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CLINICAL—LIVER

Effects of Early Placement of Transjugular Portosystemic Shunts in Patients With High-Risk Acute Variceal Bleeding: a Meta-analysis of Individual Patient Data

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e23. Learning Objective: Upon completion of this CME activity, successful learners will be able to correctly identify the indication for early placement of transjugular intrahepatic portosystemic shunt (TIPS) (preemptive TIPS) in patients with cirrhosis and acute variceal bleeding.

BACKGROUND & AIMS: Compared with drugs plus endoscopy, placement of transjugular portosystemic shunt within 72 hours of admission to the hospital (early or preventive transjugular intrahepatic portosystemic shunt [TIPS], also called preemptive TIPS) increases the proportion of high-risk patients with cirrhosis and acute variceal bleeding who survive for 1 year. However, the benefit of preemptive TIPS is less clear for patients with a Child-Pugh score of B and active bleeding (CP-B+AB). We performed an individual data meta-analysis to assess the efficacy of preemptive TIPS in these patients and identify factors associated with reduced survival of patients receiving preemptive TIPS. **METHODS:** We searched publication databases for randomized controlled trials and observational studies comparing the effects of preemptive TIPS versus endoscopy plus nonselective beta-blockers in the specific population of high-risk patients with cirrhosis and acute variceal bleeding (CP-B+AB or Child-Pugh C, below 14 points), through December 31, 2019. We performed a meta-analysis of data from 7 studies (3 randomized controlled trials and 4 observational studies), comprising 1327 patients (310 received preemptive TIPS and 1017 received drugs plus endoscopy). We built adjusted models to evaluate risk using propensity score for baseline covariates. Multivariate Cox regression models were used to assess the factors associated with survival time. The primary endpoint was effects of preemptive TIPS versus drugs plus endoscopy on 1-year survival in the overall population as well as CP-B+AB and Child-Pugh C patients. **RESULTS:** Overall, preemptive TIPS significantly increased the proportion of high-risk patients with cirrhosis and acute variceal bleeding who survived for 1 year, compared with drugs plus endoscopy (hazard ratio [HR] 0.443; 95% CI 0.323–0.607; $P < .001$). This effect was observed in CP-B+AB patients (HR 0.524; 95% CI 0.307–0.896; $P = .018$) and in patients with Child-Pugh C scores below 14 points (HR 0.374; 95% CI 0.253–0.553; $P < .001$). Preemptive TIPS significantly improved control of bleeding and ascites without increasing risk of hepatic encephalopathy in Child-Pugh C and CP-B+AB patients, compared with drugs plus endoscopy. Cox analysis of patients who received preemptive TIPS showed that patients could be classified into 3 categories for risk of death, based on age, serum level of creatinine, and Child-Pugh score. In each of these risk categories, preemptive TIPS increased the proportion of patients who survived for 1 year, compared with drugs plus endoscopy. **CONCLUSIONS:** In a meta-analysis of data from 1327 patients with cirrhosis, acute variceal bleeding, and Child-Pugh score between 10 and 13 points or CP-B+AB, preemptive TIPS increased the proportion who survived for 1 year, in both subgroups separately, compared with drugs plus endoscopy.

Keywords: AVB; HE; Liver Disease; Treatment.

The management of acute variceal bleeding (AVB) in patients with cirrhosis has improved over the past decades. According to international guidelines, treatment is based on careful replacement of blood volume, early administration of vasoactive drugs, antibiotic prophylaxis, and endoscopic treatment. Baveno VI consensus conference,[1] and subsequently American Association for the Study of Liver Disease guidelines for portal hypertensive bleeding in cirrhosis,[2] incorporated for the first time the use of preemptive (also called early) transjugular intrahepatic portosystemic shunt (p-TIPS), as a treatment option in patients with AVB at high risk of treatment failure to prevent failure to control acute bleeding and to prevent variceal rebleeding. To achieve these goals, p-TIPS must be placed as soon as possible to increase the possibilities of preventing early treatment failures. Thus, in most occasions p-TIPS was placed in the first 24 hours after admission, although, for logistic reasons, timing to consider TIPS as early p-TIPS was extended up to 72 hours provided treatment failure has not yet occurred. The efficacy and safety of the p-TIPS strategy has been evaluated in 3 randomized controlled trials (RCTs)[3–5] and 5 observational studies[6–10] so far. Criteria adopted for definition of high risk were HVPG $\geq$20 mm Hg in the first RCT[3] and Child-Pugh up to 13 points (CP-C) or Child-Pugh B plus active variceal bleeding during endoscopy (active bleeding: variceal jet /oozing) (CP-B + AB) despite being under intravenous vasoactive agents in the second RCT[4] and in the subsequent observational studies.[6–9] One observational study[10] included all Child-Pugh bleeders (among them 495 Child A) excluding only those with a Child-Pugh score $>$ 14. A third most recent RCT,[5] compared the use of p-TIPS vs standard-of-care treatment in AVB. However, in this RCT, most patients were Child-Pugh B without active bleeding and only 56 patients were at high risk according to the previous criteria.

Consistently, all of these studies showed the advantage of p-TIPS over current standard of care in terms of achieving a better control of variceal bleeding, lower risk of rebleeding, and better control of ascites. Moreover, most studies demonstrated an improvement in survival by p-TIPS when the overall population of high-risk patients is evaluated.[4,6,9,11] However, when the population is stratified by Child-Pugh class, the benefit was strongly seen in Child-Pugh C patients but was less clear in Child-Pugh B+ AB patients.[9–11] However, none of the available studies had enough power to detect differences in survival in the different Child-Pugh categories. This, together with the expected lower mortality in Child-Pugh B than in Child-Pugh C patients[12] may, at least in part, explain the lack of solid data on survival on the Child-Pugh B population. Some meta-analyses and systematic reviews have attempted to overcome these issues[13–16]; however, the lack of individual data on time to death and the fact that some studies did not show separately the outcomes in the 2 different Child-Pugh categories reduced the clinical impact of these attempts.

WHAT YOU NEED TO KNOW:

BACKGROUND AND CONTEXT

Compared with drugs plus endoscopy, placement of transjugular portosystemic shunts within 72 hrs of admission to the hospital (preemptive TIPS) increases survival times of high-risk patients with cirrhosis and acute variceal bleeding, but the benefit is less clear for patients with a Child-Pugh score of B and active bleeding.

NEW FINDINGS

In a meta-analysis of data from 7 studies of patients with cirrhosis, acute variceal bleeding, and Child-Pugh score C below 14 points or Child-Pugh B plus acute variceal bleeding, preemptive placement of TIPS reduced risk of death within 1 year compared with drugs plus endoscopy, and reduced bleeding and ascites without increasing the risk of hepatic encephalopathy.

LIMITATIONS

This was a meta-analysis of randomized controlled and observation studies. Additional prospective studies are needed.

IMPACT

Patients with cirrhosis and Child-Pugh score C (below 14 points) or Child-Pugh B plus acute variceal bleeding should receive preemptive placement of TIPS, rather than drugs plus endoscopy.

In addition, there is concern on whether there is a subgroup of the included high-risk patients in which p-TIPS might be futile. Thus, although patients considered to have very severe disease (Child-Pugh $>$ 14 points) were excluded from all but one[7] of the previously mentioned studies, it is possible that some patients may still have a high risk of mortality after p-TIPS placement. Again, this could not be defined in previous meta-analyses because of lack of individual patient data.

In this study, we have performed a meta-analysis of individual patient data from previous multicenter international studies evaluating the efficacy of p-TIPS versus standard-of-care treatment with the aim of reevaluating the effect of p-TIPS in survival and detecting basal predictors of poor outcome in the p-TIPS group. In this way, we intended to overcome the limitations associated with the use of literature data and to increase the statistical power and effect size.

*** Authors share co-first authorship.**

Abbreviations used in this paper: **AB, active bleeding; AVB, acute variceal bleeding; CP-, Child-Pugh class; Drugs + Endo, pharmacological treatment plus endoscopy; HE, hepatic encephalopathy; MELD, Model for End-Stage Liver Disease; NSBB, nonselective beta-blocker; p-TIPS, preemptive transjugular intrahepatic portosystemic shunt; RCT, randomized controlled trial.**

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Material and Methods

Studies eligible for inclusion in this meta-analysis were those that included patients with cirrhosis and AVB from RCTs and observational studies aimed to compare the use of medical treatment (endoscopy plus nonselective beta-blockers [NSBBs]) vs p-TIPS. All patients included in the studies should have fulfilled the current accepted high-risk criteria (Child-Pugh B + AB or Child-Pugh C < 14 points).

For this, we have manually searched the literature up to December 31, 2019, for prospective observational studies and RCTs that have included cohorts of patients with cirrhosis and AVB treated with early/preventive TIPS within 72 hours from admission (Preemptive-TIPS). The following keywords were searched in MEDLINE: 'early TIPS', 'early transjugular intrahepatic portosystemic shunt', 'preemptive transjugular intrahepatic portosystemic shunt', 'preemptive TIPS', 'high-risk patients', 'TIPS placement', 'acute variceal bleeding'. Nine studies were identified as possible candidates for inclusion in the meta-analysis. The principal investigators of the previous RCTs[3–5] and observational studies were contacted[6,7,9,10] for possible inclusion. One of the RCTs[5] and 1 of the observational studies[10] included patients in all Child-Pugh categories, therefore only individual data of those patients fulfilling the current high-risk criteria (Child-Pugh B plus active bleeding and Child-Pugh C up to 13 points) were included in the individual meta-analysis. The 2 other studies comparing the outcome of patients treated with p-TIPS vs Drugs + Endo were not included because the criteria defining high-risk patients were not clearly described[17] or the study included very selected referred patients since 1994 (most before the first manuscript defining the early-TIPS concept) and, after careful review, most patients did not meet the criteria of previous studies.[8] Therefore, our meta-analysis included individual data from 7 previous studies[3–7,9,10] comparing p-TIPS vs Drugs + Endo for patients with cirrhosis and AVB and a high risk of treatment failure (Supplementary Table 1).

All studies excluded subjects aged <18 or >75 years, Child-Pugh >13, hepatocellular carcinoma outside Milano criteria, bleeding from isolated gastric or ectopic varices, previous TIPS, portal vein thrombosis with total vessel occlusion, creatinine greater than 3 mg/dL, heart failure, and pregnancy. Previous recurrent hepatic encephalopathy (HE) was reported as exclusion criteria in 3 of these studies.

In one RCT, TIPS was performed using bare stents,[3] whereas in the remaining 6 studies TIPS was performed with PTFE-covered stents.[4–7,9,10] In the RCT using bare stents, the non-TIPS group received only NSBBs to prevent rebleeding. Endoscopic band ligation was used in patients in whom NSBBs were not tolerated or were contraindicated. We have decided to include these patients as well because it was the first RCT in the issue. However, a sensitivity analysis excluding this RCT was also performed. All other studies used the current standard of care.

Individual data of each patient were incorporated in a new database specifically designed for this study collecting information related to clinical and laboratory baseline characteristics, AVB characteristics and its treatment, outcome, and eventual adverse events or complications.

The primary endpoint was to compare the 2 types of treatment, p-TIPS and Drugs + Endo, in terms of 1-year survival in the overall population as well as in the 2 different Child-Pugh classes (Child-Pugh B with active bleeding at endoscopy and Child-Pugh C <14 points), separately. Secondary endpoints were to seek for differences at 1-year follow-up in (1) the composite outcome of failure in controlling AB/preventing variceal rebleeding, (2) in developing new or worsening ascites, and (3) in the incidence of HE.

In a second analysis, we focused on identifying independent baseline predictors of poor outcome in patients treated with p-TIPS.

Meta-analysis was performed in accordance to the principles of Good Clinical Practice and the Declaration of Helsinki and its appendices. All the studies included were approved by the local ethics committees of all participating hospitals. All patient data were coded to preserve patient privacy.

Statistical Analysis

Categorical variables were described with frequencies and percentages and continuous variables with median [interquartile range: 25th–75th percentiles], and the survival function was described using the Kaplan-Meier function.

We used standardized differences, defined as differences between groups divided by pooled standard deviation to assess heterogeneity between groups for baseline covariables. The Inverse Probability of the Treatment Weights (IPTW) approach[18] was used to create a pseudo-population in which the 2 groups (Drugs + Endo and p-TPS) were balanced across baseline covariates. The stabilized weights were calculated using propensity scores (PS)[19] obtained from a logistic regression model aimed to minimize the between arms standardized differences.[20] Covariate balance was assessed using the standardized differences with the goal to achieve values < .10 to define insignificant difference in potential confounders. The final covariates included in the PS calculation were (1) for all high-risk patients: age, gender, etiology, previous bleeding, previous ascites, Model for End-Stage Liver Disease (MELD), bilirubin, platelets, creatinine, and international normalized ratio; (2) for C-B+ AB patients: etiology, active alcoholism, shock, Child-Pugh, MELD, bilirubin, platelets and hematocrit; and (3) for CP-C patients: etiology, active alcoholism, shock, MELD, platelets and hematocrit. Baseline categorical data were compared using the $\chi 2$ test and continuous variables using analysis of variance with rank-transformed data, for raw and IPTW-adjusted analyses. Raw and IPTW-weighted Cox regression models were used to estimate hazard ratios (HR) with 95% confidence intervals [95% CI].

For the analysis of predictive factors, univariate models were first assessed to identify potential predictors of mortality. Those variables with a P < .10 were further assessed in multivariate analyses and the Harrel's C-statistic index was calculated as a discriminative measure criterion. For continuous variables, cutoffs were selected either by using the Youden method or based on already validated cutoffs in the literature.

All inferential analyses including tables and figures were IPTW weighted, except for the analysis of predictive factors, or otherwise specified.

Statistical analysis was performed with SAS version 9.4 or higher (SAS Institute Inc., Cary, NC) and statistical significance was established at the 2-sided 5% level.

Results

The meta-analysis included individual data of 1327 patients, among which 602 (45.3%) were CP-B+AB and 725 (54.7%) Child-Pugh C (<14 points). A total of 310 patients

Table 1. Baseline Characteristics of Patients Included in the Studies

	RAW				IPTW			
Variable at admission	Drugs+Endo	p-TIPS	*P*-value	StdDiff, %	Drugs+Endo	p-TIPS	*P*-value	StdDiff, %
Gender: male	769 (75.6)	220 (71.0)	0.100	−10.9	759 (74.6)	232 (75.5)	0.7506	1.2
Age	53 (46–61)	54 (45−62)	0.8301	3.9	53 (46–61)	53 (44.9–62)	0.2617	5.3
Etiology								
Alcohol	566 (55.7)	151 (48.7)	0.0317	−15.2	555 (54.5)	168 (54.8)	0.9237	0.4
Viral	415 (40.8)	115 (37.1)	0.2430	−11.8	400 (39.4)	118 (38.6)	0.7920	−1.1
Other	76 (7.5)	15 (4.8)	0.1081	**−18**	68 (6.7)	16 (5.2)	0.3547	−4.7
Child Pugh Class								
Child Pugh C	553 (54.3)	172 (55.5)	0.7315	3.6	553 (54.3)	170 (55.1)	0.8131	2.8
Child B+ AB	464 (45.6)	138 (44.5)	0.7315	3.6	464 (45.6)	137 (44.9)	0.8131	−2.8
Child Pugh score	9.6 (8–11)	10 (8–11)	0.6333	−0.6	10 (8–11)	10 (8–11)	0.8310	1.0
Previous variceal bleeding	354 (34.8)	120 (38.7)	0.2095	8.2	358 (35.2)	100 (32.6)	0.3921	−3.5
Previous HE	271 (26.6)	63 (20.3)	0.0247	−4.7	266 (26.1)	64 (20.7)	0.0532	−4.5
Previous ascites	571 (56.1)	197 (63.5)	0.0208	12.2	583 (57.4)	171 (55.9)	0.6568	−3.8
MELD	14.7 (11–19)	15 (12− 19.9)	0.0509	11.8	14.9 (11–19)	14.6 (11.7–19.9)	0.4951	−4.8
≤11	285 (28.02)	66 (21.3)			275 (27)	73 (23.8)		
12–18	437 (42.9)	152 (49)			437 (42.9)	146 (47.6)		
≥19	295 (29)	92 (29.7)			305 (30)	88 (28.7)		
Creatinine (*mg/dL*)	0.81 (0.64–1.10)	0.83 (0.68–1.08)	0.9726	1.4	0.82 (0.64–1.12)	0.83 (0.67–1.09)	0.9958	−0.4
Bilirubin (*mg/dL*)[a]	2.47 (1.25–4.40)	1.91 (1.20–3.27)	<.0001	−21.8	2.40 (1.23–4.30)	2.10 (1.30–3.8)	0.9974	−4.9
INR [a]	1.60 (1.33–1.97)	1.63 (1.36–2.0)	0.0811	2.3	1.61 (1.33–1.98)	1.60 (1.32–1.99)	0.7731	−1.7
ALT (*U/L*)	36 (24–59)	35 (22–56)	0.9543	−12.4	36 (23–60)	35 (22–55)	0.4267	−6.3
AST (*U/L*)	72 (44–120)	64 (45–116)	0.6016	−15.1	72 (44–120)	69 (45–113)	0.2919	−7.3
Albumin (*mg/dL*)	26 (23–29)	25.5 (22–29.4)	0.5520	−2.1	26 (23–29.00)	25.7 (22–29.5)	0.5809	−1.3
Na (*mEq/L*)	137 (134–141)	138 (134–141)	0.2315	7.3	137.5 (134− 141)	138 (134–141)	0.5106	4.2
Platelets	80.000 (52.000– 118.000)	77.000 (50.000–114.000)	0.0619	−15.5	78.000 (50.000–114.000)	81.000 (54.000–128.0000	0.2807	1.7

NOTE. Descriptive statistics are frequencies (%) for categorical variables and median (25%–75% interquartile range) for continuous variables.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; StdDiff, standardized difference; TIPS, transjugular intrahepatic portosystemic shunt.
[a]Values above 25%. For INR: range 0.9–10; for Bilirubin range 0.10–43 mg/dL.

Table 2. Summary of Efficacy Measurement Variables at 1 Year

Variable	Child-Pugh class	Drugs+Endo (n = 1017), n (%)	TIPS (n = 310), n (%)
Posttreatment hepatic encephalopathy	B+AB	107 (23.1)	40 (29.0)
	C	156 (28.2)	69 (40.1)
Posttreatment new or worsening ascites	B+AB	126 (25.2)	14 (10.1)
	C	237 (42.8)	22 (13.3)
Failure to control bleeding plus variceal rebleeding	B+AB	117 (42.8)	13 (13.8)
	C	192 (44.8)	15 (6.4)
Liver transplantation	B+AB	18 (4.0)	10 (8.3)
	C	31 (5.6)	22 (12.8)
Mortality	B+AB	111 (23.9)	18 (13.1)
	C	242 (43.8)	37 (21.5)
Bacterial peritonitis	B+AB	15 (3.2)	2 (1.5)
	C	30 (5.5)	0 (0.0)

were treated with p-TIPS (138 CP-B+ AB and 172 CP-C) and 1017 patients (464 CP-B+AB and 553 CP-C) with Drugs + Endo therapy. Available data on 74% of the patients treated with p-TIPS shows that 66% of TIPS were placed in the first 24 hours, 21% were placed in the first 48 hours, and 13% were placed in the first 72 hours. There were no major differences in baseline characteristics between patients treated with p-TIPS or Drugs + Endo (Table 1). When using the IPTW approach, we obtained standardized difference always below the target cutoff of 10% (Table 1). Table 2 shows the summary of events and Table 3 shows the risk of events on raw and IPTW analyses.

Table 3. Risk of Death, Ascites, Hepatic Encephalopathy, and Failure to Control Bleeding and Rebleeding Using Noncompetitive Risk Approaches in the Whole High-Risk Cohort and the Child Pugh B + AB and Child Pugh C Groups

		RAW analysis		IPTW analysis	
		HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Death	All	0.475 [0.350–0.646]	<.001	0.443 [0.323–0.607]	<.001
	Child B+AB	0.519 [0.303–0.886]	.016	0.524 [0.307–0.896]	.018
	Child C	0.423 [0.292–0.614]	<.001	0.374 [0.253–0.553]	<.001
Ascites	All	0.233 [0.152–0.358]	<.001	0.255 [0.173–0.378]	<.001
	Child B+AB	0.334 [0.171–0.652]	.001	0.285 [0.144–0.563]	<.001
	Child C	0.166 [0.094–0.294]	<.001	0.201 [0.121–0.335]	<.001
Hepatic Encefalopathy	All	1.092 [0.854–1.397]	.483	1.078 [0.841–1.382]	.553
	Child B+AB	1.043 [0.702–1.551]	.833	1.034 [0.690–1.549]	.872
	Child C	1.112 [0.815–1.518]	.502	1.107 [0.807–1.516]	.529
Failure to control bleeding and rebleeding	All	0.287 [0.210–0.391]	<.001	0.338 [0.252–0.453]	<.001
	Child B+AB	0.263 [0.160–0.432]	<.001	0.276 [0.168–0.453]	<.001
	Child C	0.298 [0.199–0.445]	<.001	0.354 [0.243–0.515]	<.001

NOTE. Drugs+Endo treatment is the reference category for risk calculation.
CI, confidence interval; HR, hazard ratio.

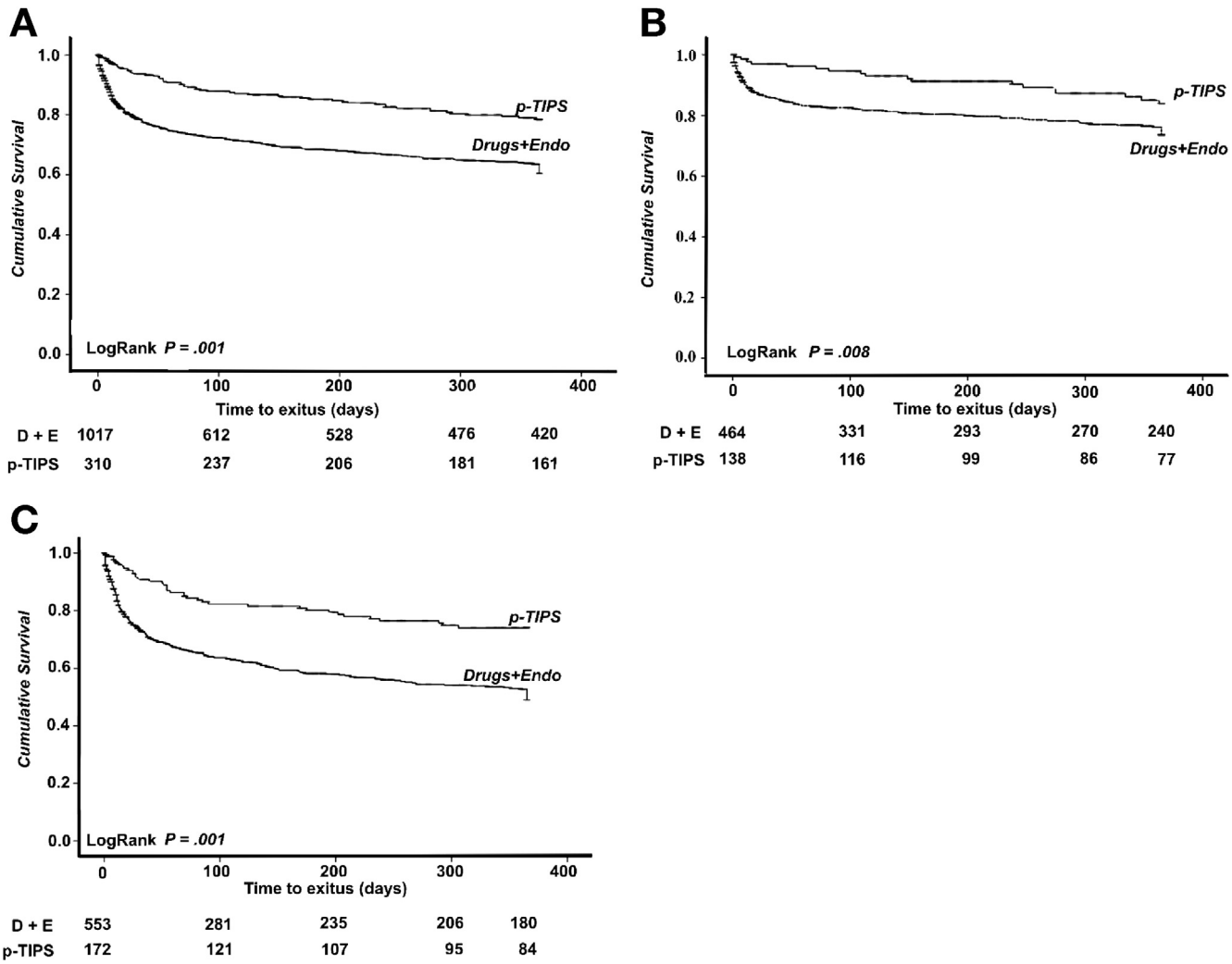

Figure 1. Survival at 1 year in (*A*) all population; (*B*) Child-Pugh B +AB population; (*C*) Child-Pugh C population.

Survival

At 1 year, 408 patients died (353 in the Drugs + Endo group and 55 in the p-TIPS group). Supplementary Table 2 depicts causes of death in relation to treatment group and Child-Pugh class. Six-week and 1-year survival were significantly higher in the p-TIPS than in the Drugs + Endo group (93% vs 76.8% and 79% vs 62%, Log Rank P < .001, Figure 1*A*). The benefit of p-TIPS was observed in both CP-B + AB patients (96% vs 85% at 6 weeks and 84% vs 74% at 1 year, Log Rank P = .008; Figure 1*B*) and in CP-C patients (90% vs 70% at 6 weeks and 75% vs 51% at 1 year, Log Rank P < .001, Figure 1*C*).

There was a survival benefit for p-TIPS over Drugs + Endo (HR 0.443; 95% CI 0.323–0.607; *P* < .001). This effect was observed in both Child B+AB (HR 0.524; 95% CI 0.307–0.896; *P* = .018), and in CP-C patients (HR 0.374; 95% CI 0.253–0.553; *P* < .001) (Table 3). Number of patients needed to treat to save 1 life is 4.23 (95% CI 3.57–6.94).

Similar results were observed when data were analyzed considering liver transplantation as a competitive event (Supplementary Table 3). To increase the homogeneity across studies and to eliminate possible bias, we also analyzed the data after excluding the patients from the first RCT performed by Monescillo et al.[3] Similar results regarding survival were observed in overall, CP-B+AB and CP-C patients (Supplementary Table 4).

Except for 1 study,[7] the effect of p-TIPS on survival had the same trend in all the studies analyzed in the overall population or in CP-B+AB or CP-C (Supplementary Figure 1).

Because of previous concerns about the benefit in survival in CP-B+AB and despite that the individual meta-analysis showed a significant improvement in survival in these patients, we decided to further analyze variables predicting survival in the 464 CP-B+AB patients not treated with p-TIPS (Drugs + Endo CP-B+AB group). Age, albumin, bilirubin, creatinine, CP, and MELD scores were factors associated with mortality at univariate analysis (all P < .05). At multivariate analysis, either MELD or CP score were significantly associated with survival; however, CP score revels as the best model able to stratify CP-B+AB patients into 2 risk categories (Supplementary Tables 5, 6). According to this model, patients with a CP score >7 points (n = 299), had a significantly worse survival than those with CP score = 7 points (n = 165) (Log Rank P < .0001) allowing to stratify them into a "low-risk CP-B+AB" category and a "high-risk CP-B+AB category" (Supplementary Figure 2). Importantly, p-TIPS markedly

improved survival in CP-B+AB high-risk category (CP-B+AB with a score of 8 and 9 points; Log Rank P = .0006; Figure 2*A*) but did not in patients with CP-B+AB of 7 points (CP-B+AB low risk group) (Log Rank P = .68; Figure 2*B*).

Composite Endpoint: Failure in Controlling Acute Bleeding/Prevention of Rebleeding

A total of 337 patients reached the composite endpoint (309 or 30.3% in the Drugs + Endo group and 28 or 9% in the p-TIPS group). P-TIPS significantly reduced the risk of failure to control bleeding/preventing variceal rebleeding (HR 0.338; 95% CI 0.252–0.453; $P < .001$) (Table 3). The beneficial effect of p-TIPS was observed both in CP-B+AB (HR 0.276; 95% CI 0.168–0.453; P < .001) by reducing it with 73% and in the CP-C patients (HR 0.354; 95% CI 0.243–0.515; $P < .001$) by reducing it with 65% (Supplementary Figure 3*A*–*C*). Similar results were observed when death and liver transplantation were considered as competing risk events (Supplementary Table 3). Benefit for patients treated with p-TIPS in reducing failure in controlling acute bleeding and variceal rebleeding was observed in both CB-B+AB = 7 points (Log Rank P = .0007), as well as in CP-B+AB > 7 points (Log Rank P < .0001) (data not shown).

New or Worsening Ascites

A total of 399 patients experienced new or worsening ascites (363 or 35.6% patients in the Drugs + Endo group and 36 or 11.6% in the p-TIPS group). The risk of developing new or worsening ascites was significantly reduced by the p-TIPS in the overall population (HR 0.255; 95% CI 0.173–0.378; $P < .001$) but also in both subgroup of patients, reducing it with 72% in the CP-B+AB group (HR 0.285, 95% CI 0.144–0.563; P = .001) and by 80% in the CP-C group (HR 0.201; 95% CI 0.121–0.335; P < .001) (Table 3) (Supplementary Figure 4*A*–*C*). Similar results were observed when death and liver transplantation were considered as competing risk events (Supplementary Table 3). Spontaneous bacterial peritonitis developed in 4.4% of patients in the Drugs + Endo group (1.5% in the CP-B+ AB group and 2.9% in the CP-C group) vs 0.6% in the p-TIPS group (0.6% in the CP-B+AB group and 0% in the CP-C group). Benefit for patients treated with p-TIPS in reducing the risk of developing new or worsening ascites was observed in CB-B+AB >7 points patients (Log Rank P = .0001); however, for CP-B+AB = 7 points, it could not be seen (Log Rank P = .169) (data not shown).

Posttreatment *HE*

A total of 372 patients developed at least 1 episode of posttreatment overt HE (263 or 26% in the Drugs + Endo treatment group and 109 or 35% in the p-TIPS group). The analysis showed no significant differences in the risk of developing HE either in the overall population (HR 1.078; 95% CI 0.841–1.382; $P = .553$) or in CP-B+AB (HR 1.034; 95% CI 0.690–1.549; $P = .872$) and CP-C groups (HR 1.107; 95% CI 0.807–1.516; $P = .529$) (Table 3) (Supplementary Figure 5*A*–*C*). Similar results were observed when death and liver transplantation were considered as competing risk events (Supplementary Table 3). There was no difference in the risk of HE episodes in both CP-B+AB = 7 (P = .97) and CP-B +AB > 7 (P = .51) patients treated with p-TIPS as compared with those treated with Drugs + Endo (data not shown).

Predictors of Poor Outcome in Patients With p-TIPS

In patients treated with p-TIPS, at univariate analysis, age, CP score and class, MELD score, bilirubin, creatinine, and albumin were factors significantly predicting survival, all with a significance level of P < .10. Multivariate analyses identified 3 models: (1) CP score, creatinine, and age (Harrel c-Statistics Index (HI) 0.71; 95% CI 0.64–0.78); (2) MELD score and age (HI 0.67; 95% CI 0.59–0.75); and (3) age, albumin, creatinine, and bilirubin (HI 0.68; 95% CI 0.62–0.74) (Table 4).

The model with the best Harrel c-Statistics Index entailed age >55 years, CP score >11 points, and creatinine ≥1.3 (Akaike information criterion [AIC] of 445, with HI of 0.71). Points were assigned for every variable in the model according to the HR. Thus, 2.5 points were assigned if the patient's age was >55 years, 3 points were assigned if CP score was >11, and 2.5 points if the creatinine was ≥1.3 mg/dL. By using this model, 142 patients (46%) from the p-TIPS population were assigned at the good p-TIPS prognosis group (0 points) and had a 1-year death-risk of 12%, 103 patients (33%) were assigned at the intermediate p-TIPS prognosis group (2.5 points) with a 1-year death-risk of 20.4%; 65 patients (21%) were assigned at the poor p-TIPS prognosis group (> 2.5 points) with a 1-year death-risk of 40.3% (Supplementary Figure 6). The application of this mathematical model to the 1017 patients not receiving p-TIPS, also allow to classify them as good prognosis (n = 439; 26.6% mortality) intermediate-prognosis (n = 338; 39.4% mortality), and poor-prognosis (n = 240; 55.2% mortality). Survival curves were compared between the 2 groups (p-TIPS and Drugs + Endo) for each risk class. Survival was significantly better in the p-TIPS groups for every risk level (Figure 3*A*–*C*).

A further analysis of potential futility on the p-TIPS group was performed analyzing the outcome of patients with high bilirubin levels. Forty-three patients treated with p-TIPS and 208 treated with Drugs + Endo had bilirubin levels >5 mg/dL. In this subgroup of patients, survival was also significantly higher in the p-TIPS than in the Drugs + Endo group ($P = .0006$). Similarly, 13 p-TIPS patients vs 71 in the Drugs + Endo had a bilirubin level >10 mg/dL. Again, survival in those patients was significantly higher in the p-TIPS group (P = .0086) (Supplementary Figure 7*A* and *B*).

Discussion

AVB is one of the most life-threating complications of cirrhosis. This is especially true for the subgroup of patients with a high risk of treatment failure even when treated with the current standard of care.[21] Patients presenting treatment failure have a high mortality rate regardless of finally controlling bleeding using rescue TIPS. This fact justifies the strong need of identifying patients at a high risk of treatment failure in whom early application of more effective treatments to control bleeding such as TIPS may prevent

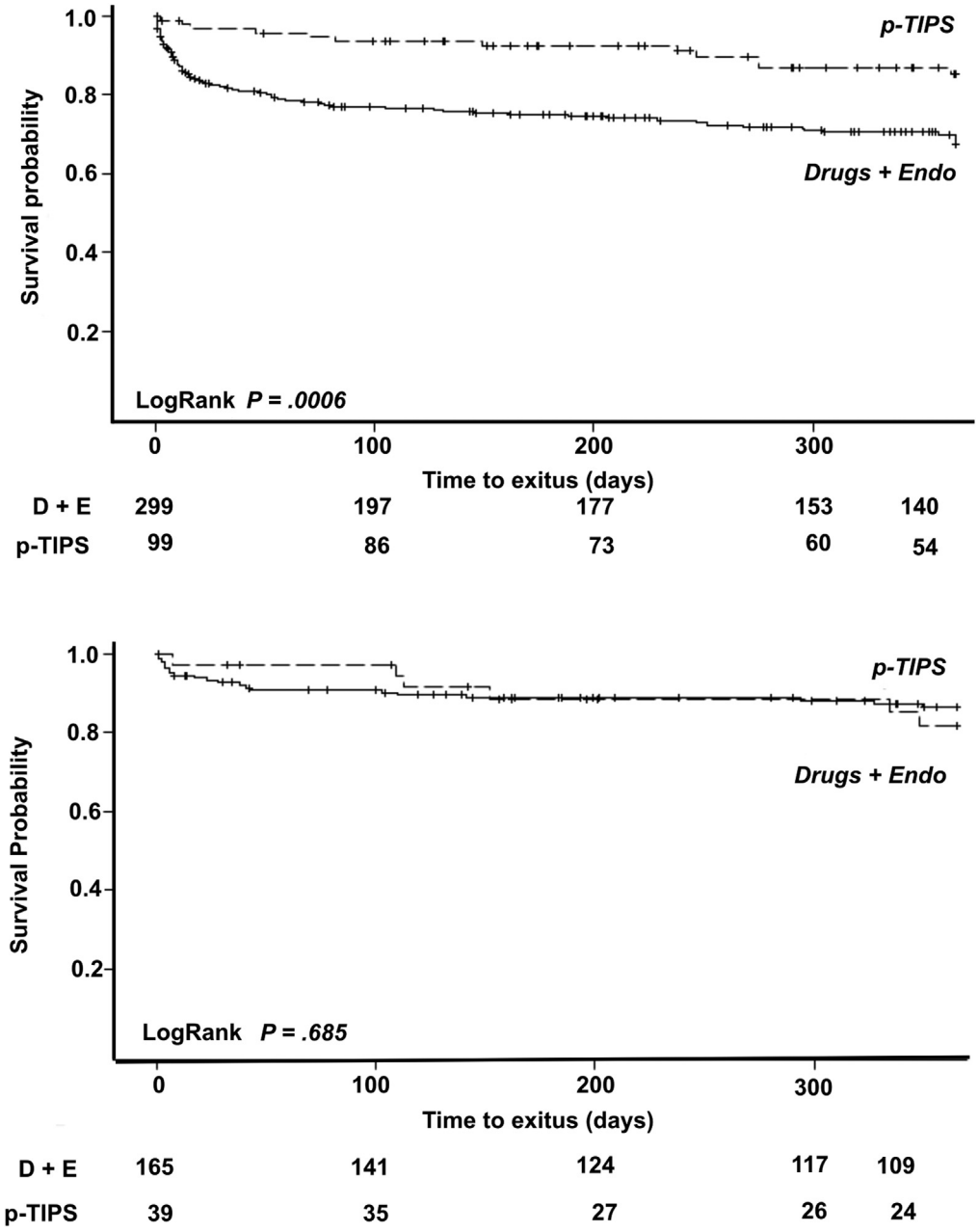

Figure 2. Survival at 1 year of patients treated with p-TIPS vs Drugs+Endo for (*A*) Child-Pugh B>7 points + AB patients and (*B*) Child-Pugh B = 7 points + AB patients.

failure and presumably mortality. The role of preemptive TIPS in the management of AVB in patients with cirrhosis has been evaluated in several studies. The first study applying the high-risk selection criteria for the application of p-TIPS used measurements of HVPG[3]; however, this is not easy applicable in clinical practice and this was the reason why the following studies used more easy clinical criteria: CP class and presence of active bleeding at diagnostic endoscopy although patients were already receiving vasoactive agents.[4,6,9] Overall, these studies clearly demonstrated that p-TIPS (always within the first 72 hours after admission) is significantly better than the use of drugs plus endoscopic treatment in controlling variceal bleeding, preventing new or worsening ascites without increasing the incidence of HE. Nonetheless, the benefit in survival is less clear. Accordingly, although it was clearer for CP-C patients, the potential effect of improving survival in CP-B+AB was more controversial. However, it must be taken into account that none of the previous studies had enough sample size to accurately analyze survival in different CP classes. This lack of strong evidence on survival is the reason why in the last update of the Baveno consensus conference,[1] p-TIPS was reported as an option for AVB in patients at high risk of treatment failure, but neither Baveno conference nor the new American Association for the Study of Liver Disease guidelines[2] recommended p-TIPS as the first choice treatment for these patients. In both guidelines it was emphasized the need to confirm survival benefit, to understand basal predictors of poor outcome, and to better define the high-risk criteria of treatment failure.

We performed this meta-analysis of individual data to reevaluate the outcome of p-TIPS in a larger study population

Table 4. Univariate and Multivariate Analysis for Survival in Patients Treated With p-TIPS

Univariate Analysis of p-TIPS Patients			Multivariate Analysis of p-TIPS Patients				
Variable	HR [95% CI]	*P* value		Variables	HR [95% CI]	*P* value	Harrel index
Gender male	0.74 [0.4–1.369]	.34	**Model 1**	Age>55 y	2.769 [1.480–5.180]	.001	0.71 [0.64–0.78]
Alcoholic etiology	1.37 [0.754–2.488]	.30		Child-Pugh>11	3.338 [1.728–6.449]	<.001	
Child Pugh score	1.29 [1.073–1.554]	**.006**		Creatinine ≥1.3 mg/dL	2.461 [1.228–4.929]	.01	
Child Pugh C	3.50 [1.008–3.508]	**.04**	**Model 2**	Age>55 y	2.855 [1.526–5.343]	.001	0.67 [0.59–0.75]
Child-Pugh >11	2.83 [1.484–5.428]	**.001**		MELD ≥19	2.341 [1.272–4.308]	.006	
Age	1.05 [1.022–1.083]	**.0001**	**Model 3**				
Age >55 y	2.664 [1.428–4.971]	**.002**		Age >55 y	2.283 [1.396–3.734]	.001	0.68 [0.62–0.74]
				Bilirubin ≥3 mg/dL	2.155 [1.331–3.492]	.002	
MELD	1.049 [0.999–0.103]	**.06**		Creatinine 1.3 mg/dL	2.051 [1.167–3.604]	.01	
MELD ≥19	2.120 [1.155–3.890]	**.01**		Albumin ≤27g/L	1.656 [0.982–2.795]	.06	
Creatinine	1.951 [1.13–3.36]	**.02**					
Creatinine ≥1.3 mg/dL	2.230 [1.125–4.421]	**.02**					
Bilirubin	1.068 [1.004–1.136]	**.04**					
Albumin	0.959 [0.914–1.007]	.09					
Albumin ≤27 g/L	2.113 [1.067–4.181]	**.03**					
Sodium	0.992 [0.945–1.04]	.73					
Platelets	1 [0.995–1.005]	.93					
INR	0.983 [0.84–1.413]	.92					

CI, confidence interval; HR, hazard ratio; INR, international normalized ratio.

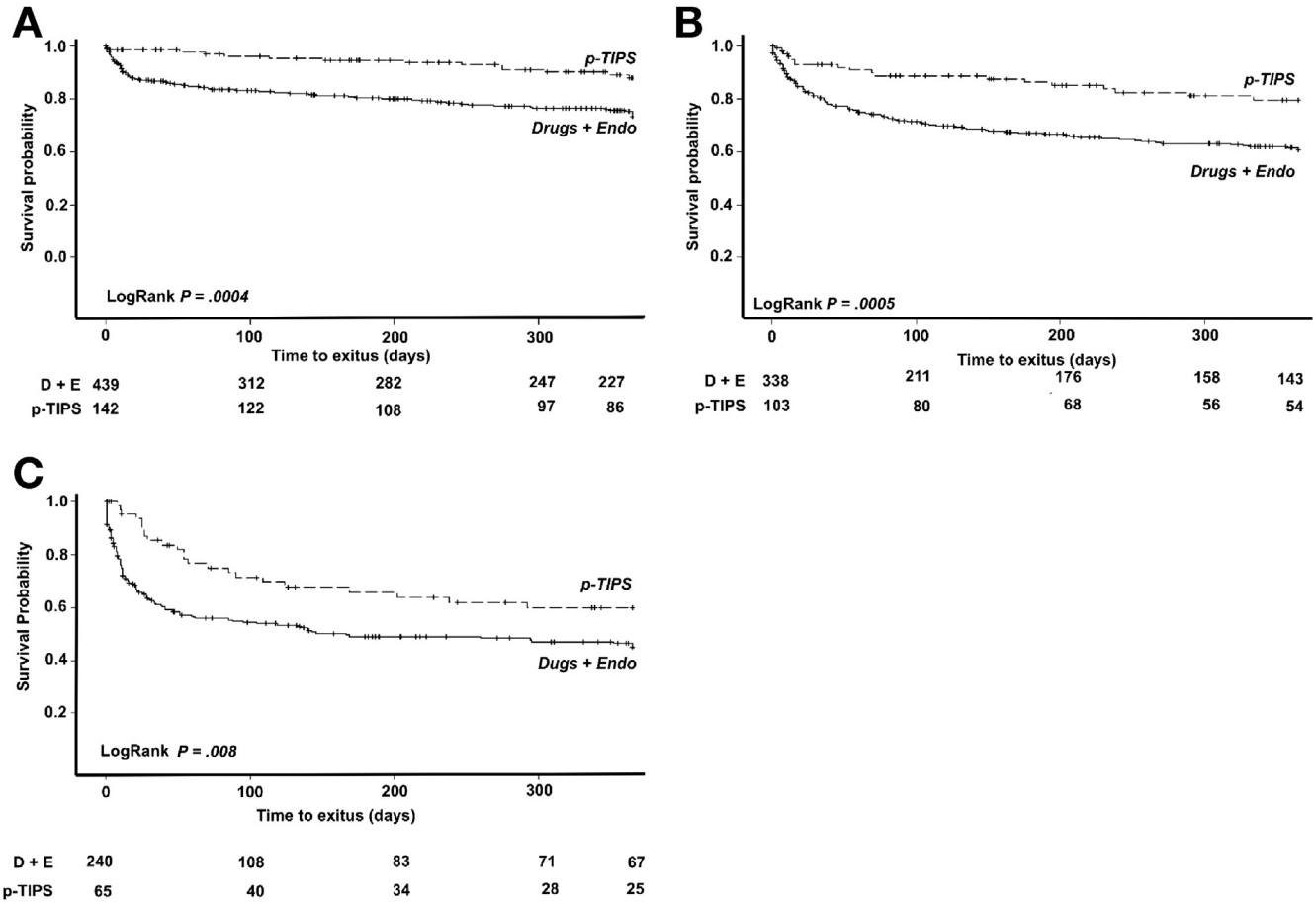

Figure 3. Survival at 1 year of patients treated with p-TIPS vs Drugs+Endo in (*A*) good p-TIPS prognosis group, (*B*) intermediate p-TIPS prognosis group, and (*C*) poor p-TIPS prognosis group.

and in attempt to evaluate the different endpoints separately in patients with CP-B and CP-C class. Furthermore, the unique opportunity to gather a large number of patients with different severity of liver disease treated with p-TIPS allowed us to evaluate whether there is a subgroup of these high-risk patients with AVB in whom p-TIPS could be futile.

The results of the current metanalysis of individual patient data including a large number of patients with cirrhosis and a high-risk of AVB confirms that the use of preemptive TIPS significantly reduces mortality. Indeed, the number of patients with a high-risk AVB treated with a p-TIPS required to save a life is only 4. This figure compares very well with other medical approaches completely accepted to treat severe medical conditions.[22] Even more important, the current study clearly demonstrates that the beneficial effect on survival is strong and clear in both CP-C and CP-B+AB patients. Indeed, by including a large number of patients, it allowed us to demonstrate the benefit of p-TIPS over standard of care in CP-B+AB patients with AVB. Nevertheless, to avoid the impact of minor differences in baseline clinical characteristics among patients treated with p-TIPS and with Drugs + Endo, prompted us to look at whether there was a subgroup of CP-B+AB that could benefit the most from p-TIPS. Indeed, when we analyzed the survival in CP-B+AB patients, mortality was clearly worse in those with a CP score of 8 and 9 points in comparison with that "good" CP-B of 7 points. Interestingly, although p-TIPS did not modify prognosis in the 7 points "good" CP-B+AB patients, it significantly improved survival in CP-B+AB with a CP score greater than 7. These results may explain, at least in part, the previous conflicting results on the benefit on survival in CP-B+AB patients that may be related to the different proportion of CP-B of 7 points in the cohorts of patients evaluated. Anyhow, even without a survival benefit, the CP-B = 7 + AB, patients did benefit from TIPS by reducing the risk of the combined endpoint of failure in controlling bleeding/rebleeding or by reducing, however not significantly, the risk of new onset or worsening of ascites without increasing the risk of HE. Although in the first RCT,[3] compared with the other studies in the meta-analysis, both arms did not use the current considered "gold" standard (stents were noncovered and the medical arm only used sclerotherapy for first endoscopic treatment and monotherapy, NSBBs or banding, for prevention of rebleeding), we decided to include it in the individual patient data meta-analysis to be as inclusive as possible. Besides, NSBB alone seem to have a major role in reducing rebleeding and mortality in Child B and Child C patients.[23] Nevertheless, this study accounted for only 2.5% from the overall population included. Moreover, we performed a sensitivity analysis regarding survival after excluding this study, and the results remained the same.

Additionally to the effect on survival, the p-TIPS–treated patients had a better control of bleeding, less rebleeding, best control of ascites, and very importantly without increasing the probability of developing HE at adjusted as well as at unadjusted analysis. These effects were homogeneous in CP-C and in CP-B+AB patients, overall emphasizing the benefit of p-TIPS patients with cirrhosis and high-risk AVB.

In this meta-analysis, we looked at whether there is a subgroup of patients treated with p-TIPS in whom this treatment might be risky. Although we were able to identify different risk categories in the p-TIPS population based on age, CP score, and creatinine, in all risk categories patients with p-TIPS proved beneficial in comparison with those treated with Drugs + Endo. Moreover, even in patients with severe liver impairment (defined by a bilirubin >5 mg/dL or >10 mg/dL) p-TIPS did not increase the mortality. These findings suggest that even in patients with high risk of death, p-TIPS might still be the treatment of choice. However, these results should be taken with caution because only 6% of the patients included in the meta-analysis had bilirubin >10 mg/dL.

This meta-analysis has several strengths: first, it succeeded to include the largest population of high-risk patients according to the current criteria; second, by doing an individual patient data analysis it was able to increase the statistical relevance and the effect size; third, by including a high number of CP-B+AB patients it was able to clarify the indication of p-TIPS in this population and to identify the subgroup of high-risk patients that strongly benefit from p-TIPS placement in terms of survival; fourth, it was able to detect predictive factors of poor survival in patients treated with p-TIPS; although, irrespective of this, the outcome was always better with p-TIPS than with Drugs + Endo which confirms the benefit of p-TIPS in Child C patients .

The limitations of this analysis reside on the fact that it included only patients who fulfilled 1 specific high-risk criterion without being able to analyze if other high-risk criteria might have better classified patients with cirrhosis and AVB. Another limitation is the inclusion of more observational studies than RCTs (3 RCTs vs 4 Observational), which is prone to inclusion confounding factor because the TIPS placement was left to the choice of each center. However, the IPTW statistical approach was used to minimize between arms differences. The expertise of TIPS placement might not have been homogeneous across all studies. This together with the heterogeneity of treatment in the standard-of-care arm might be other limitations of the study.

In conclusion, the present individual patient data meta-analysis shows that in patients with cirrhosis who present with AVB, p-TIPS placement in high-risk patients (defined as CP-B+AB > 7 points and CP-C <14 points) significantly improves survival in comparison with Drugs + Endo, significantly reduces failure to control bleeding and rebleeding, and decreases new or worsening ascites without increasing the risk of HE.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.09.026.

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Conflict of interest

Jaime Bosch has received speaker fees from Gore; and served as a consultant for Actelion, Ambys, BioVie, Brudy, BMS, BLB, Chiasma, Exalenz, Lipocine, and Surrozen. Virginia Hernández-Gea has received consultant fees from Gore. Juan Carlos García-Pagán has received consultant fees from Shionogi and research grants from Novartis and Gore. Christophe Bureau has received speaker fees from GORE and is a board member in Alfawassemran/Norgine. Alvaro Giraldez, Agustin Albillos, Dominique Thabut, Jonel Trebicka, and Frederik Nevens have received speaker fees from GORE. The other authors disclose no conflicts.

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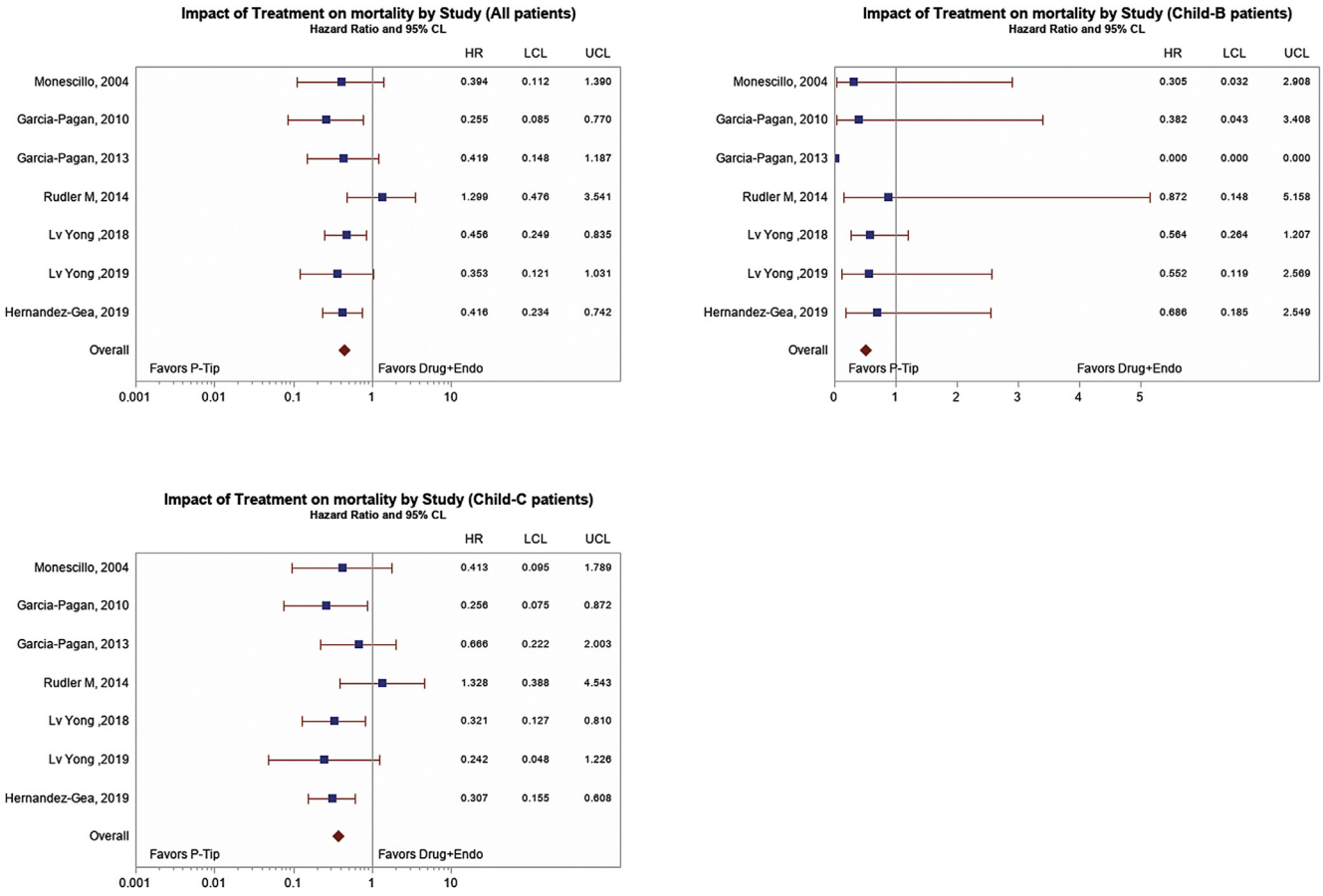
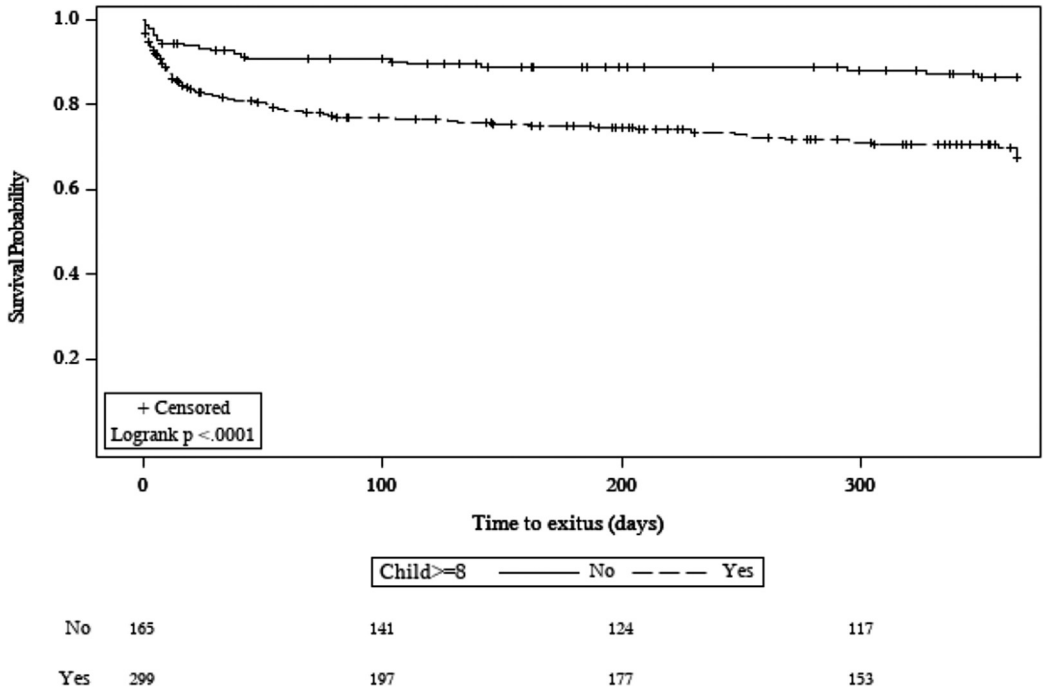
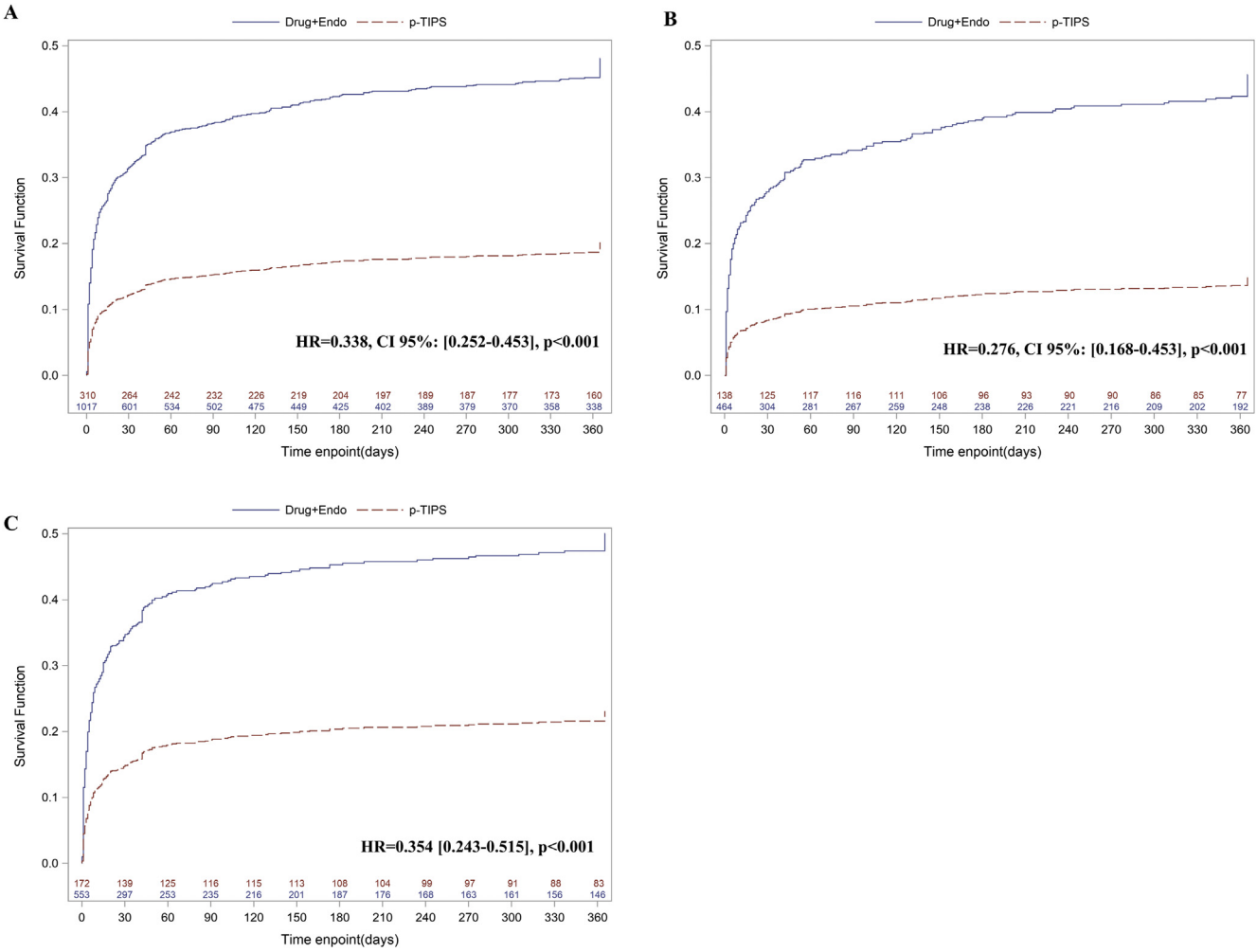


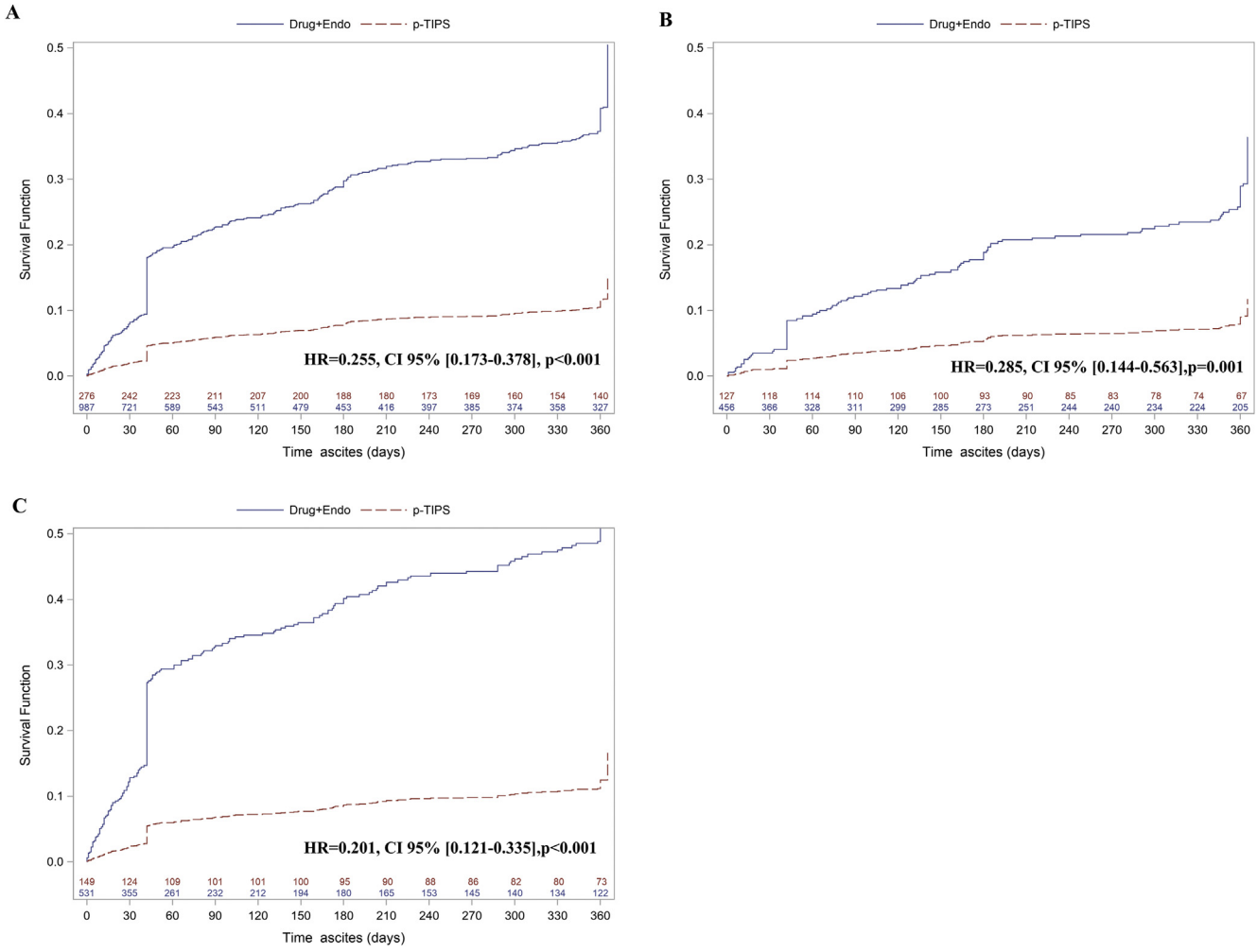
Supplementary Figure 1. Forest plot of survival at 1 year of patients with cirrhosis treated with p-TIPS vs Drugs + Endo in: all population, Child-Pugh B plus active bleeding and Child-Pugh C <14 points population.



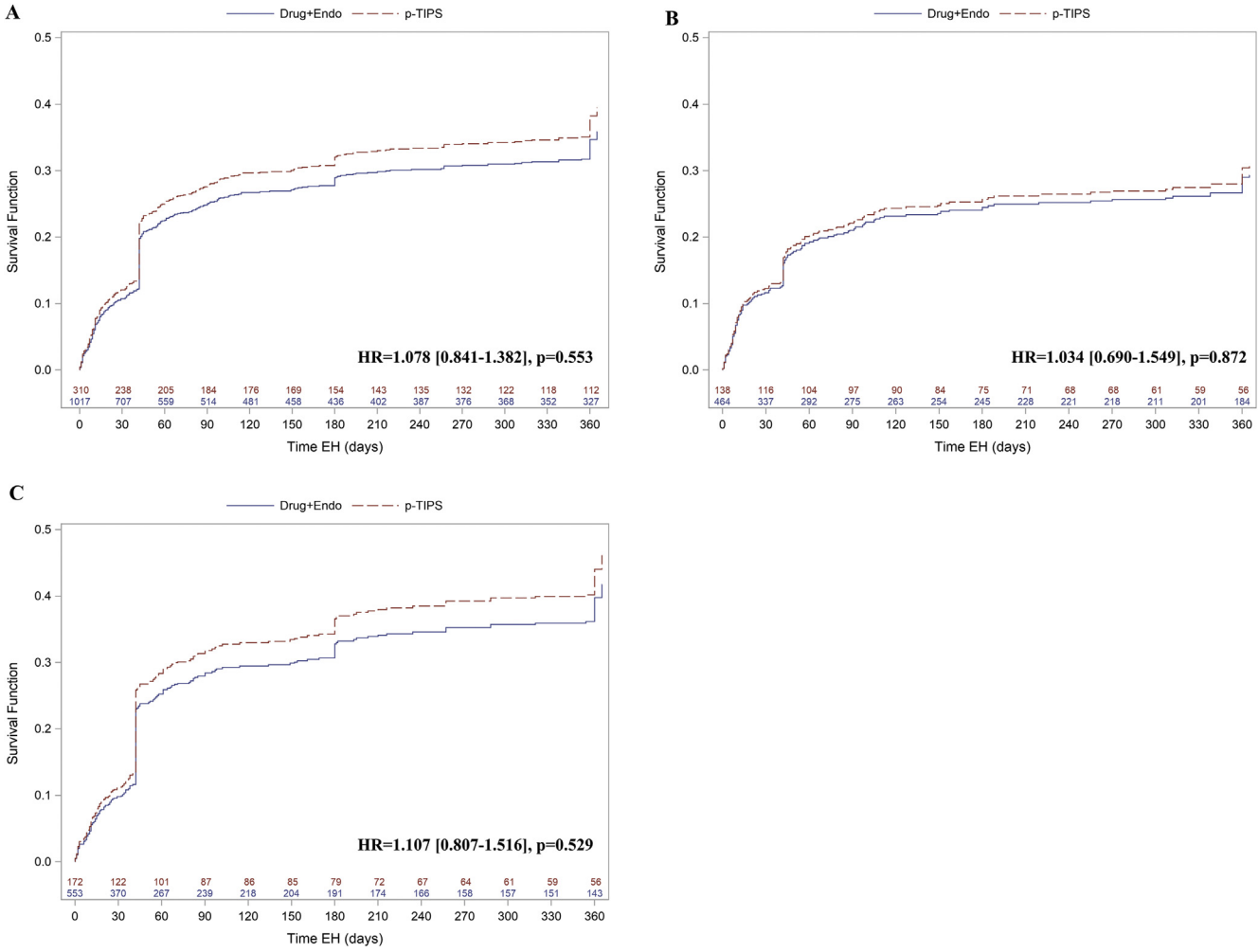
Supplementary Figure 2. Survival at 1 year of patients with Child-Pugh B+AB =7 points vs patients with Child Pugh B + AB >7 points treated with Drugs+Endo.



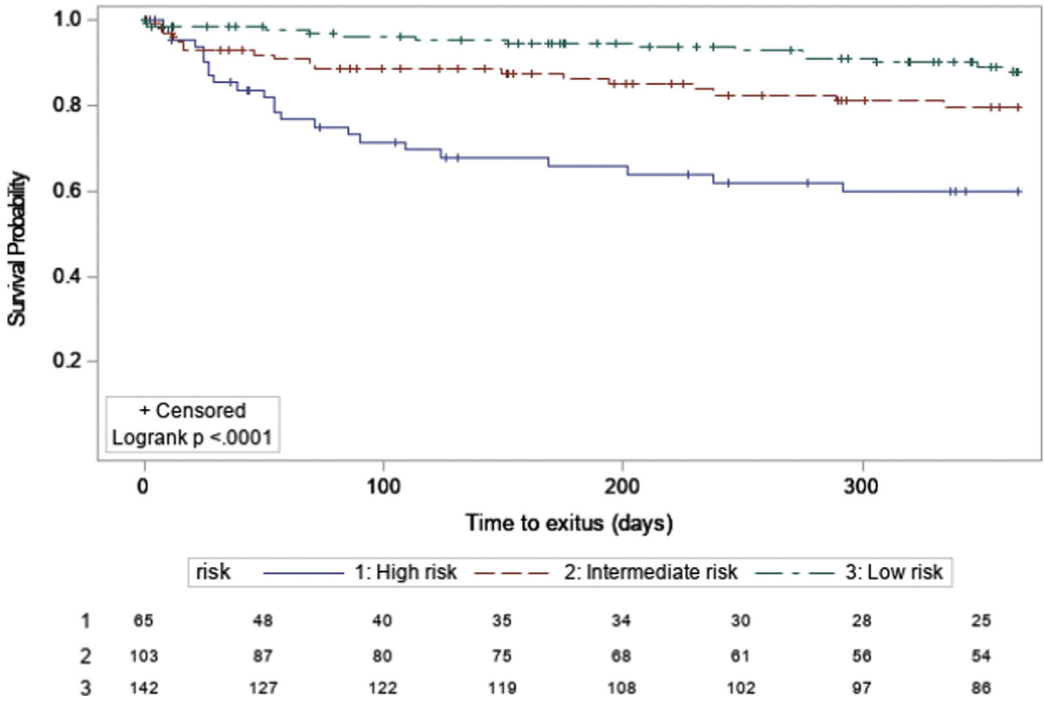
Supplementary Figure 3. Reach of composite endpoint of patients treated with p-TIPS vs Drugs+Endo in A. all population; B. Child-Pugh B + AB population and C. Child-Pugh C <14 points population.



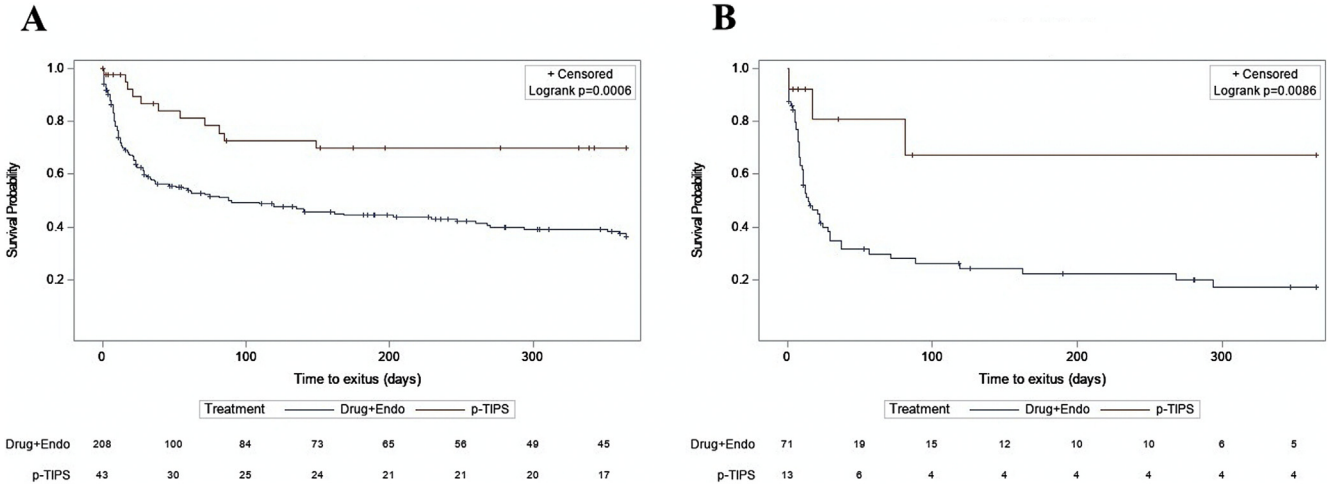
Supplementary Figure 4. Development of new or worsening ascites at 1 year, in patients treated with p-TIPS vs Drugs + Endo in A. all population; B. Child-Pugh B + AB population and C. Child-Pugh C <14 points population.



Supplementary Figure 5. Development of hepatic encephalopathy at 1 year, in patients treated with p-TIPS vs Drugs + Endo in A. all population; B. Child-Pugh B + AB population and C. Child-Pugh C <14 points population.



Supplementary Figure 6. Stratification of prognosis in the p-TIPS population according to the risk of death at 1 year. 1- poor prognosis group; 2- intermediate prognosis group; 3- good prognosis group.



Supplementary Figure 7. Survival at 1 year of patients treated with p-TIPS vs Drugs + Endo in A. patients with Bilirubin > 5 mg/dL and B. patients with Bilirubin > 10 mg/dL.

Supplementary Table 1. The Characteristics of every Study Included in the Meta-analysis

Study	Year of publication	Type	Centers	High risk definition	No. patients/ No. p-TIPS	Protocol
Monescillo A[3]	2004	RCT	2 centers in Spain	HVPG >20 mm Hg used in the original study We included only the patients that fulfilled the current high-risk criteria: Child-Pugh C<14 or Child- Pugh B≥7 with AB	34/17	Starting vasoactive drugs (somatostatin) and performing a single session of injection sclerotherapy as treatment of episode. HVPG measured within 24 h after admission. Patients with HVPG ≥20 mm Hg were randomized for treatment with p-TIPS or pharmacological treatment (NSBB). EBL was performed when NSBB were contraindicated/not tolerated. In patients assigned to p-TIPS arm, TIPS was placed as soon as possible and always within 24 h from admission.
Garcia-Pagan JC[4]	2010	RCT	9 centers in Europe	Child-Pugh C<14 or Child-Pugh B≥7 with active bleeding	63/32	Starting standard of care treatment with vasoactive drugs and performing initial endoscopic treatment within 12 h with endoscopic banding ligation or injection sclerotherapy if necessary. Then randomization to E+P or p-TIPS. In p-TIPS arm, TIPS was placed as soon as possible and always within 72 h from admission.
Garcia-Pagan JC[6]	2013	Observational retrospective	9 centers in Europe	Child-Pugh C<14 or Child- Pugh B≥7 with AB	75/45	Starting standard of care protocol at admission according to Baveno guidelines; p-TIPS was a medical decision; it was always performed within 72 h from ABV.
Rudler M[7]	2014	Observational prospective	1 center France	Child-Pugh C<14 or Child- Pugh B≥7 with AB	59/30	Starting standard of care protocol at admission according to Baveno guidelines; p-TIPS was a medical decision; it was always performed within 72 h from ABV.
Hernandez-Gea[9]	2019	Observational prospective	33 centers in Europe + 1 center in Canada	Child-Pugh C<14 or Child- Pugh B≥7 with AB	671/64	Starting standard of care protocol at admission according to Baveno guidelines; p-TIPS was a medical decision; it was always performed within 72 h from ABV.

Supplementary Table 1. Continued

Study	Year of publication	Type	Centers	High risk definition	No. patients/ No. p-TIPS	Protocol
Lv Y[10]	2018	Observational retrospective	12 centres in China	Child-Pugh C<14 or Child- Pugh B≥7 with AB	369/86	Starting standard of care protocol at admission according to Baveno guidelines; p-TIPS was a medical decision; it was always performed within 72 h from ABV.
Lv Y[5]	2019	RCT	1 centre in China	Child-Pugh C<14 or Child- Pugh B≥7 with AB	56/36	Starting standard of care protocol at admission according to Baveno guidelines; p-TIPS was a medical decision; it was always performed within 72 h from ABV.

NOTE. Patients were included only if they fulfilled the current high-risk criteria (CP-B+AB, CP-C<14).
EBL, endoscopic band ligation; HVPG, hepatic venous pressure gradient.

Supplementary Table 2. Causes of Death Stratified by Treatment Group and Child-Pugh Class

	Drugs+Endo		TIPS	
Cause of Death	CP-B+AB n = 111	CP-C n = 242	CP-B+AB n = 18	CP-C n = 37
Sepsis/MSOF	18 (16)	56 (23)	3 (17)	13 (35)
Liver failure	28 (25.5)	94 (39)	9 (50)	16 (43)
Variceal bleeding	42 (38)	54 (22.5)	1 (5)	0 (0.0)
Other/NA	23 (21)	38 (16)	5 (28)	8 (21.6)

NOTE. Values are n (%).
MSOF, multi systemic organ failure, NA, not available.

Supplementary Table 3. Risk of Death, Ascites, Hepatic Encephalopathy, and Failure to Control Bleeding and Rebleeding Using Competitive Risk Approaches in the Whole High-Risk Cohort and the Child Pugh B + AB and Child Pugh C Groups

		RAW		IPTW	
		HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Ascites	All	0.255 [0.167–0.391]	<.0001	0.276 [0.118–0.406]	<.0001
	CP-B + AB	0.353 [0.181–0.689]	.0023	0.304 [0.155–0.597]	.0005
	CP-C	0.197 [0.112–0.349]	<.0001	0.232 [0.14–0.386]	<.0001
Hepatic Encefalopathy	All	1.264 [0.985–1.623]	.0656	1.231 [1.035–1.734]	.08
	CP-B + AB	1.197 [0.805–1.78]	.373	1.175 [0.805–1.78]	.1373
	CP-C	1.319 [0.961–1.812]	.086	1.307 [0.952–1.796]	.098
Failure to control bleeding and rebleeding	All	0.291 [0.214–0.359]	<.0001	0.281 [0.174–0.455]	<.0001
	CP-B + AB	0.267 [0.165–0.43]	<.00	0.283 [0.169–0.475]	<.0001
	CP-C	0.303 [0.202–0.453]	<.0001	0.361 [0.246–0.53]	<.0001
Death	All	0.468 [0.346–0.632]	<.0001	0.431 [0.316–0.5989	<.0001
	CP - B + AB	0.518 [0.301–0.891]	.017	0.523 [0.307–0.892	.017
	CP- C	0.412 [0.287–0.59]	<.0001	0.359 [0.246–0.525]	<.0001

NOTE. Drugs+ Endo is the reference category for risk calculation.
CI, confidence interval; HR, hazard ratio.

Supplemetary Table 4. Sensitivity Analysis of Risk of Death Using Noncompetitive Risk Approaches in the Whole High-Risk Cohort and the Child Pugh B + AB and Child Pugh C Groups After Removal of Monescillo et al Patient Data

		RAW analysis		IPTW analysis	
		HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Death	All	0.488 [0.356–0.668]	<.001	0.447 [0.323–0.620]	<.001
	Child B+AB	0.548 [0.315–0.954]	.0333	0.548 [0.316–0.952]	.0329
	Child C	0.430 [0.294–0.628]	<.001	0.373 [0.249–0.559]	<.001
Ascites	All	0.235 [0.152–0.364]	<.001	0.260 [0.175–0.386]	<.001
	Child B+AB	0.317 [0.157–0.638]	.0013	0.275 [0.136–0.556]	.0003
	Child C	0.176 [0.099–0.311]	<.001	0.214 [0.128–0.356]	<.001
HepaticEncefalopathy	All	1.108 [0.862–1.423]	.4243	1.095 [0.851–1.409]	.482
	Child B+AB	1.018 [0.675–1.536]	.9308	1.016 [0.670–1.540]	.9419
	Child C	1.153 [0.843–1.577]	.3743	1.153 [0.841–1.582]	.3763
Failure to control bleeding and rebleeding	All	0.290 [0.210–0.400]	<.001	0.344 [0.254–0.466]	<.001
	Child B+AB	0.257 [0.152–0.434]	<.001	0.276 [0.165–0.463]	<.001
	Child C	0.308 [0.204–0.466]	<.001	0.378 [0.258–0.554]	<.001

Drugs + Endo treatment is the reference category for risk calculation.
CI, confidence interval; HR, hazard ratio.

Supplementary Table 5. Univariate Analysis of Factors Predicting Survival in CP- B+AB Patients

Variable	HR	95% CI		*P* Value
Age	1.026	1.008	1.045	.0043
Albumin	0.959	0.928	0.991	.0115
Bilurrubin	1.063	1.018	1.11	.0055
Child	1.52	1.197	1.929	.0006
Creatinine	2.431	1.532	3.856	.0002
Meld	1.068	1.029	1.109	.0005
AgeGe56	1.632	1.107	2.405	.0134
AlbuGe27	1.745	1.157	2.631	.0079
Creatinine 1.3	2.492	1.566	3.965	.0001
Bilirrubin 3	1.237	0.692	2.214	.4728
Etiology	0.96	0.647	1.425	.8403

Supplementary Table 6. Multivariate Analysis of Factors Predicting Survival in CP- B+AB Patients

Model	Variable	*P* value	HR	95% CI		C Statistics
model 1	Age	.0045	1.026	1.008	1.045	0.643
	Albumina at admission	.0125	0.96	0.93	0.991	
	MELD at admission	.0007	1.065	1.027	1.105	
model 2	Albumin ≤27	.0127	1.686	1.118	2.544	0.6479
	MELD ≥15	<.0001	2.418	1.597	3.662	
	Age ≥56	.0133	1.632	1.107	2.406	
Model 3	Age ≥56	.0128	1.637	1.11	2.412	0.61
	MELD ≥15	<.0001	2.474	1.634	3.747	
Model 4	Albumina at admission	.0133	0.961	0.931	0.992	0.6198
	MELD at admission	.0006	1.067	1.028	1.108	
Model 5	Albumin ≤27	.0123	1.691	1.121	2.551	0.6324
	MELD ≥15	<.0001	2.406	1.589	3.644	
Model 6	MELD ≥15	<.0001	2.468	1.63	3.737	0.578
Model 7	Age	.0422	1.019	1.001	1.038	0.6522
	Creatinine at admissi	.0084	1.9	1.178	3.062	
	ChildPugh Score at ad	.0036	1.429	1.124	1.818	
Model 8	**Child ≥8**	**<.0001**	**2.612**	**1.617**	**4.221**	**0.5964**
Model 9	Age ≥56	.015	1.618	1.098	2.385	0.6318
	Child ≥8	<.0001	2.599	1.609	4.2	
Model 10	Creatinine ≥1.04	<.0001	2.372	1.588	3.544	0.6494
	Child ≥8	.0002	2.53	1.565	4.089	

CI, confidence interval; HR, hazard ratio.