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Pre-emptive TIPS in high-risk acute variceal bleeding. An updated and revised individual patient data meta-analysis.

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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 + Endoscopy: pharmacological treatment plus endoscopy

HE: hepatic encephalopathy

PHT: portal hypertension

p-TIPS: pre-emptive transjugular portosystemic shunt

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Conflicts of Interest:

Ferran Torres consults for Archivel, EnteraHealth, and UniversalDX. He advises Archivel, Argenx, Basilea, BV, Cellaion, and Rovi. He is on the speakers' bureau for Ferrer and Janssen. Jaime Bosch consults for Actelion, Ambys, AstraZeneca, BioVie, BLB, Boehringer Ingelheim, Bristol Myers Squibb, Brudy, Chiasma, Exalenz, Lipocine, Novo Nordisk,

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Resolution, and Surrozen. He is on the speakers' bureau for Gore. Peter C. Hayes advises and is on the speakers' bureau for Gore. Dominique Thabut consults and received grants from AbbVie and Gilead. She consults for Alfa-Sigma, Cellaion, and Gore. Virginia Hernández-Gea is on the speakers' bureau for Cook and Gore. Juan Carlos García-Pagán is on the speakers' bureau, and received grants from Gore. He consults for Shionogi. He received grants from AstraZeneca, Cook, Mallinkrodt, and Novartis. The remaining authors have no conflicts to report.

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Graphical Abstract

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Abstract:

Background & Aims: A previous individual patient data meta-analysis (IPD-MA) showed that compared with drugs+endoscopy, placement of transjugular portosystemic shunt within 72 hrs of admission (preemptive TIPS: p-TIPS) increases the survival of high-risk patients (Child-Pugh B+active bleeding and Child-Pugh C<14points) with cirrhosis and acute variceal bleeding (AVB). However, previous IPD-MA was not a two-stage MA, did not take into consideration the potential risk of selection bias of observational studies, and did not include the most recent RCT. We performed an updated and revised IPD-MA to reassess the efficacy of p-TIPS addressing all previous issues.

Approach & Results: We included all studies from the previous IPD-MA and searched for other possible eligible publications until September 2022. We performed a two-stage IPD-MA of data from 8 studies (4 RCTs and 4 observational). In addition, we performed a sensitivity analysis excluding those patients dying up to the first 72 hours after admission, in the Drugs+Endoscopy arms of the 4 observational studies. The primary endpoint was the effects of p-TIPS vs Drugs+Endoscopy on 1-year survival.

We identified 1389 patients (342 p-TIPS and 1047 Drugs+Endoscopy). The two-stage IPD-MA, showed that p-TIPS significantly reduced the mortality in overall population, HR=0·43, 95% CI 0·32-0·60, p<0·001. This effect was observed in both subgroups of Child-Pugh patients. The sensitivity analysis, confirmed the survival benefit of p-TIPS.

Conclusions: The updated two-stage IPD-MA confirms the significant survival advantage of p-TIPS in high-risk patients with cirrhosis and AVB. As a result, we recommend p-TIPS as the preferred first-choice treatment for these patients.

KEY WORDS: Acute variceal bleeding; Hepatic encephalopathy; liver disease; treatment

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Introduction

Patients with cirrhosis of Child-Pugh C (<14 points) or Child-Pugh B>7 points and active variceal bleeding at endoscopy (AB) despite the use of vasoactive agents during the acute variceal bleeding episode (AVB), are at a high risk of failure to control bleeding, early rebleeding, and death. To address this issue, the Baveno VII guidelines recommend the use of preemptive TIPS (p-TIPS) placed within 72 hours of the index endoscopy as it has been shown to be more effective in controlling bleeding, reducing the risk of rebleeding, lessening the occurrence of new or worsening ascites, and improving overall survival.[1]

The basis for this recommendation lies in the findings of various randomized clinical trials (RCTs) and prospective observational studies.[2-8] A comprehensive meta-analysis of these studies, comparing Drugs +Endoscopy to p-TIPS, provided clear evidence of the benefits of p-TIPS in this high-risk patient population.[9] Nevertheless, a recent randomized study partially questioned the conclusions drawn from the published meta-analysis.[10]

Additionally, the previous meta-analysis failed to account for potential selection bias, as all patients from observational studies who died within 72 hours after the index endoscopy were automatically assigned to the drugs + endoscopy group, which could have resulted in an overestimation of mortality rates in this treatment group.[11]Additionally, it is important to note that the results obtained from different approaches to IPD-MA, such as one-stage and two-stage methods, may vary. According to current recommendations, a two-stage meta-analysis is preferred for prospective meta-analyses, considering its advantages and suitability.[12,13]

The objective of this study was to revise the IPD-MA1) by incorporating the latest studies satisfying our eligibility criteria,[10] 2) accounting for the possibility of selection bias in the observational studies and 3) using the two-stage individual patient data meta-analysis method whenever feasible.

Methodology

The current study was performed according to the Preferred reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.[12,14]

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Eligibility criteria for inclusion of the studies in the current metanalysis:

We considered eligible for inclusion all prospective studies designed to compare the efficacy of p-TIPS vs NSBB plus endoscopic band ligation (Drugs + Endoscopy) in cirrhotic patients with a high-risk variceal bleeding at diagnostic endoscopy. A search in EMBASE and MEDLINE databases was done until September 2022 using, the following keywords: 'early TIPS', 'early transjugular intra-hepatic portosystemic shunt', 'preemptive transjugular intra-hepatic portosystemic shunt', 'preemptive TIPS'. Studies published until December 2019 were already included in a previous meta-analysis and were considered for inclusion in the current IPD-MA as well.[9] Reasons for not including other potential studies published in this period were previously discussed.[9] The studies published from January 2020 until September 2022 were reviewed by ONF and JCGP. Only one additional study satisfied the above criteria and was considered for inclusion in the current IPD-MA.[10]

Assessment for risk of bias in the studies considered for inclusion:

All studies considered for inclusion were assessed for the risk of bias by two investigators (ONF, JCGP): RoB 2 for RCTs[15] and ROBINS for non-RCTs.[16] In accordance with the recommended tools, we classified studies as being at low, high, or unclear risk of bias.[17]

Obtaining individual data

The IPD of the studies that were already included in the first meta-analysis were obtained previously and were used for this meta-analysis as well. After January 2020, there was only one study satisfying the eligibility criteria, and the principal investigator was contacted to obtain the relevant data that satisfied the aim of this meta-analysis.[10] Two investigators (ONF and EN) checked for completeness and congruence of the requested information and solved potential discrepancies with the authors. All individual patient data were merged into a unique database.

Endpoints

The primary endpoint was one-year all-cause mortality. Secondary endpoints included the assessment of the treatment effect at one year on: 1) bleeding control and prevention of variceal rebleeding, 2) developing new or worsening ascites, and 3) developing hepatic encephalopathy (HE) .

As a sensitivity analysis, the main endpoint was tested after excluding patients who died in the Drugs + Endoscopy group during the first 24 hours, 48 hours, and 72 hours respectively after index endoscopy. These results are presented in a supplementary file.

Ethical consideration:

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All patients gave an informed consent to participate in each study. In addition, local ethics committees approved the use of available data for this IPD MA.

Statistical analysis:

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range (IQR)), as appropriate. Discrete variables were reported as frequencies (percentages). The baseline characteristics of the treatment groups were compared using either an unpaired t-test or Wilcoxon rank-sum test for continuous variables and a Chi-square test for discrete variables.

Two different statistical methods were employed. 1) A two-stage approach where each trial was initially analyzed separately to obtain relevant aggregate data (treatment effect estimates and their variance), and then, in a second stage using random-effects on trials[18] the resulting aggregate estimates were combined to produce summary results using traditional meta-analytic methods. Additionally, the heterogeneity of the summary results was evaluated using the I^2 statistics (percentage of the variability in effect estimates between studies) and the Cochrane Q test for homogeneity.[19] 2) A one-stage approach was used to obtain the summary results by analyzing the individual patient data (IPD) from all trials together in a single step using an appropriate statistical model. In both meta-analytical approaches, the clustering effects of patients within trials were taken into account by allowing each study to have its own baseline hazard (stratified analysis).

For this study, the two-stage approach was planned for all analyses. However, due to problems with model regression convergence, mostly due to the small sample size, in some cases, we opted for the one-stage meta-analysis as our last resort. For the primary endpoint using the entire cohort and for the subset with Child-Pugh C, a Cox regression was used within the framework of a two-stage meta-analysis. Child-Pugh B+AB was analyzed with a one-stage meta-analysis. For the secondary endpoints, a one-stage approach was used for all subgroups due to the above-mentioned reasons, using competing-risks regression models according to the method of Fine and Gray.[20] In the analysis of the secondary endpoints, death and liver transplant were used as competing risk events. The Fine and Gray models in one-stage meta-analyses were stratified by the baseline hazard to account for the clustering of patients within trials. All regression models included age, gender, Child-Pugh score, MELD score, etiology, creatinine, bilirubin, INR, albumin, and Na as covariates. All summary results were presented as hazard ratios (HR) and sub-hazard ratios (sHR) with their 95% confidence intervals. Probabilities for event occurrence were estimated with the Cumulative incidence function (CIF), and comparisons were performed using Gray's Test.

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A 2-sided p-value of <0.05 was the threshold used for significance in all analyses. Stata 17.0 was used for data clean-up and for analyses. The two-stage MA was implemented with ipdmetan[21] package within Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

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Results

We did not find high or unclear risk of bias in the 4 included RCTs, while the 4 observational studies were at risk of bias due to their observational nature – unbalanced in treatment arms due to insufficient confounder adjustment or unknown confounding. We were unable to ask for supplementary information to the authors to manage this risk, because of unavailability of the appropriate data. The assessment of the risk of bias is shown in Supplementary Figures 1, http://links.lww.com/HEP/I25 and 2, http://links.lww.com/HEP/I26. The impact of the potential biases on the overall treatment effect was explored by sensitivity analyses excluding the relevant studies. Supplementary Table 1, http://links.lww.com/HEP/I27 shows the characteristics of the studies included in the meta-analysis. It is important to mention, that despite six patients in the p-TIPS arm in one RCT, for logistical reasons, never received the allocated treatment, and eight patients in the p-TIPS group received p-TIPS after the 72 h window, these patients were included in the analysis in the p-TIPs group. Also, 14 patients with Child-Pugh B from the same study did not have active bleeding at endoscopy, however we decided to include them in the current IPD-MA for statistical reasons, to increase the sample size. A sensitivity analysis excluding these patients was performed for the primary end-point.[10]

Baseline characteristics of the population:

The current IPD meta-analysis included 1389 cirrhotic patients (342 in the p-TIPS group and 1047 in the Drugs + Endoscopy group). Seven hundred sixty-two were Child-Pugh C class (571 in the Drugs + Endoscopy group and 191 in the p-TIPS group) and 627 Child B+AB class (476 in the Drugs + Endoscopy group and 151 in the p-TIPS group). The baseline characteristics are shown in Table 1.

Assessment of one-year survival

Death occurred in 361 (34·5%) patients in the Drugs + Endoscopy group and in 63 (18·4%) in the p-TIPS group. The causes of death are described in Supplementary Table 2, http://links.lww.com/HEP/I28.

Mortality in the overall population (Child-Pugh score C & B + AB)

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The 2-stage IPD MA showed a significantly better 1-year survival in patients treated with p-TIPS vs those receiving Drugs +Endoscopy, HR=0.43, 95% CI 0.32-0.60, p<0.001 (Figure 1A). Improvement in survival was also observed when only the RCTs were included in the IPD MA (Figure 1A; upper section). The number needed to be treated is 6.

The sensitivity analysis after excluding patients from observational studies that died in the first 72h (n=63), showed similar results (Supplementary Figure 3A, http://links.lww.com/HEP/I29). Also, pTIPS increased the survival at one year compared to Drugs + Endoscopy, in patients with or without other decompensating events at admission (ascites or hepatic encephalopathy) (Supplementary Figure 4, http://links.lww.com/HEP/I30, 5, http://links.lww.com/HEP/I31).

Mortality in the Child-Pugh C < 14 points population

In patients with Child-Pugh C score <14 points, the 2 stage IPD MA showed a beneficial effect of p-TIPS in one-year survival, HR=0.39, 95% CI 0.26-0.59, p<0.001 (Figure 1B). The number needed to treat is 4.7. The sensitivity analysis shows similar results (Supplementary Figure 3B, http://links.lww.com/HEP/I29).

Mortality in the Child B + AB population

The benefit of p-TIPS was also confirmed in patients with Child-Pugh score B + AB. For this analysis, the small sample size (n=627; 133 events) precluded the use of 2-stage MA. Thus, for this subset, we pooled all eight studies and analyzed it as a one-stage IPD MA: HR=0.48, 95% CI 0.29-0.80, p=0.005 (Table 2). Using the same approach, we found that p-TIPS was associated with improved survival for patients with Child Pugh B + AB of 8 and 9 points (n=423; 105 events), HR 0.38, 95% CI 0.21-0.68, p=0.001, but not for the subset of patients with Child Pugh B + AB of 7 points (n=204; 28 events), HR 0.96 95% CI 0.32-2.85, p=0.936 (Table 2). The number needed to treat is 6.7. The sensitivity analysis shows similar results (Table 2). Also, the sensitivity analysis after excluding the patients without AB at endoscopy showed similar results (HR 0.36 95% CI 0.20-0.67, p=0.001), even after excluding those patients from the observational studies that died in the first 72h (HR 0.45 95% CI 0.23-0.87, p=0.017) for Child-Pugh B + AB of 8 and 9 points.

The differences in secondary outcomes between patients that died and those who survived, are presented as Supplementary table 3, http://links.lww.com/HEP/I32.

Failure to control bleeding or rebleeding at 1 year

Three hundred fifty-eight patients had failure to control bleeding or rebleeding in the Drugs + Endoscopy group (179 in Child-Pugh C and 179 in Child-Pugh B + AB patients) and 46 rebled in the p-TIPS group (25 in Child Pugh C and 21 in Child Pugh B + AB patients). The

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2-stage IPD MA confirmed the benefit of p-TIPS reducing the risk of failure to control bleeding/rebleeding in each study as well as in the overall population, sHR 0.22, 95% CI 0.13-0.37, p<0.001 (Supplementary Figure 6A, http://links.lww.com/HEP/I33). A similar benefit was observed when only considering Child Pugh C patients, sHR 0.22, 95% CI 0.12-0.39), p<0.001 (Supplementary Figure 6B, http://links.lww.com/HEP/I33). The heterogeneity was not significant among the studies in the overall population (I^2=40.7%, p=0.107) or in Child C patients (I^2= 12.1%, p = 0.337), all studies having the same effect direction.

Due to low sample size, the two-stage IPD MA in the Child Pugh B+AB population, was not able to be performed. Therefore, we performed a one-stage meta-analysis that confirms the superiority of the p-TIPS over Drugs + Endoscopy in preventing failure to control bleeding/rebleeding in Child-Pugh B + AB patients (sHR 0.27, 95% CI 0.17-0.44, p<0.001). The beneficial effect on bleeding was observed either in Child-Pugh B > 7 (sHR 0.29, 95% CI 0.17-0.49, p<0.001) but also in those Child B + AB of 7 points (sHR 0.17, 95% CI 0.05-0.56, p=0.003).

Assessment of new/worsening ascites at 1 year

New/worsening ascites occurred in 365 patients in the Drugs + Endoscopy group (240 in Child Pugh C<14 and 125 in Child Pugh B+AB) and in 37 patients of the p-TIPS group (23 Child Pugh C and 14 Child Pugh B +AB). The 2-stage IPD MA showed a reduction in the risk of new/worsening ascites by p-TIPS in the overall population sHR 0.32, 95% CI 0.17-0.59, p<0.001) (Supplementary Figure 7, http://links.lww.com/HEP/I34) with a non-significant heterogeneity amongst studies (I^2=37%, p=0.13). Due to insufficient number of events, the impact of p-TIPS on new/worsening ascites was evaluated using one-stage MA in Child-Pugh C subgroup (sHR = 0.18, 95% CI 0.11-0.30; p<0.001), in Child-Pugh B + AB patients (sHR = 0.31, 95% CI 0.18-0.56; p<0.001), in Child B>7 + AB patients (sHR 0.29 95% CI 0.14-0.57,p<0.001), and in Child B + AB of 7 points (sHR 0.50 95% CI 0.20-1.28; p=0.151).

Assessment of development of hepatic encephalopathy (HE) at 1 year

Post treatment HE occurred in 370 patients of the Drugs + Endoscopy group (238 Child Pugh C<14 and 132 Child Pug B + AB) and in 131 of the p-TIPS group (85 Child-Pugh C<14 and 46 Child Pugh B + AB). Using 2-stage approach, we found that there was a not-significant trend towards higher risk of encephalopathy with pTIPS (sHR:1.19, 95%CI: 0.96-1.49, p=0.120) in the overall population, as well as in Child-Pugh C patients (sHR = 1.11, 95% CI 0.82-1.50; p=0.501) (Supplementary Figure 8, http://links.lww.com/HEP/I35) with a non-significant heterogeneity of (I^2=0.0%, p=0.717) or (I^2=1.2%, p=0.420) respectively. The

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results for Child-Pugh B + AB subgroup using one-stage MA show similar results; indeed, no statistical significant differences were found on the risk of development of HE between the two treatments groups considering all patients (sHR = 1.07, 95% CI 0.77-1.50; p=0.674), those with Child-Pugh B 8 and 9 points (sHR = 1.14 95% CI 0.78-1.66; p=0.499) or in those with 7 points (sHR = 0.81, 95% CI 0.36-1.84] p=0.62).

Effect on survival of delaying time "0" in the setting of AVB.

Mortality after an AVB accumulates in the first days/weeks after admission. Thus, in the current IPD-MA, 361 patients of the 1047 receiving Drugs + Endoscopy died, 63 (17.5%) in the first 72 hours and 106 (29.4%) in the first week after admission (time "0"). Therefore, there is a direct relationship between the delay in initiating a given treatment and the survival of these patients., the so called "survival bias". As such, we excluded the patients from the Drugs + Endoscopy group in the observational studies that either died in the first 72 h, 1 week, 2 weeks and 3 weeks and compared the survival with the pTIPS group. As shown in Figure 2 , as the delay from the index endoscopy increases, the mortality of the remaining patients (surviving to this time), decreases progressively. Because mortality is higher in Child C than in Child B patients, "survival bias" is more pronounced in the first. As shown in Figure 2A, mortality in Child C patients in the group Drugs + Endoscopy surviving 72 hours although still significantly higher than that observed in patients of similar characteristics treated with p-TIPS, the difference shortens. This difference is even less evident as the delay from time "0" increases and is no longer present if we analyze those patients in the Drug + Endoscopy group that survive up to three weeks. A detailed analysis showed that the difference in mortality indeed disappears when analyzing those patients surviving 16 days. Similar phenomenon was observed in Child B + AB>7 points. However, and because of the already lower mortality in Child B patients, differences in mortality disappears when only those Child B patients surviving 6 days were analyzed (Figure 2B).

Discussion

In our previous IPD-MA, we demonstrated that p-TIPS treatment, is associated with improved 1-year survival and decreased incidence of variceal rebleeding and of new/worsening ascites in high-risk cirrhotic patients with AVB, compared to medical therapy, a benefit that was not accompanied by an increased risk of hepatic encephalopathy.[9] This update aims to address concerns about potential selection bias caused by early deaths in the medical arm of observational studies. Also, some authors have suggested that the benefits of p-TIPS may extend beyond the 72-hour timeframe that was evaluated in previous studies and meta-analyses. In addition, some authors have challenged the previous meta-analysis

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results because it did not utilize the current recommended methodology (i.e., two-stage meta-analysis).[12,22] These unresolved questions motivated us to address these issues in the current two-stage IPD-MA, which allows for the evaluation of heterogeneity between studies and examination of differences in treatment effect across subgroups. In the current IPD-MA, the heterogeneity between studies was low, resulting in similar outcomes between both methods. The two-stage approach is often preferred to one-stage approach for a number of reasons.[23,24] Specifically, the two-stage approach utilizes commonly used meta-analysis methods that are well-established and extensively documented, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[25] This characteristic makes the two-stage approach accessible to a wide range of researchers, including those without a background in statistics. Moreover, in most scenarios, the two-stage approach demonstrates comparable performance to a one-stage approach, while often offering computational efficiency.[13]Additionally, it inherently distinguishes within-trial information from across-trial information, which holds significant value. Another advantage of the second stage is its ability to incorporate aggregate data from trials that do not provide individual participant data, presenting a convenient framework for such integration.[26] Although the two-stage approach was our preferred method, it was not always feasible, in which case we utilized the one-stage approach.

Using this approach, we were able to confirm that treatment with p-TIPS significantly improved 1-year survival compared to treatment with Drugs + Endoscopy in those with Child-Pugh C <14 points and those with Child-Pugh B + AB > 7 points, irrespective of the presence or absence of other decompensating events such as ascites or hepatic encephalopathy. Addressing previous concerns, we found that the benefit of p-TIPS on survival was consistent when analyzing only RCTs (including the most recent one) and accounting for potential mortality bias in observational studies by considering deaths occurring within 72 hours after admission as not related to treatment. We also adjusted for relevant confounders to prevent bias in the observational studies. These findings strongly support the use of p-TIPS in high-risk patients with AVB. Interestingly, a recent small RCT[27] in patients with cirrhosis bleeding from gastric fundal varices, a type of varices not included in the previous studies of the IPD-MA, also suggested that p-TIPS may be superior to drugs + endoscopic therapy in this specific population.

The current IPD-MA further affirms that, although there is a trend, the treatment with p-TIPS does not significantly increase the risk of developing hepatic encephalopathy in the overall population or in those with Child-Pugh C or Child-Pugh B + AB.

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Notably, we confirm our previous findings that treatment with p-TIPS did not improve survival in patients with Child-Pugh B+AB of 7 points compared to treatment with Drugs + Endoscopy. However, there was still a significant reduction in failure to control bleeding/rebleeding and in the risk of progression or onset of ascites without increasing the risk of hepatic encephalopathy. Therefore, the indication of p-TIPS should not be entirely ruled out but rather discussed with the patient in this subgroup of Child-Pugh B+AB of 7 points.

Our study allowed us to evaluate the impact of delaying interventions or inclusions in studies on the potential survival benefit. We found that a significant percentage of patients who received medical treatment and died, did so within the first few days after admission. This suggests that delaying interventions will likely result in selecting patients with better spontaneous survival, which can lead to survival bias in clinical trials. Recent studies have suggested that delaying p-TIPS placement until 28 days post-admission may result in even greater survival benefits than placing p-TIPS within 72 hours of admission.[28] However, our results show that any intervention applied to patients who have already survived will be associated with better survival. For example, a patient who was initially classified as Child C at admission, would have a much better survival if the decision for a p-TIPS is delayed for three weeks. Our data suggest that p-TIPS can offer a survival benefit that that extends beyond the initial 72-hour timeframe, suggesting that even if the decision is delayed until 16 days in patients with Child C and 6 days in Child B patients >7 points, patients still benefit from the pTIPS strategy. However, to definitively answer this question, an RCT comparing p-TIPS vs Drug + endoscopy at these delayed time points would be necessary. We already know from different studies that the lower the baseline risk of a population (Child A or Child B without AB), the lower the probability that p-TIPS offers a survival benefit.

We would like to acknowledge several limitations of our study. Firstly, due to the small sample size or limited number of events in some subgroups, such as Child-Pugh B and secondary endpoints, it was not feasible to apply a two-stage meta-analysis approach to all analyses as planned, and consequently, we had to rely on a one-stage approach in these cases. Nevertheless, the results of these two analytical approaches may not differ.[13] Secondly, despite observing the benefit of p-TIPS when only RCT were considered and accounting for mortality bias and adjusting for well-known prognostic factors, we cannot ignore the fact that many patients included in the IPD-MA came from observational studies where there may be a significant heterogeneity regarding patients' management.

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In summary, our meta-analysis shows that p-TIPS treatment has several benefits for cirrhotic patients at high risk of variceal rebleeding. Specifically, we confirm that p-TIPS improves 1-year survival rates, reduces the risk of rebleeding or worsening/development of ascites, and does not increase the risk of hepatic encephalopathy. These benefits were observed in patients with cirrhosis of Child-Pugh C <14 points or Child-Pugh B + AB >7 points with active variceal bleeding at endoscopy. Our data suggests that the benefit of placing a TIPS extends beyond the acute setting, in both if the decision for p-TIPS is delayed up to 2 weeks in Child C patients and up to one week in Child B patients. However, the earlier p-TIPS is placed, the larger the survival benefit.

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Figure 1 AB. IPD meta-analysis of 8 studies of p-TIPS vs Drugs + Endoscopy for 1 year mortality. Treatment effect adjusted by age, gender, Child-Pugh score, MELD score, etiology, creatinine, bilirubin, INR, albumin, and Na. Studies are identified by the name of the first author, type of study and year of publication. Treatment effect is reported as hazard ratio (solid squares weighted by sample size) and 95% CI (horizontal lines) computed by the Cox model. The vertical lines represent the identity of treatment effects (hazard ratio = 1). A. Overall population. B. Child-Pugh C population

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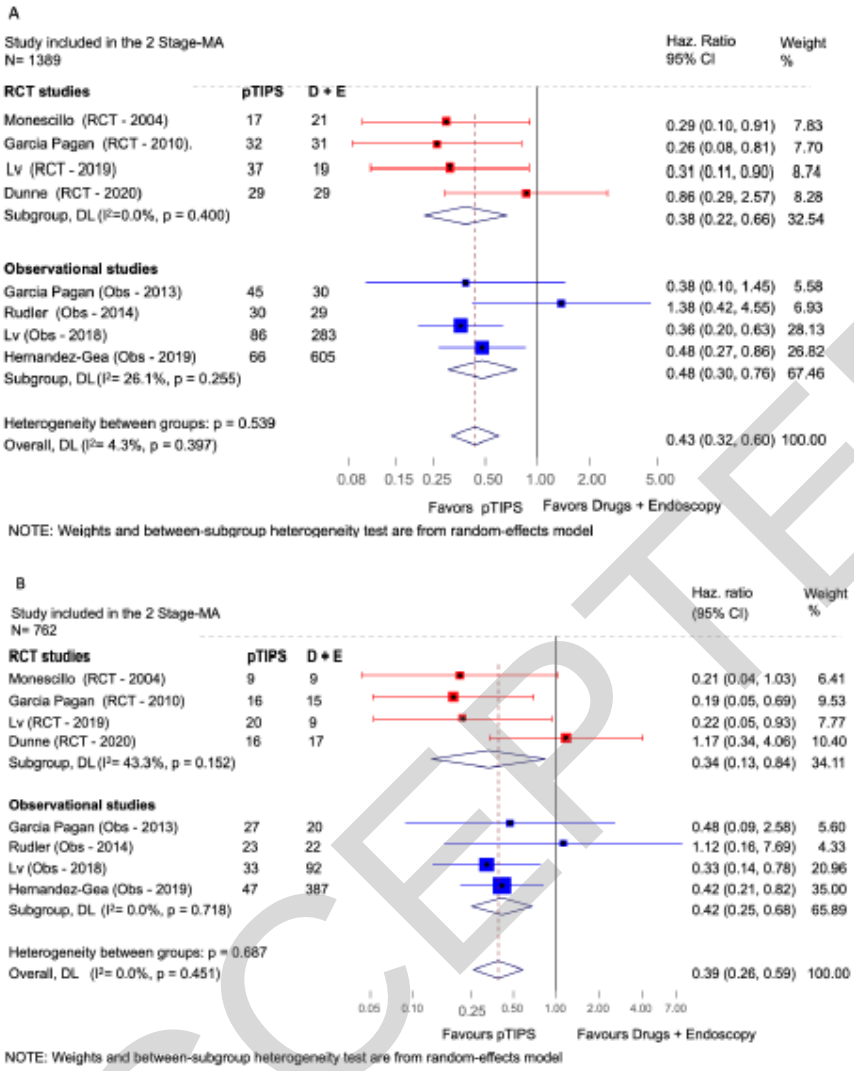

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

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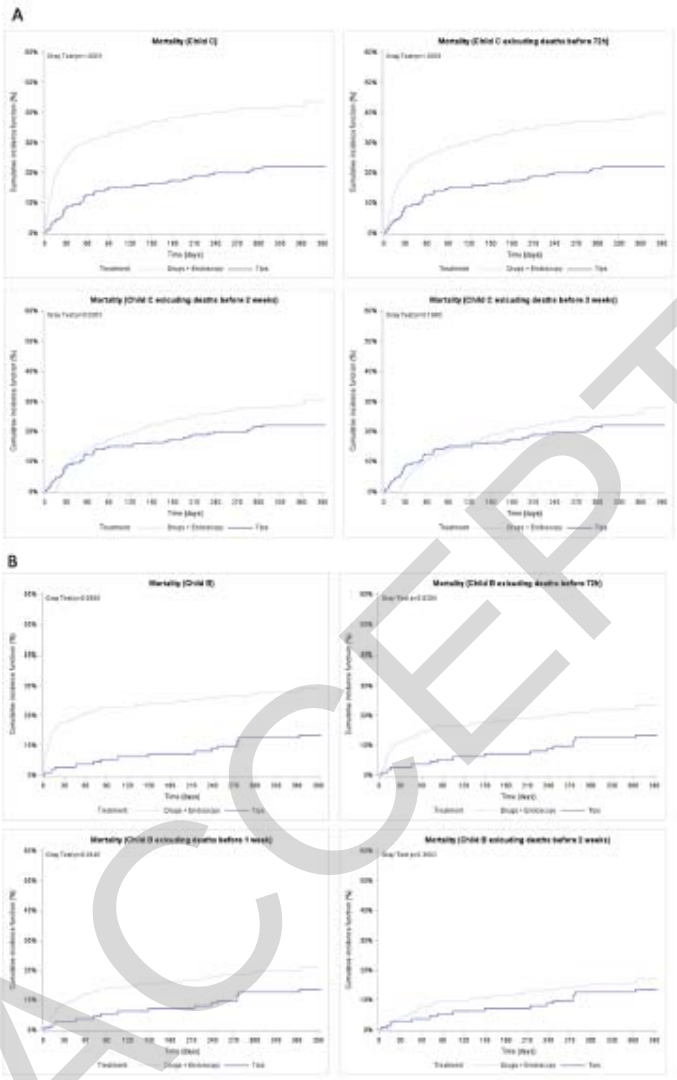
Figure 2 AB. Cumulative incidence function of 1 year mortality in A. Child-Pugh C patients after excluding the patients who died in the first 72h, 2 weeks and 3 weeks and B. Child-Pugh B + AB patients after excluding the patients who died in the first 72h, 1 week and 2 weeks in the observational studies



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Author Contributions:

Oana Nicoară-Farcău - drafting the manuscript, assembly, collection and interpretation of data

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Marika Rudler- generation of data, revision of the manuscript

Debora Angrisani - drafting the manuscript, assembly, collection and interpretation of data

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Jaime Bosch - revision of the manuscript

Yong Lv – generation of data, revision of the manuscript

Dunne Philip D.J.- generation of data, revision of the manuscript

Hayes Peter C.- revision of the manuscript

Dominique Thabut- revision of the manuscript

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Virginia Hernández-Gea - generation of data, revision of the manuscript

Juan Carlos García-Pagán– generation of data, conception and design of the study, interpretation of data, revision of the manuscript, approval of the final version of the manuscript

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	Drugs + Endoscopy group N=1047	p-TIPS group N=342	P value
Age	53.6 (10.59)	53 (11.3)	0.534
Sex male	646 (62%)	221 (64.6%)	0.333
Etiology of cirrhosis			
Alcohol	454 (43.4%)	168 (49%)	0.063
Viral	126 (12%)	61 (17.8%)	**0.006**

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Other	69 (6.6%)	16 (4.7%)	0.201
Child-Pugh class			0.673
Child B + AB	476 (45.5%)	151(44%)	
Child C	571 (54.5%)	191 (56%)	
Child-Pugh score at admission	10 (3)	10 (3)	0.539
MELD score at admission	15 (8)	15 (7)	0.157
Laboratory values			
Albumin	25.6 (6.3)	25.5 (5.6)	0.578
Bilirubin mg/dl	4.2 (5.4)	3.4 (3.5)	**0.012**
Creatinine mg/dl	0.94 (0.5)	0.92 (0.4)	0.327
INR	1.72 (0.6)	1.79 (0.7)	0.107
For continuous variables age and laboratory values, the data are expressed as Mean (±SD) and for Child Pugh and MELD score the data are presented as Median (IQR).			
Table 1 . Baseline characteristics of the population included in the IPD meta-analysis			

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	Child-Pugh B + AB 7, 8, 9 points N=627		Child-Pugh B + AB 7 points N= 204		Child-Pugh B + AB 8, 9 points N=423	
p-TIPS vs Drugs + Endoscopy	HR 95% CI	P value	HR 95% CI	P value	HR 95% CI	P value
Main analysis	0.48 [0.29-0.80]	0.005	0.96 [0.32-2.85]	0.936	0.38 [0.21-0.68]	0.001
Sensitivity analysis*	0.60 [0.35-1.02]	0.062	1.10 [0.36-3.35]	0.872	0.50 [0.27-0.93]	0.029
* Exclusion of deaths in the first 72h from the Drugs + Endoscopy group of the observational studies						

Table 2. One-stage Individual Patient Data meta-analysis of mortality in patients with Child B and active bleeding

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