Journal Pre-proof

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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Abbreviations:

AASLD: American Association for the Study of Liver Disease

AB: active bleeding

AVB: acute variceal bleeding

CP- Child Pugh class

Drugs + Endo: pharmacological treatment plus endoscopy

HE: hepatic encephalopathy

PHT: portal hypertension

p-TIPS: pre-emptive transjugular portosystemic shunt

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Abstract:

Background & Aims: Compared with drugs plus endoscopy, placement of transjugular portosystemic shunt within 72 hrs of admission to the hospital (early or preventive 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 a 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 vs endoscopy plus non-selective 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 vs 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 (HR=0.443, CI 95%: [0.323-0.607], p<0.001). This effect was observed in CP-B+AB patients (HR=0.524, CI 95%: [0.307–0.896], p=0.018) and in patients with Child-Pugh C scores below 14 points (HR=0.374, CI 95%: [0.253-0.553], p<0.001). 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 10-13 points or CP-B+AB, preemptive TIPS increased the proportion who survived for 1 year, in both subgroups separately, compared with drugs plus endoscopy.

KEY WORDS: AVB, HE, liver disease, treatment

Introduction

The management of acute variceal bleeding (AVB) in patients with cirrhosis has improved over the last 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 AASLD guidelines for portal hypertensive bleeding in cirrhosis[2], incorporated for the first time the use of preemptive (also called early) TIPS (p-TIPS), as a treatment option in patients with AVB at high risk of treatment failure in order 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 three randomized clinical trials (RCTs)[3,4,5] and five observational studies[6,7,8,9,10] so far. Criteria adopted for definition of high risk were HVPG $\geq$ 20 mmHg 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 iv vasoactive agents in the second RCT[4] and in the subsequent observational studies[6,7, 8,9,]. 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[9,11,10]. 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 be, at least in part, explain the lack of solid data on survival on the Child-Pugh B population. Some meta-analysis and systematic reviews have attempted to overcome these issues[13,14,15,16]. However, the lack of individual data on time to death and the fact that some studies did not show separately the outcomes in the two different Child-Pugh categories reduced the clinical impact of these attempts.

Additionally, there is a 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-analysis due to 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 re-evaluating 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.

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 non-selective beta-blockers) 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 acute variceal bleeding 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[3,4,5] and observational studies were contacted[6,7,9,10] for possible inclusion. One of the RCTs[5] and one 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 two 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 year 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 seven previous studies[3,4,5,6,7,9,10] 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 was reported as exclusion criteria in three of these studies.

In one RCT, TIPS was performed using bare stents[3] while in the remaining 6 studies TIPS was performed with PTFE-covered stents[4,5,6,7,9,10]. In the RCT using bare stents, the non-TIPS group received only NSBB to prevent rebleeding. Endoscopic band ligation was used in patients in whom NSBB 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 utilized 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 end-point was to compare the two types of treatment, p-TIPS and Drugs + Endo, in terms of one-year survival in the overall population as well as in the two different Child-Pugh classes (Child-Pugh B with active bleeding at endoscopy and Child-Pugh C <14 points), separately. Secondary end-points were to seek for differences at one-year follow-up in: a) the composite outcome of failure in controlling AB/preventing variceal rebleeding; b) in developing new or worsening ascites and c) in the incidence of hepatic encephalopathy.

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´s data was coded in order to preserve patients' 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 <0.10 to define insignificant difference in potential confounders. The final covariates included in the PS calculation were (a) for all high-risk patients: age, gender, etiology, previous bleeding, previous ascites, MELD, bilirubin, platelets, creatinine, and INR, (b) for C-B+ AB patients: etiology, active alcoholism, shock, Child-Pugh, MELD, bilirubin, platelets and hematocrit, and (c) for CP-C patients: etiology, active alcoholism, shock, MELD, platelets and hematocrit. Baseline categorical data were compared using the chi-square test and continuous variables using ANOVA 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 <0.10 were further assessed in multivariate analyses and the Harrel's C-statistic index was calculated as a discriminative measure criterion. For continuous variables cut-offs were selected either by using the Youden method or based on already validated cut-offs 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, USA) and statistical significance was established at the two-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). Three hundred ten patients 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.

Survival

At one 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<0.001, Figure 1A). 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=0.008; Figure 1B) and in CP-C patients (90% vs 70% at 6 weeks and 75% vs 51% at 1 year, Log Rank p<0.001, Figure 1C).

There was a survival benefit for p-TIPS over Drugs + Endo (HR=0.443, CI 95%: [0.323-0.607], p<0.001). This effect was observed in both Child B+AB (HR=0.524, CI 95%: [0.307–0.896], p=0.018) and in CP-C patients (HR=0.374, CI 95%: [0.253-0.553], p<0.001) (Table 3). Number of patients needed to be treated (NNT) to save one life is 4.23 (CI 95%: [3.57-6.94)].

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

Except for one 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<0.05). 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 two risk categories (Supplementary Table 5 A and B). 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 <0.0001) 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=0.0006; Figure 2.A) but did not in patients with CP-B+AB of 7 points (CP-B+AB low risk group) (Log Rank p=0.68; Supplementary Figure 2.B).

Composite end-point: Failure in controlling acute bleeding/prevention of rebleeding

Three hundred thirty-seven patients reached the composite end-point (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, CI 95%: [0.252-0.453], p<0.001) (Table 3). The beneficial effect of p-TIPS was observed both in CP-B+ AB (HR=0.276, CI 95%: [0.168-0.453], p<0.001) by reducing it with 73% and in the CP-C patients (HR=0.354 [0.243-0.515], p<0.001) by reducing it with 65% (Supplementary Figures 3 A, B and C). Similar results were observed when death and liver transplant 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=0.0007) , as well as in CP-B +AB> 7 points (Log Rank p<0.0001) (data not shown).

New or worsening ascites

Three hundred-ninety-nine 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, CI 95% [0.173-0.378], p<0.001) but also in both subgroup of patients, reducing it with 72% in the CP-B +AB group (HR=0.285, CI 95% [0.144-0.563],p=0.001) and by 80% in the CP-C group (HR=0.201, CI 95% [0.121-0.335],p<0.001)(Table 3) (Supplementary Figure 4 A, B and C). Similar results were observed when death and liver transplant 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 (LogRank p=0.0001), however, for CP-B +AB= 7 points, it could not be seen (LogRank p=0.169) (data not shown).

Post treatment hepatic encephalopathy

Three hundred seventy-two patients developed at least one episode of post treatment 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 [0.841-1.382], p=0.553) or in CP-B+ AB (HR=1.034 [0.690-1.549], p=0.872) and CP-C groups (HR=1.107 [0.807-1.516], p=0.529) (Table 3) (Supplementary Figure 5 A, B and C). Similar results were observed when death and liver transplant 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=0.97) and CP-B +AB > 7 (p=0.51) patients treated with p-TIPS as compared to 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 $p<0.10$. Multivariate analyses identified 3 models: 1) CP score, creatinine and age (Harrel c-Statistics Index (HI): 0.71 [0.64-0.78]); 2) MELD score and age (HI: 0.67 [0.59-0.75]) and 3) age, albumin, creatinine and bilirubin (HI: 0.68 [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 (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 two 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, B,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=0.0006). 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=0.0086) (Supplementary Figure 7 A, B).

Discussion

Acute variceal bleeding 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 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 failure and presumably mortality. The role of pre-emptive TIPS in the management of acute variceal bleeding 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 despite the fact that 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 hepatic encephalopathy. Nonetheless, the benefit in survival is less clear. Accordingly, while it was clearer for CP-C patients, the potential effect of improving survival in CP-B+ AB was more controversial. However, it must be taking 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 AASLD 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 in order to re-evaluate the outcome of p-TIPS in a larger study population 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 pre-emptive 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 four. 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, in order 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 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 to that “good” CP-B of

7 points. Interestingly, while 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 end-point 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 hepatic encephalopathy. Despite the fact in the first RCT[3], compared to the other studies in the meta-analysis, both arms did not use the current considered "gold" standard (Stents were non covered and the medical arm only used sclerotherapy for first endoscopic treatment and monotherapy -non selective beta blockers 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 hepatic encephalopathy at adjusted as well as at unadjusted analysis. These effects were homogenous 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 whether there is a subgroup of patients treated with p-TIPS where 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 to 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 since only 6% of the patients included in the meta-analysis had bilirubin > 10 mg/dl.

This meta-analysis has several strengths: firstly, it succeeded to include the largest population of high-risk patients according to the current criteria; secondly, by doing an individual patient data analysis it was able to increase the statistical relevance and the effect size; thirdly, 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; fourthly, 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 that fulfilled one specific high-risk criteria 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 since the TIPS placement was left to the choice of each center. However, the inverse Probability of the Treatment Weights statistical approach was used to minimize between arms differences. The expertise of TIPS placement might not have been homogenous 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 acute variceal bleeding, 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 hepatic encephalopathy.

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Figure 1 Survival at one year in A. all population; B. Child Pugh B +AB population; C. Child Pugh C population

Figure 2 Survival at one 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

Figure 3 Survival at one 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

Table 1 Baseline characteristics of patients included in the studies

Variable at admission	RAW				IPTW			
	Drugs+Endo	**p-TIPS**	**p-value**	**StdDiff**	**Drugs+Endo**	**p-TIPS**	**p-value**	**StdDiff**
Gender: male	769 (75.6%)	220 (71.%)	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%
Ethiology								
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)*	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*	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%

TIPS, transjugular intrahepatic portosystemic shunt; HE, hepatic encephalopathy

Descriptive statistics are frequencies (%) for categorical variables and median (25–75% interquartile range) for continuous variables.

* 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)**	**TIPS (n=310)**
Post-Treatment Hepatic Encephalopathy	B+AB	107 (23.1%)	40 (29.0%)
	C	156 (28.2%)	69 (40.1%)
Post-treatment 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%)

TIPS, transjugular intrahepatic portosystemic shunt; AB, active bleeding

Table 3. Risk of Death, Ascites, Hepatic Encephalopathy and Failure to control bleeding and rebleeding using non competitive risk approaches in the Whole High-Risk cohort and the Child Pugh B + AB and Child Pugh C groups

		RAW analysis		**IPTW analysis**	
		HR [IC95%]	**P-value**	**HR [IC95%]**	**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]	0.016	0.524 [0.307 – 0.896]	0.018
	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]	0.001	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]	0.483	1.078 [0.841 - 1.382]	0.553
	Child B+AB	1.043 [0.702-1.551]	0.833	1.034 [0.690 - 1.549]	0.872
	Child C	1.112 [0.815-1.518]	0.502	1.107 [0.807 - 1.516]	0.529
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

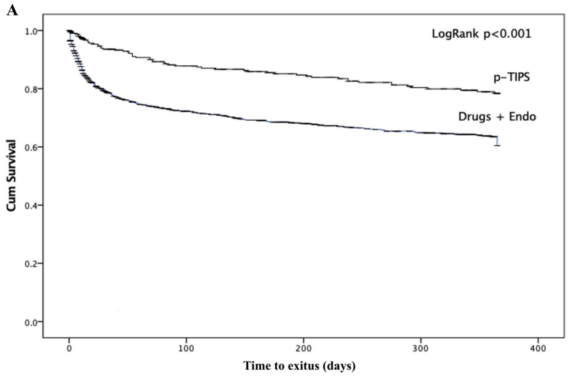
Drugs+Endo treatment is the reference category for risk calculation

Table 4. Univariate and multivariate analysis for survival in patients treated with p-TIPS.

Univariate analysis of p-TIPS patients		
Variable	**HR [95% CI]**	**P value**
Gender male	0.74 [0.4-1.369]	0.34
Alcoholic etiology	1.37 [0.754-2.488]	0.30
Child Pugh score	1.29 [1.073-1.554]	**0.006**
Child Pugh C	3.50 [1.008-3.508]	**0.04**
Child-Pugh>11	2.83 [1.484-5.428]	**0.001**
Age	1.05 [1.022-1.083]	**0.0001**
Age >55y	2.664 [1.428-4.971]	**0.002**
MELD	1.049 [0.999- 0.103]	**0.06**
MELD ≥19	2.120 [1.155-3.890]	**0.01**
Creatinine	1.951 [1.13-3.36]	**0.02**
Creatinine ≥1.3 mg/dl	2.230[1.125-4.421]	**0.02**
Bilirubin	1.068 [1.004-1.136]	**0.04**
Albumin	0.959 [0.914-1.007]	0.09
Albumin ≤27 g/l	2.113 [1.067-4.181]	**0.03**
Sodium	0.992 [0.945-1.04]	0.73
Platelets	1 [0.995-1.005]	0.93
INR	0.983 [0.84-1.413]	0.92

Multivariate analysis of p-TIPS patients				
	Variables	**HR [95% CI]**	**P value**	**Harrel index**
Model 1	Age>55 years	2.769 [1.480-5.180]	0.001	
	Child - Pugh>11	3.338 [1.728-6.449]	<0.001	0.71 [0.64-0.78]
	Creatinine≥1.3 mg/dl	2.461[1.228-4.929]	0.01	
Model 2	Age>55 years	2.855 [1.526-5.343]	0.001	
	MELD≥19	2.341 [1.272-4.308]	0.006	0.67 [0.59-0.75]
Model 3	Age>55 years	2.283 [1.396-3.734]	0.001	
	Bilirubin≥3 mg/dl	2.155 [1.331-3.492]	0.002	0.68 [0.62-0.74]
	Creatinine1.3mg/dl	2.051 [1.167-3.604]	0.01	
	Albumin ≤27g/l	1.656 [0.982-2.795]	0.06	

A



D+E	1017	740	612	560	528	491	476	420
pTIPS	310	273	237	214	206	192	181	161

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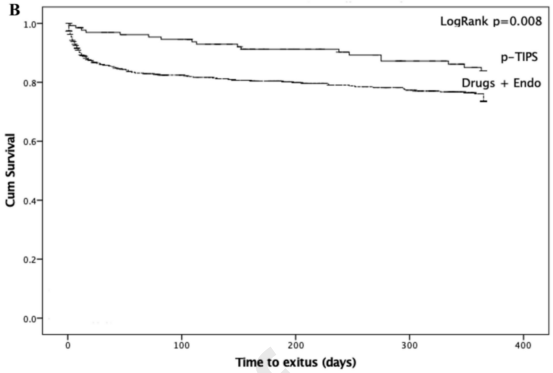

D+E	464	352	331	311	293	281	270	240
pTIPS	138	124	116	102	99	92	86	77

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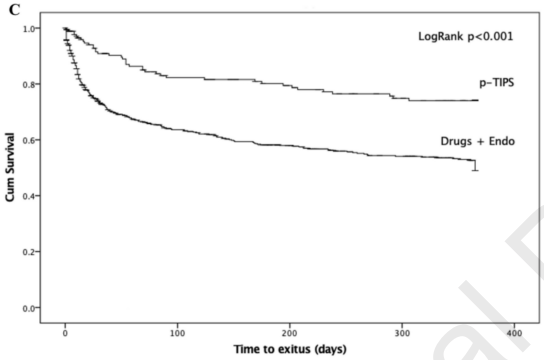
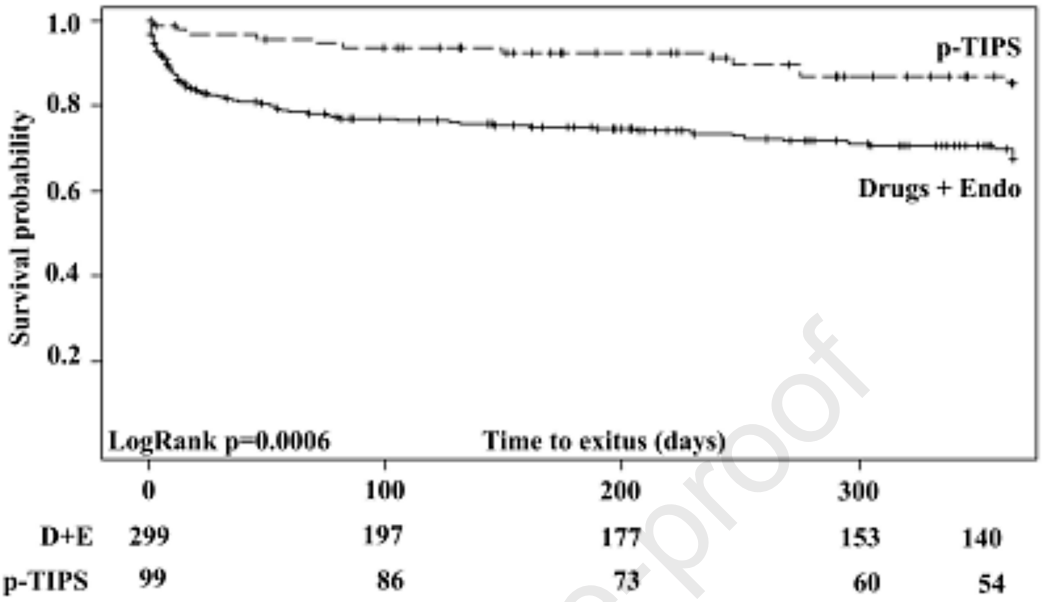
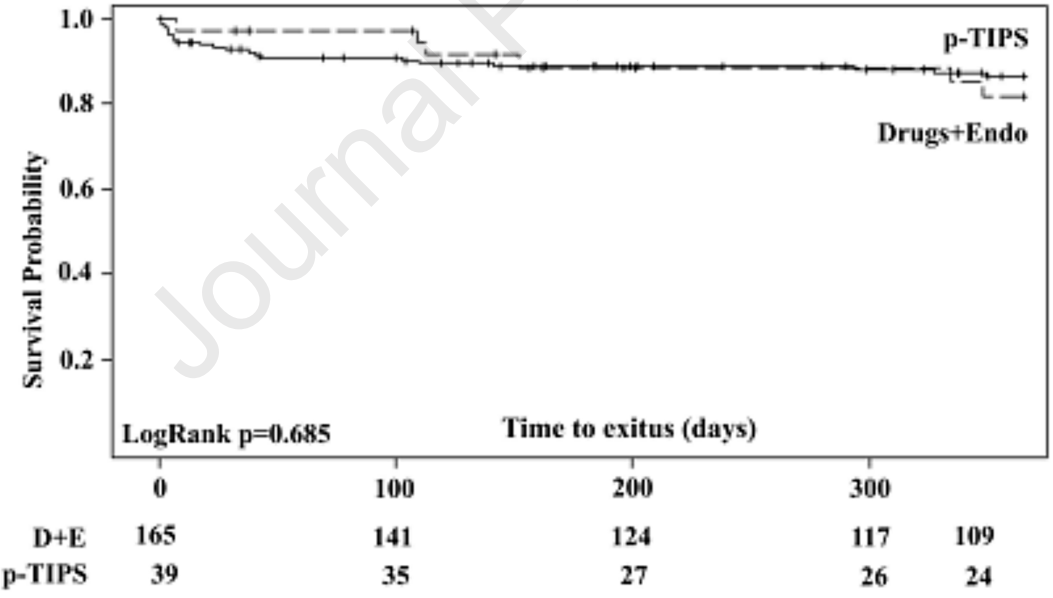


D+E	553	325	281	249	235	210	206	180
pTIPS	172	132	121	112	107	100	95	84





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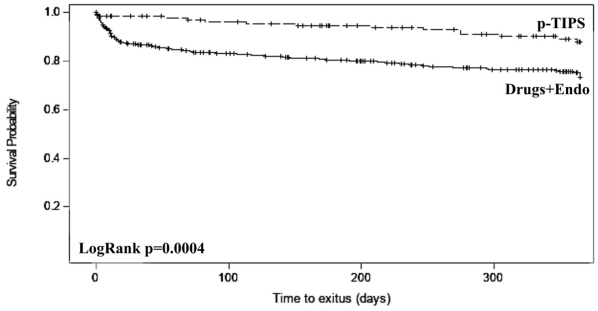

D+E	439	312	282	247	227
p-TIPS	142	122	108	97	86

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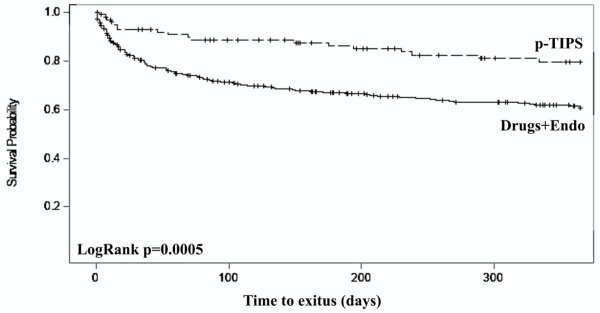

D+E	338	211	176	158	143
p-TIPS	103	80	68	56	54

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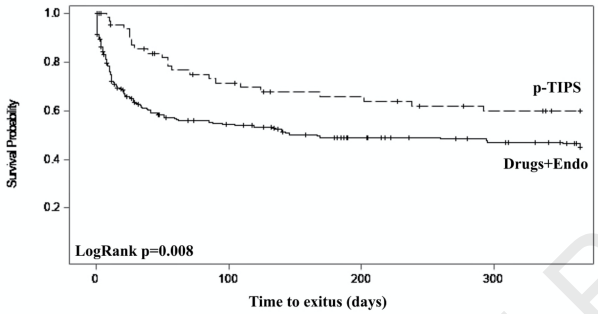


D+E	240	108	83	71	67
p-TIPS	65	40	34	28	25

What you need to know:

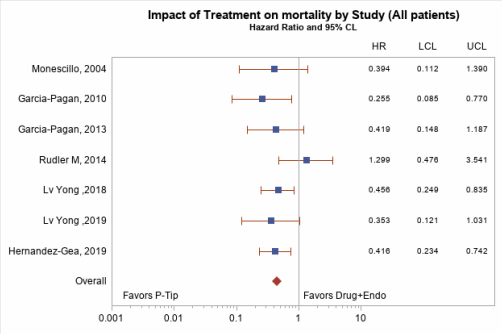
Background and Context: Compared with drugs plus endoscopy, placement of transjugular portosystemic shunts within 72 hrs of admission to the hospital (preemptive TIPS) increases survival times of high-risk patients with cirrhosis and acute variceal bleeding, but the benefit is less clear for patients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

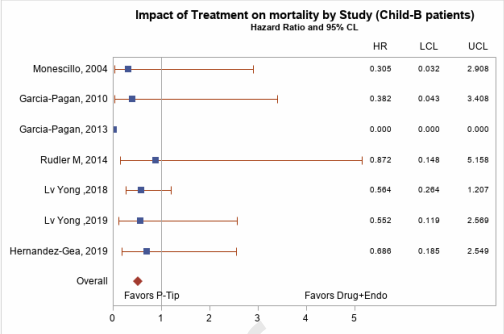
New Findings: In a meta-analysis of data from 7 studies of patients with cirrhosis, acute variceal bleeding, and Child-Pugh score C below 14 points or Child-Pugh B plus acute variceal bleeding, preemptive placement of TIPS reduced risk of death within 1 year compared with drugs plus endoscopy, and reduced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

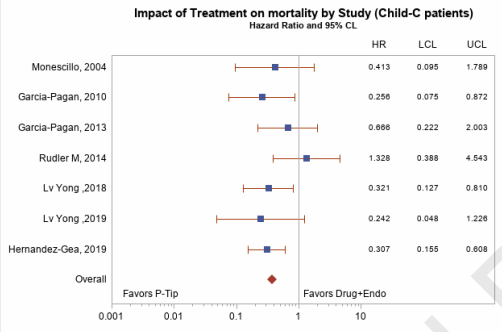
Limitations: This was a meta-analysis of randomized controlled and observation studies. Additional prospective studies are needed.

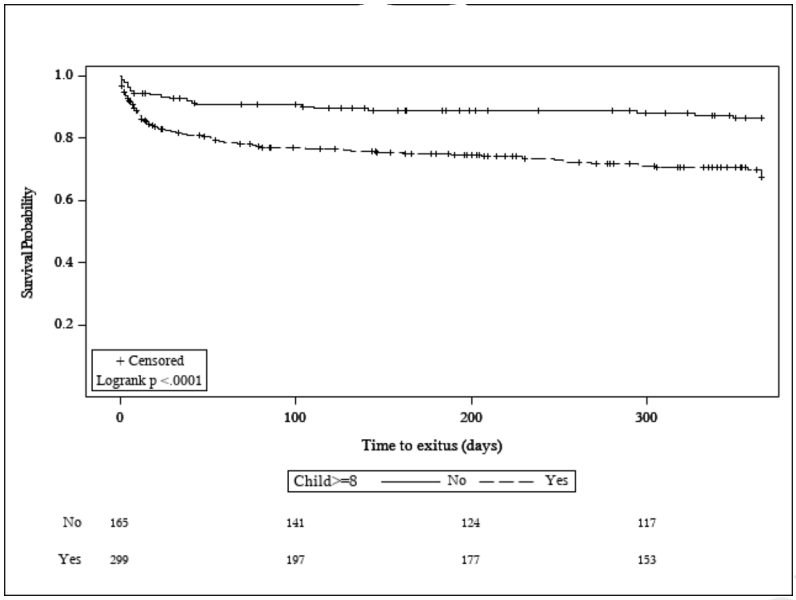
Impact: Patients with cirrhosis and Child-Pugh score C (below 14 points) or Child-Pugh B plus acute variceal bleeding should receive preemptive placement of TIPS, rather than drugs plus endoscopy.

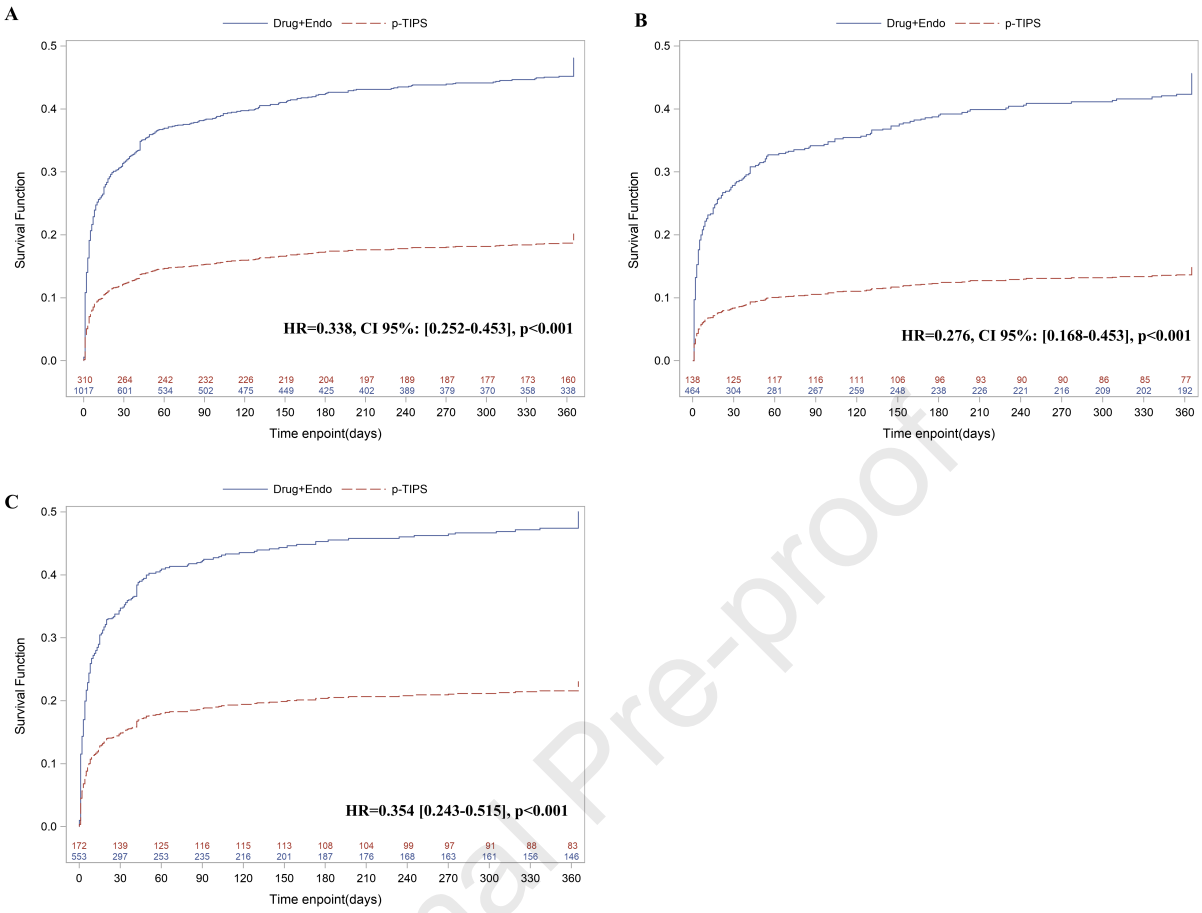
Lay Summary: This study analyzed data from 7 studies of high-risk patients with cirrhosis and acute variceal bleeding and found that preemptive placement of TIPS reduces the risk of death and controls bleeding and ascites better than treatment with drugs and endoscopy.

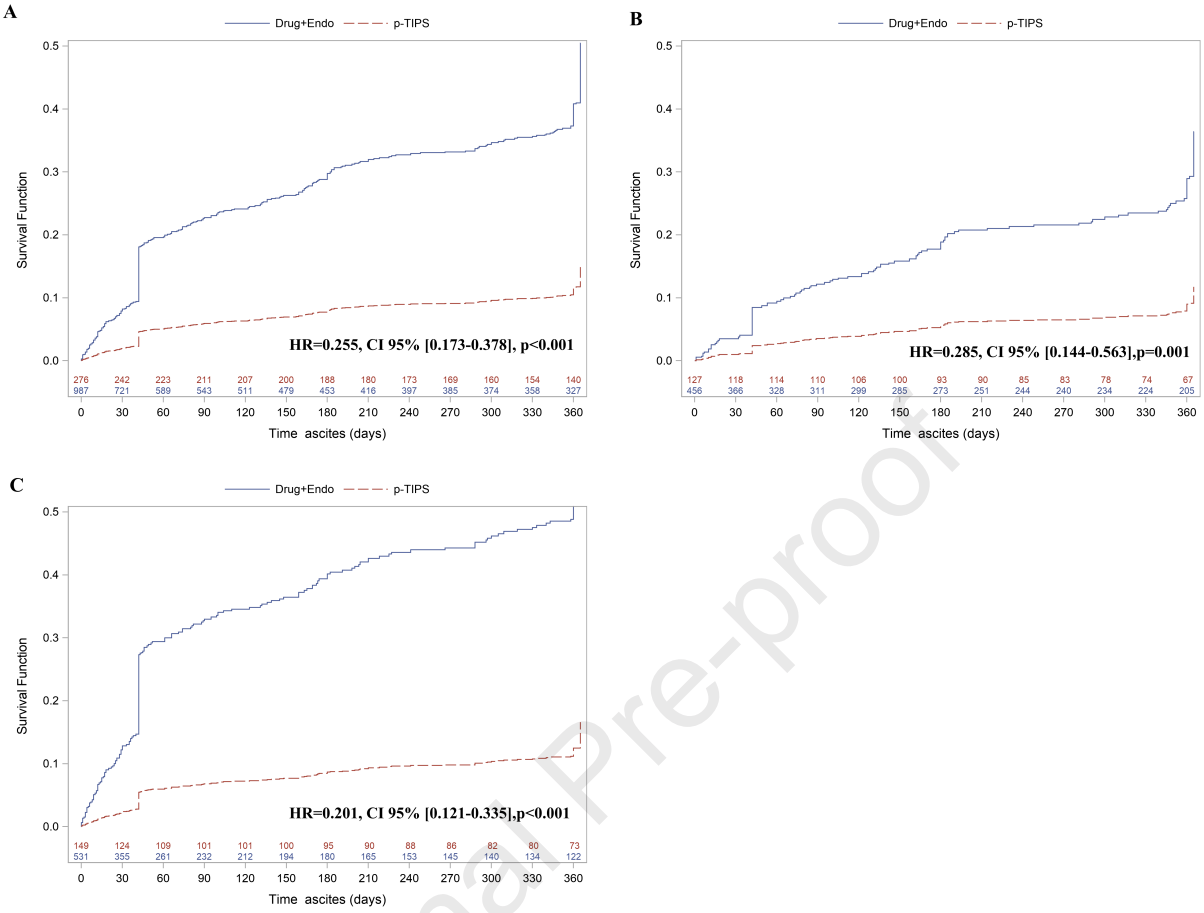


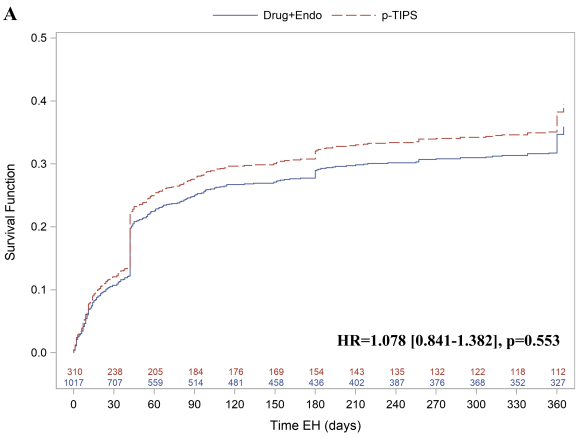


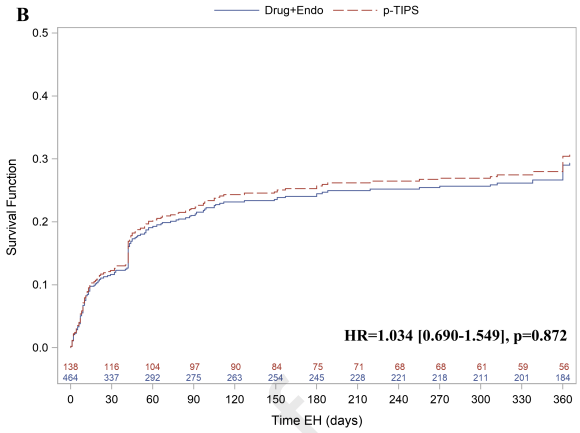


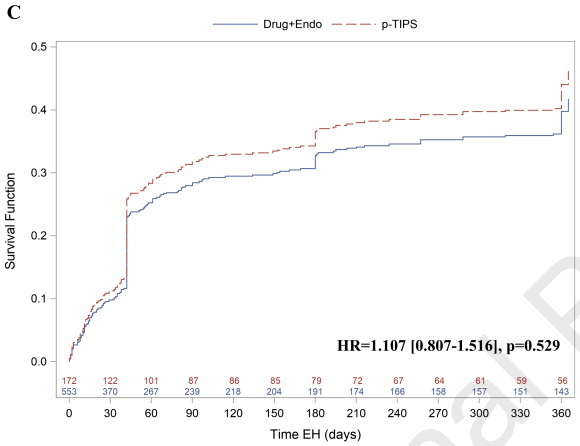


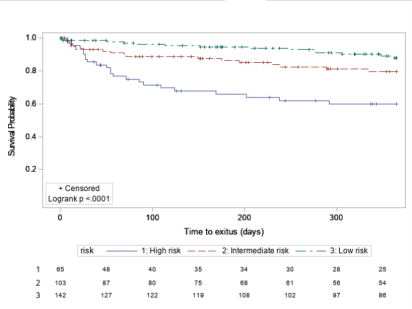


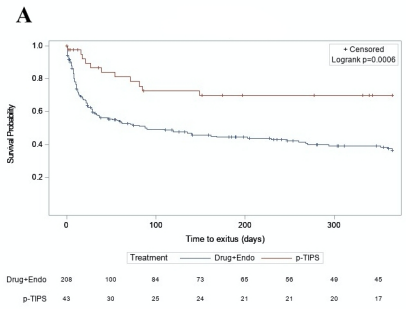


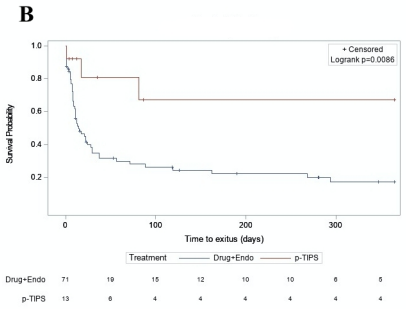












Supplementary tables

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 mmHg 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 hours 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 hours 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 hours 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 hours 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.

Yong Lv[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.
Yong Lv[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.

TIPS, transjugular intrahepatic portosystemic shunt; RCT, randomized controlled trial; HVPG, hepatic venous pressure gradient; AB, active bleeding, NSBB, non selective beta blockers; EBL, endoscopic band ligation
Patients were included only if they fulfilled the current high-risk criteria (CP-B+AB, CP-C<14)

Supplementary Table 2. Causes of death stratified by treatment group and Child-Pugh Class

Cause of Death	Drugs+Endo		TIPS	
	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%)

Drugs + Endo, pharmacological treatment + endoscopy, TIPS, transjugular intrahepatic portosystemic shunt, CP-B, Child Pugh B + active bleeding, CP-C, Child Pugh C, 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 [CI95%]	**P-value**	**HR [CI95%]**	**P-value**
Ascites	All	0,255 [0.167-0.391]	<0.0001	0.276 [0.118-0.406]	<0.0001
	CP-B + AB	0.353 [0.181-0.689]	0.0023	0.304 [0.155-0.597]	0.0005
	CP-C	0.197 [0.112-0.349]	<0.0001	0.232 [0.14-0.386]	<0.0001
Hepatic Encefalopathy	All	1.264[0.985-1.623]	0.0656	1.231 [1.035-1.734]	0.08
	CP-B + AB	1.197 [0.805-1.78]	0.373	1.175 [0.805-1.78]	0.1373
	CP-C	1.319 [0.961-1.812]	0.086	1.307 [0.952-1.796]	0.098
Failure to control bleeding and rebleeding	All	0.291 [0.214-0.359]	<0.0001	0.281 [0.174-0.455]	<0.0001
	CP-B + AB	0.267 [0.165-0.43]	<0.00	0.283 [0.169-0.475]	<0.0001
	CP-C	0.303 [0.202-0.453]	<0.0001	0.361 [0.246-0.53]	<0.0001
Death	All	0.468 [0.346-0.632]	<0.0001	0.431 [0.316-0.5989	<0.0001
	CP - B + AB	0.518 [0.301-0.891]	0.017	0.523 [0.307-0.892	0.017
	CP- C	0.412 [0.287-0.59]	<0.0001	0.359 [0.246-0.525]	<0.0001

Drugs+ Endo is the reference category for risk calculation

Supplemetary Table 4 Sensitivity analysis of risk of Death using non-competitive 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 [IC95%]	**P-value**	**HR [IC95%]**	**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]	0.0333	0.548 [0.316 – 0.952]	0.0329
	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]	0.0013	0.275 [0.136 - 0.556]	0.0003
	Child C	0.176 [0.099-0.311]	<.001	0.214 [0.128 - 0.356]	<.001
Hepatic Encefalopathy	All	1.108 [0.862-1.423]	0.4243	1.095 [0.851 - 1.409]	0.482
	Child B+AB	1.018 [0.675-1.536]	0.9308	1.016 [0.670 - 1.540]	0.9419
	Child C	1.153 [0.843-1.577]	0.3743	1.153 [0.841 - 1.582]	0.3763
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

Supplementary Table 5 A. Univariate analysis of factors predicting survival in CP- B+AB patients

Variable	HR	95% CI		P Value
Age	1.026	1.008	1.045	0.0043
Albumin	0.959	0.928	0.991	0.0115
Bilurrubin	1.063	1.018	1.11	0.0055
Child	1.52	1.197	1.929	0.0006
Creatinine	2.431	1.532	3.856	0.0002
Meld	1.068	1.029	1.109	0.0005
AgeGe56	1.632	1.107	2.405	0.0134
AlbuGe27	1.745	1.157	2.631	0.0079
Creatinine 1.3	2.492	1.566	3.965	0.0001
bilirrubin 3	1.237	0.692	2.214	0.4728
etiology	0.96	0.647	1.425	0.8403

Supplementary table 5 B. Multivariate analysis of factors predicting survival in CP- B+AB patients

Model	Variable	P value	HR	95% CI		C Statistics
model 1	Age	0.0045	1.026	1.008	1.045	0.643
	Albumina at admission	0.0125	0.96	0.93	0.991	
	MELD at admission	0.0007	1.065	1.027	1.105	
model 2	Albumin<=27	0.0127	1.686	1.118	2.544	0.6479
	Meld>=15	<0.0001	2.418	1.597	3.662	
	Age>=56	0,0133	1.632	1.107	2.406	

Model 3	Age>=56	0.0128	1.637	1.11	2.412	0.61
	Meld>=15	<0.0001	2.474	1.634	3.747	
Model 4	Albumina at admission	0.0133	0.961	0.931	0.992	0.6198
	MELD at admission	0.0006	1.067	1.028	1.108	
Model 5	Albumin<=27	0.0123	1.691	1.121	2.551	0.6324
	Meld>=15	<0.0001	2.406	1.589	3.644	
Model 6	Meld>=15	<0.0001	2.468	1.63	3.737	0.578
Model 7	Age	0.0422	1.019	1.001	1.038	0.6522
	Creatinine at admissi	0.0084	1.9	1.178	3.062	
	ChildPugh Score at ad	0.0036	1.429	1.124	1.818	
Model 8	**Child>=8**	**<0.0001**	**2.612**	**1.617**	**4.221**	**0.5964**
Model 9	Age>=56	0.015	1.618	1.098	2.385	0.6318
	Child>=8	<0.0001	2.599	1.609	4.2	
Model 10	Creatinine>=1.04	<0.0001	2.372	1.588	3.544	0.6494
	Child>=8	0.0002	2.53	1.565	4.089	