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Preemptive-TIPS improves outcome in high-risk variceal bleeding: An observational study

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Virginia Hernández-Gea and Juan Carlos Garcia-Pagan: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript, data quality control and validation and study supervision.

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Conflict of interest statements

Christophe Bureau has received speaker fees from GORE and is a board member in Alfawassemran/Norgine

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Ethics committee approval:

The ethics committees of all participating hospitals approved the study protocol.

Abstract

Objective

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. Preemptive TIPS (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.

Design

Multicenter, international, observational study including 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 preemptive TIPS (p-TIPS) was based on individual center policy.

Results

p-TIPS in the setting of AVB is associated with a lower mortality in Child C patients compared to 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 reduces treatment failure and rebleeding (1 year CIF-probability of remaining free of the composite endpoint: 92% vs 74% in the D+E group; $P=0.017$), 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. Due to the strong benefit in preventing further bleeding and ascites, p-TIPS could be a good treatment strategy for CP-B+AB patients.

Introduction

AVB remains the most severe and life-threatening complication of portal hypertension in patients with cirrhosis. The better understanding of AVB pathophysiology has led in the last decades to a significant improvement in its management and a reduction in mortality rates. However, despite applying the gold-standard therapy, 10-15% patients with AVB experience treatment failure, 21% re-bleed and 24% die during the first 6 weeks(1). Moreover, there is a subgroup of patients with AVB with worse prognosis in which re-bleeding 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 poor outcome that may help to select patients that 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 (HVPG) >20 mmHg and a MELD-based score have been identified as predictors of poor outcome in patients with cirrhosis and AVB(3-9). In this subgroup of high-risk patients, several studies have shown that placement of TIPS (Transjugular intrahepatic portosystemic shunt) within 72 hours from admission before uncontrolled bleeding or rebleeding occurs (called early or p-TIPS) is effective in preventing treatment failure and rebleeding (2, 10, 11) (9) without increasing either hepatic encephalopathy (HE) rate or other adverse events. In addition, 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) evaluate real life results in 58 centers in France (including academic and non-academic center) an only 6.7% of the high-risk patients included were treated with p-TIPS, underscoring the lack of adherence of physicians in a real-life setting.

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

Methods

Study design and patients

We performed a multicenter, international, observational study in 33 referral centers in Europe & one center in Canada, between October 2011 and May 2015. All the 34 centers collected data prospectively from all patients with cirrhosis admitted for AVB from October 2013 to May 2015. In addition, patients that 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 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 2138 patients were consecutively registered in the database. For this study, from the whole sample registered, only data from high-risk patients were analyzed. Although MELD score has been appointed as a prognostic factor in the setting of AVB (13), we started the study before publication of the paper demonstrating the value of the modified MELD. Moreover, centers performing p-TIPS selected high-risk patients based on Child C < 14 points and Child B plus active bleeding 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 μ mol 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, decision of placing p-TIPS or using drug plus endoscopic therapy in patients with a high-risk AVB was based on the internal hospital policy and the treating physician's opinion regardless our study. Only 9 centers from the 34 participating had incorporated p-TIPS in their daily clinical management algorithm; 4 of them were also involved in the previous trials (2, 10) and 5 incorporated the p-strategy once the current study have already began (Suppl. Table 1)

All patients were initially treated with standard of care treatment (vasoactive drugs, antibiotic 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 endpoint 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); 3) development of hepatic encephalopathy.

Hepatic encephalopathy (HE) was diagnosed following the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver Practice Guidelines (14). Only clinical HE was considered for the study and grade of HE I-IV was defined according to the severity of manifestations. Ascites and ascites-related complications (spontaneous bacterial peritonitis & Hepatorenal syndrome) were defined and graded according to the AASLD Practice Guidelines (15)

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, 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(16). A steering committee was created in order to regularly monitor data to detect inconsistencies or errors; when find, 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(17). Data were described as frequencies and percentages, means and standard deviation (SD) or median (interquartile range), as appropriate. Baseline characteristics were compared using the Fisher's exact test for categorical variables, the 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 (CIF) 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 a competing risk. 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, or otherwise specified.

All the analyses were performed using SAS software (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 1334 patients with cirrhosis admitted for AVB. Further, 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 2138 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 Suppl Figure 1, 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 differences in baseline characteristics between the two groups (Table 1).

211 (31.4%) patients in the whole cohort were lost during the 1 year follow up, 89 (37.6%) in the CP-B+AB and 122 (28.1%) in the CP-C. When considered 42 days follow up, 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: 6 weeks: 92% vs 77%; 1 year: 78% vs 62%; $P=0.014$ (Figure 1A). To assess whether CP-C and CP-B+AB patients equally benefit 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 (6w 90% vs 70%; 1 y: 78% vs 53%; Figure 1C; $P=0.002$). Mortality rate in the subgroup CP-B+AB was low and not significantly different in the D+E and in the p-TIPS group (6 w: 94% vs 90%; 1 y: 77% vs 75%; $P=0.935$) (Figure 1B).

We also calculated the probability of death at 6 weeks by using the MELD-based model due to its demonstrated ability to predict mortality (13). To calculate the observed mortality, we grouped the study population by using quintiles of the observed MELD. The results are plotted in Figure 2. The analysis of lineal correlation was $r=0.999$ ($p<0.001$) for Drug+Endo group confirming that the mortality observed in our study was similar to the one predicted by the MELD-based model. However, the p-TIPS group had 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) fitting a logistic regression model, and then we include that probability as a covariate in the survival models (Table 2 and Supplementary Table 1). 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 [95%CI] to save one life during 1 year estimated using PS-adjusted competing risk was 4.2 [2,6-24,4].

A total of 224 patients (33.4%) died; 212 (35%) patients in the D+E group died as compared with 12 (18%) in the p-TIPS group. Nineteen, 19 (4.9%), patients in the D+E group received OLT vs 6 (12.8%) in the p-TIPS group. Causes of death are represented in Table 3.

Despite having incorporated routinely the p-TIPS strategy, 92 patients (from the 9 p-TIPS centers) did not receive p-TIPS due to unavailability, a few “non-believers” physicians and in 5 of the centers the delay in routinely adopting the p-TIPS strategy. Although PS robustly guarantee 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 Suppl Fig 3, patients not managed with p-TIPS had similar outcome regardless

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 & preventing rebleeding

In the D+E group 141 (23.3%) patients had failure to control bleeding or rebleeding vs 3 (4.5%) in the p-TIPS group and 44 (7%) patients in the D+E group 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 vs the D+E group (HR: 0.17; CI 95%: 0.05-0.53, Figure 3A; P=0.002) (Figure 3A). Failure to control bleeding or rebleeding was significantly lower in the p-TIPS group either in the CP-B+AB or in the CP-C patients (Figure 3B and 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 vs 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 vs 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; CI 95%: 0.07-0.35); Figure 4A: P<0.001). The marked benefit of p-TIPS over ascites was observed both in CP-B+AB and CP-C patients (Figure 4B and 4C) and observed in the unadjusted analysis (Table 2).

Hepatic encephalopathy (HE)

228 (37.7%) patients had any episode of HE in the D+E group vs 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; CI 95%: 0.73-1.45); Figure 5: P=0.863). There were no differences between groups and the similar rate of HE was observed both in CP-B+AB and CP-C patients (Figure 5B and 5C). 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 placing a p-TIPS (also call early TIPS) within 72 hours from admission before uncontrolled bleeding or re-bleeding occurs, improves outcome. Precisely, all the data available have shown that this strategy is associated with a reduction in failure, rebleeding and development of “de novo “or worsening of ascites (9) (2) (10) (11). In addition, all the studies but one(11), also demonstrated a clear benefit for p-TIPS on survival. However, despite all 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 noticeable 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 from the 671 patients without any contraindication, only 66 (13%) received p-TIPS. This is in agreement with a recent multicentric study performed in France (12) also confirms this data and from 326 eligible only 22 (6.7%) of them received p-TIPS, underscoring the lack of adherence of physicians in a real-life setting. When specifically evaluated, the main reasons are either that treating physicians do not believe in p-TIPS benefit or the lack of availability of the technique. The first limitation could be overcome carefully analyzing these and previous 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 death could have been reduced significantly from 224 to 65 and we could have saved 159 deaths.

The second one should be focused on programs aimed at easily transferring patients to centers of expertise. As recently demonstrated(18) centers placing more than 20 TIPS per year have the best outcome possible and lower in-patient mortality, therefor efforts aimed to better equip high volume institutions should be implemented. Therefore, in centers with no access to TIPS placement, the policy to be adopted will be to transfer patients to centers of expertise instead of trying to implement it. It is also of note that other diseases with similar mortality rates and successful treatments able to improve survival such as stroke and heart attack, have motivated changes in the sanitary policy worldwide with the main aim to treat patients as soon as possible in centers of expertise.

Based on this results, all the efforts directed to implemented and guarantee the access to p-TIPS treatment are widely justify.

Other potential reason may have been the fear for the high rate of HE and TIPS dysfunction reported in previous studies using TIPS as a salvage therapy for refractory bleeding and using bare stents (19) (20) (21). However, none of the studies evaluating the role of p-TIPS increased HE (9) (2) (10) (11) and the rate of TIPS dysfunctions 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. With this aim, we collected all the consecutive portal hypertension related bleeding episodes in the participating centers and analyze the outcome only in those patients fulfilling the previously identified high-risk criteria. The decision of placing a p-TIPS was based on the internal hospital policy and the treating physician's opinion, regardless our study.

Our study, including 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 "de novo" or worsening in the control of ascites, did not increase hepatic encephalopathy and improves survival.

We also evaluate whether the use of p-TIPS equally benefits CP-B+AB and CP-C patients. The All the benefits of p-TIPS, but improvement in survival, were homogeneously found either in Child C or in CP-B+AB patients. P-TIPS was not able to have a significant impact in CP-B+AB survival, probably due to the low mortality rate observed in CP-B+AB patients (19%) that makes 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 hepatic encephalopathy, could justify the use of p-TIPS in this subgroup of patients.

Our study proves that tailoring treatment to patient's risk is a real option in the setting of AVB. Child-Pugh classification together with endoscopic findings simply identify early after admission patients in who p-TIPS improves outcome. These criteria are easy to apply in daily clinical practice but the accuracy and reproducibility of these parameters face some difficulties. On one hand performing endoscopy in bleeding patients and identifying active bleeding can be challenging. On the other hand, 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 de modified MELD model (8), we decided to use CP-C and CP-B+AB as they were the criteria used to determine high-risk by the participating centers. However the high-risk mortality of our cohort was confirmed when using the MELD-based model and mortality observed in the population not treated with p-TIPS was as high as the one predicted by the modified model. Nevertheless it is possible that more objective and reproducible

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predictive factors may still be identified that could perhaps improve the selection of patients that may benefit from p-TIPS. It is also important to remark that our results cannot be extrapolated to aged patients, patients with deteriorated kidney function (creatinine >3mg/dl), occlusive PVT, sepsis, heart failure or hepatocellular carcinoma out of the Milan criteria as this population was neither include in our study nor in the previous ones.

The main limitation of our study comes from its observational design that carries an inherent risk of selection bias, however the use of propensity score precisely lowers this possibility. Another potential limitation of our study 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 collecting a large number of high-risk patients (671), Nonetheless 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.

Conclusions

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 failure to control bleeding, rebleeding, "de novo" ascites development or worsening, without increasing the risk of developing hepatic encephalopathy. These results strongly support the view that p-TIPS must be the treatment of choice in CP-C patients with AVB. Due to the strong benefit in preventing further bleeding episodes and ascites without increasing HE p-TIPS could be recommended for CP-B+AB patients.

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Table 1. Baseline characteristics

Characteristic	Endo+Drug Group (N=605)	Preemptive-TIPS Group (N=66)	P Value
Age	54.5 ±9.7	52.4 ±11.2	0.128
Gender: male n(%)	466 (77.0%)	47 (71.2%)	0.335
Etiology of cirrhosis*			
Alcohol	457 (75.5%)	55 (83.3%)	0.174
Viral	187 (30.9%)	15 (22.7%)	0.201
Other	76 (12.6%)	4 (6.1%)	0.161
Active alcoholism (last 3 m)	326 (55.5%)	34 (52.3%)	0.692
Charlson Comorbidity Index Mean (SD)	4.561 (1.326)	4.709 (1.51)	0-623
Previous Bleeding			
Child B	80 (36.7%)	6 (31.6%)	0.656
Child C	110 (28.4%)	11 (23.4%)	0.469
MELD Score	15.5 ±7.2	15.2 ±5.7	0.668
Child-Pugh Score	9.9 ±1.8	10.1±1.5	0.446
Child-Pugh C (n)	387 (64.0%)	47 (71.2%)	0.242
Child-Pugh B + Active bleeding	218 (36.0%)	19 (28.8%)	

Descriptive data are mean±SD and n (%)

*More than one answer is possible

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.

	Child	Raw analysis		Propensity score* adjusted analysis	
		p-value	HR [IC 95%]	p-value	HR [IC 95%]
Mortality					
	High-Risk	0.0087	0.480 [0.273 to 0.844]	0.0141	0.491 [0.278 to 0.867]
	Child-B+AB	0.9585	0.966 [0.303 to 3.082]	0.9348	0.953 [0.298 to 3.045]
	Child-C	0.0013	0.366 [0.192 to 0.699]	0.0023	0.363 [0.189 to 0.696]
Failure to control bleeding & rebleeding					
	High-Risk	0.0004	0.176 [0.057 to 0.542]	0.0022	0.170 [0.055 to 0.53]
	Child-B+AB	0.0286	NE	NE	NE
	Child-C	0.0055	0.241 [0.078 to 0.743]	0.0175	0.251 [0.08 to 0.785]
Ascites					
	High-Risk	<.001	0.170 [0.078 to 0.37]	<.001	0.161 [0.073 to 0.353]
	Child-B+AB	0.0006	NE	NE	NE
	Child-C	<.001	0.225 [0.104 to 0.488]	<.001	0.227 [0.105 to 0.494]
Encephalopathy					
	High-Risk	0.4477	1.146 [0.823 to 1.597]	0.8634	1.031 [0.731 to 1.452]
	Child-B+AB	0.8777	0.925 [0.353 to 2.421]	0.9240	0.954 [0.363 to 2.505]
	Child-C	0.579	1.116 [0.792 to 1.572]	0.7832	1.051 [0.739 to 1.494]

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.

Table 3. Summary of Efficacy Measurement

Variable	Endo+Drug Group (N=605)	Preemptive-TIPS Group (N=66)
Child C (no. of patients)	387	47
Child B+AB (no. of patients)	218	19
Composite Endpoint (no. of patients)		
Child B+AB	50 (22.9%)	0 (0.0%)
Child C	91 (23.5%)	3 (6.4%)
Rescue TIPS		
Child B+AB	20 (9.2%)	0 (0.0%)
Child C	24 (6.2%)	0 (0.0%)
Death (no. of patients)		
Child B+AB	43 (19.7%)	3 (15.8%)
Child C	169 (43.7%)	9 (19.1%)
Cause of death		
Bleeding	34 (16.0%)	0 (0.0%)
Liver failure	80 (37.7%)	1 (8.3%)
Sepsis/multiorgan failure	66 (31.1%)	8 (66.7%)
Unknown	6 (2.8%)	1 (8.3%)
Other	26 (12.3%)	2 (16.7%)
Orthotopic liver transplantation		
Child B+AB	1 (0.5%)	1 (5.3%)
Child C	19 (4.9%)	6 (12.8%)
Hepatic encephalopathy		
Child B+AB	55 (25.2%)	4 (21.1%)
Child C	173 (44.7%)	24 (51.1%)
Ascites		
Child B+AB	96 (44.0%)	0 (0.0%)
Child C	192 (49.6%)	6 (12.8%)
Spontaneous Bacterial Peritonitis/ Hepato-renal Syndrome		
Child B+AB	19 (8.7%)	0 (0.0%)
Child C	80 (20.7%)	1 (2.1%)

* Percentages calculated from the total number of Child B+AB or Child C patients









