significantly higher survival than the D+E group (6-week survival: 90% vs. 70%; 1-year survival: 78% vs. 53%; P = 0.002; Fig. 1C). Mortality rate in the subgroup CP-B+AB was low and not significantly different in the D+E and p-TIPS groups (6-week survival: 94% vs. 90%; 1-year survival: 77% vs. 75%; P = 0.935; Fig. 1B).

We also calculated the probability of death at 6 weeks by using the MELD-based model because of its demonstrated ability to predict mortality. To calculate the observed mortality, we grouped the study population by using quintiles of the observed MELD. The results are plotted in Fig. 2. The analysis of lineal correlation was r = 0.999 (P < 0.001) for the D+E group, confirming that the mortality observed in our study was similar to that predicted by the MELD-based model. However, the p-TIPS group had a lower mortality than predicted for any given MELD value (lineal correlation r = 0.758 [P = 0.137]), confirming the benefit of the p-TIPS strategy.

To estimate the adjusted effect of p-TIPS accounting for the covariates that were predictors of receiving the treatment, we first estimated that probability (i.e., propensity scores) fit to a logistic regression model, and then we included that probability as a covariate in the survival models (Table 2 and Supporting Table S1). Results shown in Table 2 confirm that the benefit in survival depended on the placement of p-TIPS.

The number of patients needed to be treated to save one life during 1 year, estimated using PS-adjusted competing risk, was 4.2^{(2,4,6,20)}

A total of 224 patients (33.4%) died; 212 (35%) patients in the D+E group died and 12 (18%) in the p-TIPS group. Nineteen (4.9%) patients in the D+E group received OLT, versus 6 (12.8%) in the p-TIPS group. Causes of death are represented in Table 3.

Despite having routinely incorporated the p-TIPS strategy, 92 patients (from the nine p-TIPS centers) did not receive p-TIPS because of unavailability, a few “nonbeliever” physicians, and, in five of the centers, differences in baseline characteristics between the two groups (Table 1).

Two hundred eleven (31.4%) patients in the whole cohort were lost during the 1-year follow up; 89 (37.6%) in the CP-B+AB group and 122 (28.1%) in the CP-C group. At 42 days, 78 patients (11.6%) were lost to follow up; 21 patients (8.8%) in the CP-B+AB group and 53 patients (12.2%) in the CP-C group.

**TABLE 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Endo+Drug Group (N = 605)</th>
<th>Preemptive-TIPS Group (N = 66)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.5 ± 9.7</td>
<td>52.4 ± 11.2</td>
<td>0.128</td>
</tr>
<tr>
<td>Gender: male n (%)</td>
<td>466 (77.0%)</td>
<td>47 (71.2%)</td>
<td>0.335</td>
</tr>
<tr>
<td>Etiology of cirrhosis*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>457 (75.5%)</td>
<td>55 (83.3%)</td>
<td>0.174</td>
</tr>
<tr>
<td>Viral</td>
<td>187 (30.9%)</td>
<td>15 (22.7%)</td>
<td>0.201</td>
</tr>
<tr>
<td>Other</td>
<td>76 (12.6%)</td>
<td>4 (6.1%)</td>
<td>0.161</td>
</tr>
<tr>
<td>Active alcoholism (last 3 m)</td>
<td>326 (55.5%)</td>
<td>34 (52.3%)</td>
<td>0.692</td>
</tr>
<tr>
<td>Charlson Comorbidity Index Mean (SD)</td>
<td>4.561 (1.326)</td>
<td>4.709 (1.51)</td>
<td>0.623</td>
</tr>
<tr>
<td>Previous Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child B</td>
<td>80 (36.7%)</td>
<td>6 (31.6%)</td>
<td>0.656</td>
</tr>
<tr>
<td>Child C</td>
<td>110 (28.4%)</td>
<td>11 (23.4%)</td>
<td>0.469</td>
</tr>
<tr>
<td>MELD Score</td>
<td>15.5 ± 7.2</td>
<td>15.2 ± 5.7</td>
<td>0.668</td>
</tr>
<tr>
<td>Child-Pugh Score</td>
<td>9.9 ± 1.8</td>
<td>10.1 ± 1.5</td>
<td>0.446</td>
</tr>
<tr>
<td>Child-Pugh C (n)</td>
<td>387 (64.0%)</td>
<td>47 (71.2%)</td>
<td>0.242</td>
</tr>
<tr>
<td>Child-Pugh B + Active bleeding</td>
<td>218 (36.0%)</td>
<td>19 (28.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Descriptive data are mean ± SD and n (%).
*More than one answer is possible.
a delay in routine adoption of the p-TIPS strategy. Although PS robustly guarantees that the two groups analyzed were comparable to further discard a selection bias effect, we analyzed survival—comparing patients who did not receive TIPS in the p-TIPS centers with the patients treated in the non-p-TIPS centers. As seen in Supporting Fig. S3, patients not managed with p-TIPS had similar outcomes regardless of their management in p-TIPS or non-p-TIPS centers, corroborating the bad outcome of our high-risk population.

**COMPOSITE ENDPOINT OF FAILURE TO CONTROL BLEEDING AND PREVENT REBLEEDING**

In the D+E group, 141 (23.3%) patients experienced failure to control bleeding or rebleeding, versus 3 (4.5%) in the p-TIPS group and 44 (7%) in the D+E group who required rescue TIPS (Table 3). When considering death or OLT as competing risk events, the PS-adjusted risk of achieving the composite endpoint was markedly reduced in the p-TIPS group versus the D+E group (HR: 0.17; 95% CI: 0.05-0.53; \( P = 0.002 \); Fig. 3A). Failure to control bleeding or rebleeding was significantly lower in the p-TIPS group than in either the CP-B+AB or the CP-C group (Fig. 3B,C). In the unadjusted analysis, the benefit of p-TIPS on the composite endpoint remained (Table 2).

**DE NOVO OR WORSENING ASCITES**

In the D+E group, 288 (47.6%) patients had de novo or worsening of previous ascites versus 6 (9.1%)
in the p-TIPS group (Table 3). Regarding ascites-related complications, 99 (16.3%) patients in the D+E group developed spontaneous bacterial peritonitis or hepatorenal syndrome versus 1 (1.5%) in the p-TIPS group. The 1-year risk of de novo or worsening ascites considering death as a competing risk event was dramatically reduced in the p-TIPS group for the PS-adjusted analysis (HR: 0.16 [95% CI: 0.07-0.35]; \( P < 0.001 \); Fig. 4A). The marked benefit of p-TIPS over ascites was observed both in CP-B+AB and CP-C patients (Fig. 4B,C) and observed in the unadjusted analysis (Table 2).

**HEPATIC ENCEPHALOPATHY**

Two hundred twenty-eight (37.7%) patients had any episode of HE in the D+E group versus 28 (42.4%) in the p-TIPS group (Table 3). The risk of developing any grade of hepatic encephalopathy considering death or OLT as competing risk events was similar between groups for the PS-adjusted analysis (HR: 1; 95% CI: 0.73-1.45; \( P = 0.863 \); Fig. 5). There were no differences between groups, and the

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**TABLE 2. Risk of Mortality, Rebleeding, Ascites and Encephalopathy Using Competitive Risk Approaches for the Whole High-risk Cohort and the Child-B+AB and Child-C groups**

<table>
<thead>
<tr>
<th>Child</th>
<th>Raw analysis</th>
<th>Propensity score* adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( P )-value</td>
<td>HR [IC 95%]</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-Risk</td>
<td>0.0087</td>
<td>0.480 [0.273 to 0.844]</td>
</tr>
<tr>
<td>Child-B+AB</td>
<td>0.9585</td>
<td>0.966 [0.303 to 3.082]</td>
</tr>
<tr>
<td>Child-C</td>
<td>0.0013</td>
<td>0.366 [0.192 to 0.699]</td>
</tr>
<tr>
<td>Failure to control bleeding &amp; rebleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-Risk</td>
<td>0.0004</td>
<td>0.176 [0.057 to 0.542]</td>
</tr>
<tr>
<td>Child-B+AB</td>
<td>0.0286</td>
<td>NE</td>
</tr>
<tr>
<td>Child-C</td>
<td>0.0055</td>
<td>0.241 [0.078 to 0.743]</td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-Risk</td>
<td>&lt;.001</td>
<td>0.170 [0.078 to 0.37]</td>
</tr>
<tr>
<td>Child-B+AB</td>
<td>0.0006</td>
<td>NE</td>
</tr>
<tr>
<td>Child-C</td>
<td>&lt;.001</td>
<td>0.225 [0.104 to 0.488]</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-Risk</td>
<td>0.4477</td>
<td>1.146 [0.823 to 1.597]</td>
</tr>
<tr>
<td>Child-B+AB</td>
<td>0.8777</td>
<td>0.925 [0.353 to 2.421]</td>
</tr>
<tr>
<td>Child-C</td>
<td>0.579</td>
<td>1.116 [0.792 to 1.572]</td>
</tr>
</tbody>
</table>

Sample sizes for Endo+Drug and Early Tips are 605 vs 66 in the overall high-risk cohort, 218 vs 19 in the Child B+AB group and 387 vs 47 in the Child C group.

Endo+Drug is the reference category for the risk calculation.

\( P \)-values from the Fine-Gray test (raw analysis) or the competitive Cox model (PS adjusted analyses).

NE: not estimable.

* Propensity scores model for all high-risk patients included age, Child-Pugh and bilirubin; for the Child-B+AB group: age, Albumin and INR and for the Child-C group: bilirubin.
similar rate of HE was observed both in CP-B+AB and CP-C patients (Fig. 5B and C). In the unadjusted analysis, the results were consistently similar (Table 2).

**Discussion**

Previous studies have demonstrated that treating patients at high risk of treatment failure by placing a p-TIPS (also called early TIPS) within 72 hours of admission, before uncontrolled bleeding or rebleeding occurs, improves outcome. All available data have shown that this strategy is associated with a reduction in failure, rebleeding, and development of de novo or worsening of existing ascites. In addition, all the studies but one also demonstrated a clear beneficial influence of p-TIPS on survival. However, despite this strong evidence, implementation of p-TIPS has not been widely accepted. As confirmed with this study, only 13% of high-risk patients admitted to centers participating in the study received p-TIPS. It is also noted that not all high-risk patients admitted with AVB may benefit from p-TIPS; indeed, in our study, 256 (27.6%) of them had at least one exclusion criteria. However, of the 671 patients without any contraindication, only 66 (13%) received p-TIPS. This is in agreement with a recent multicenter study performed in France that also confirms this data. Of the 326 eligible candidates, only 22 (6.7%) of them received p-TIPS, underscoring the lack of implementation by physicians in a real-life setting. When specifically evaluated, the main reasons for the lack of implementation may be either that treating physicians do not believe in the benefit of p-TIPS or that the technique is not available. The first limitation could be overcome by the data showing that patients not receiving TIPS, regardless of the expertise and/or availability of the center where they are managed, have a higher mortality rate than patients receiving p-TIPS. Remarkably, the number of patients needed to be treated to save one life is 4. This mean that if all 671 patients had been treated with p-TIPS, the number of deaths could have been reduced significantly from 224 to 65.

The second limitation should be addressed with programs aimed at easily transferring patients to centers of expertise. As recently demonstrated, centers administering more than 20 TIPS per year have the best outcome possible with lower inpatient mortality; therefore, efforts aimed at better equipping high-volume institutions should be implemented. In centers with no access to TIPS placement, the policy should be to transfer patients to centers of expertise. It is also of note that other diseases with similar mortality rates and successful treatments, such as stroke and heart attack, have motivated changes in sanitary policy worldwide, with the main aim of treating patients as soon as possible in centers of expertise.

Based on these results, all the efforts directed at implementing and guaranteeing access to p-TIPS treatment are widely justified.

Other potential reasons for lack of implementation may include a fear of the high rate of HE and TIPS
dysfunction that has been reported in previous studies using TIPS as a salvage therapy for refractory bleeding and using bare stents.\(^{16-20}\) However, none of the studies evaluating the role of p-TIPS increased HE,\(^{2,9-11}\) and the rate of TIPS dysfunction reported using covered stents is very low.\(^{2,10,11}\)

To overcome these limitations, we decided to run an observational study in centers with expertise in the management of AVB to evaluate the efficacy of p-TIPS. We collected all the consecutive portal hypertension–related bleeding episodes in the participating centers and analyzed the outcome only in those patients fulfilling the previously identified high-risk criteria. The decision to place a p-TIPS was based on the internal hospital policy and the treating physician’s opinion, regardless of our study.

Our study, which included a large number of patients (671) with high-risk criteria admitted for AVB, clearly confirms that the use of p-TIPS reduces failure to control bleeding and rebleeding, reduces \textit{de novo} or worsening ascites, did not increase HE, and improved survival.

We also evaluate whether the use of p-TIPS equally benefits CP-B+AB and CP-C patients. All the benefits of p-TIPS, except for improvement in survival, were homogeneously found either in CP-C or CP-B+AB patients. P-TIPS did not have a significant impact in CP-B+AB survival, probably due to the low mortality rate observed in CP-B+AB patients (19%), which makes it difficult to demonstrate a potential effect on survival without evaluating a very large number of patients. Despite the lack
of benefit on survival, the better control of further rebleeding and ascites without increasing the risk or severity of HE could justify the use of p-TIPS in this subgroup of patients.

Our study proves that tailoring treatment to patient risk is a real option in the setting of AVB. Child-Pugh classification, together with endoscopic findings, allows for identification of in whom p-TIPS may improve outcome early after admission. These criteria are easy to apply in daily clinical practice, but the accuracy and reproducibility of these parameters face some difficulties. Performing endoscopy in bleeding patients and identifying active bleeding can be challenging, and some components of the Child-Pugh classification have subjectivity and the limitation of having albumin determined at admission. Although other predictive factors have been shown to robustly predict outcome in the AVB scenario, such as the modified MELD model, we decided to use CP-C and CP-B+AB because they were the criteria used by the participating centers to determine risk level. However, the high-risk mortality of our cohort was confirmed using the MELD-based model, and mortality in the population not treated with p-TIPS was as high as the one predicted by the modified model. It is possible that more objective and reproducible predictive factors may still be identified that could improve the selection of patients who may benefit from p-TIPS. It is also important to note that our results cannot be extrapolated to older patients or patients with deteriorated kidney function (creatinine >3mg/dl), occlusive portal vein thrombosis, sepsis, heart failure, or hepatocellular carcinoma out of the Milan criteria, as this population was not included in our study or in the previous ones.

FIG. 4. Cumulative incidence function for development/worsening of ascites using death as competitive risk in (A) all high-risk patients, (B) CP-B+AB, and (C) CP-C.
The main limitation of our study comes from its observational design, which carries an inherent risk of selection bias, although the use of propensity score lowers this possibility. Another potential limitation may be the lower-than-expected number of patients treated with p-TIPS. Aiming at including a large sample size, the study was performed in 34 centers altogether, providing a large number of high-risk patients. However, we did not reach a very high number of p-TIPS, probably because of a low rate of p-TIPS indicated by treating physicians. Even with these limitations, this study allowed us obtaining robust data that corroborates previous evidence.

In conclusion, the use of p-TIPS with an e-PTFE-covered stent increases survival in Child-Pugh C patients admitted with AVB. In CP-C and CP-B+AB, p-TIPS decreases uncontrolled bleeding, rebleeding, and de novo or worsening ascites, without increasing the risk of developing HE. These results strongly support the view that p-TIPS must be the treatment of choice in CP-C patients with AVB. Because of the strong benefit in preventing further bleeding episodes and ascites without increasing HE, p-TIPS could also be recommended for CP-B+AB patients.

REFERENCES

3) Bambha K, Kim WR, Pedersen R, Bida JP, Kremers WK, Kamath PS. Predictors of early re-bleeding and mortality after


Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.30182/suppinfo.