CLIF-C AD score predicts survival benefit from pre-emptive TIPS in individuals with Child-Pugh B cirrhosis and acute variceal bleeding

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Supplementary methods

Missing values and multiple imputations

All patients had complete information on the treatment. The total number of patients missing data never exceeded 89 (8.7%). Among them, active bleeding was missing in 23 cases (2.2%), international normalized ratios in 6 (0.6%), albumin level in 16 (1.6%), bilirubin level in 7 (0.7%), creatinine level in 27 (2.6%), heart rate in 25 (2.5%), systolic blood pressure in 24 (2.4%), diastolic blood pressure in 24 (2.4%), white blood cell count in 9 (0.9%), hemoglobin in 11 (1.1%), platelet count in 21 (2.1%).

To use the complete set of patients for regression analysis, multiple imputations was performed with the *aregImpute* function from the *Hmisc* R package. With this method, different bootstrap resamples are used for each imputation by fitting a flexible parametric additive regression model on a sample with replacement from the original data. This model is used to predict all of the original missing and non-missing values for the target variable for the current imputation. This produces 5 sets of complete data that subsequently are used for regression analysis

Propensity score matching

The risk-stratification rules included CLIF-C ADs 48-56 grades (low risk/intermediate risk/high risk: CLIF-C ADs <48/48-56/>56), active bleeding (presence vs absence), and Child B 8-9+AB criteria (low risk: Child-Pugh B without active bleeding [Child B +no AB] and Child-Pugh B 7 points with active bleeding [Child B7+AB]; high risk: Child-Pugh B 8-9 points with active bleeding [Child B 8-9+AB]).

We used propensity score matching analysis to minimize selection bias and balance variables. Predicted probabilities (ie, the propensity score) for pre-emptive TIPS treatment were estimated for each patient by using logistic regression models. All baseline variables significantly associated with the outcome at univariable analysis and previously reported possibly influencing the decision on pre-emptive TIPS treatment or mortality (based on literature) were included in the models. A 1:1 nearest neighbour matching algorithm with a caliper of 0.05 and without replacement was used. Balance between the two comparison groups was evaluated using the standardized mean difference across covariates, with an absolute standardized mean difference below 0.1 indicating successful balance. Within each risk category, the propensity score was re-estimated, and patients were re-matched on the newly estimated propensity

score using the 1:1 nearest neighbor matching approach with a caliper width of 0.05.

The covariates included in the final multivariable logistic regression model for the propensity score calculation were:

(a) for entire cohort patients: age, HBV-DNA detectable, active bleeding at endoscopy, ascites, bilirubin, INR, albumin, creatinine, sodium, white blood cell count, platelets count, shock at admission, infection at admission, commodities, hepatocellular carcinoma.

(b) for CLIF-CADs<48 patients: age, etiology of cirrhosis, HBV-DNA detectable, active bleeding at endoscopy, ascites, encephalopathy, bilirubin, INR, albumin, creatinine, sodium, white blood cell count, platelets count, shock at admission, infection at admission, commodities, portal vein thrombosis, hepatocellular carcinoma.

(c) for CLIF-CADs 48-56 patients: age, etiology of cirrhosis, HBV-DNA detectable, active bleeding at endoscopy, ascites, bilirubin, INR, albumin, creatinine, sodium, white blood cell count, platelets count, shock at admission, infection at admission, commodities, portal vein thrombosis, hepatocellular carcinoma, previous variceal bleeding and 24-hour blood transfusion requirements;

(d) for CLIF-CADs >56 patients: age, HBV-DNA detectable, active bleeding at endoscopy, ascites, bilirubin, INR, albumin, creatinine, sodium, white blood cell count, platelets count, shock at admission, infection at admission, commodities, hepatocellular carcinoma.

(e) for active bleeding patients: age, etiology of cirrhosis, HBV-DNA detectable, active bleeding at endoscopy, ascites, encephalopathy, bilirubin, INR, albumin, creatinine, sodium, white blood cell count, platelets count, shock at admission, infection at admission, commodities, portal vein thrombosis, hepatocellular carcinoma.

(f) for no active bleeding patients: age, etiology of cirrhosis, HBV-DNA detectable, active bleeding at endoscopy, ascites, bilirubin, INR, albumin, creatinine, sodium, white blood cell count, platelets count, shock at admission, infection at admission, commodities, portal vein thrombosis, hepatocellular carcinoma, previous variceal bleeding and 24-hour blood transfusion requirements;

(g) for Child B 7 points or Child B 8-9 points without active bleeding patients: age, HBV-DNA detectable, active bleeding at endoscopy, ascites, bilirubin, INR, albumin, creatinine, sodium, white blood cell count, platelets count, shock at admission, infection at admission, commodities, hepatocellular carcinoma.

(h) for Child B 8-9 points with active bleeding patients: age, HBV-DNA detectable, active bleeding at endoscopy, ascites, bilirubin, INR, albumin, creatinine, sodium, white blood cell count, platelets count, shock at admission, infection at admission, commodities, hepatocellular carcinoma.

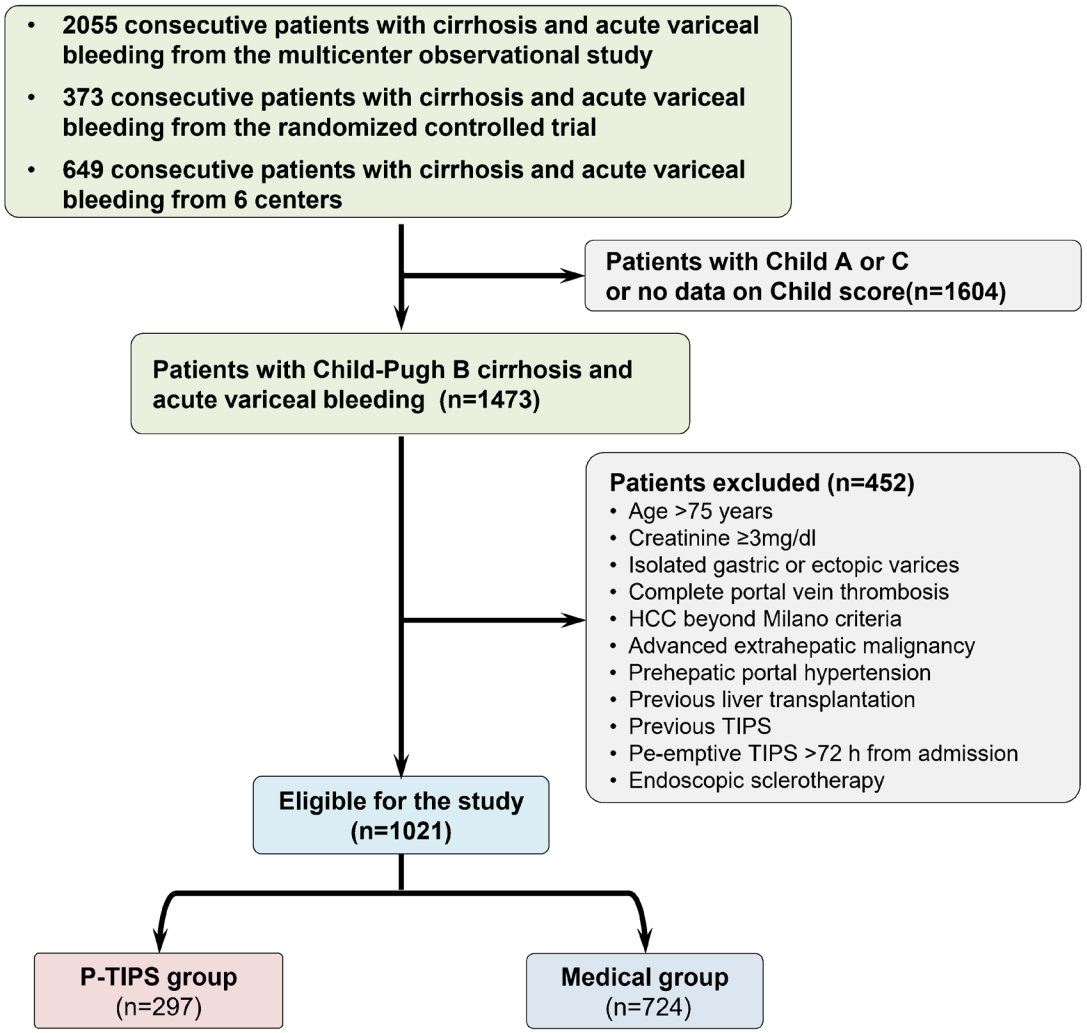


Fig. S1: Flowchart showing study design and patient disposition.

Abbreviations: HCC, hepatocellular carcinoma; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

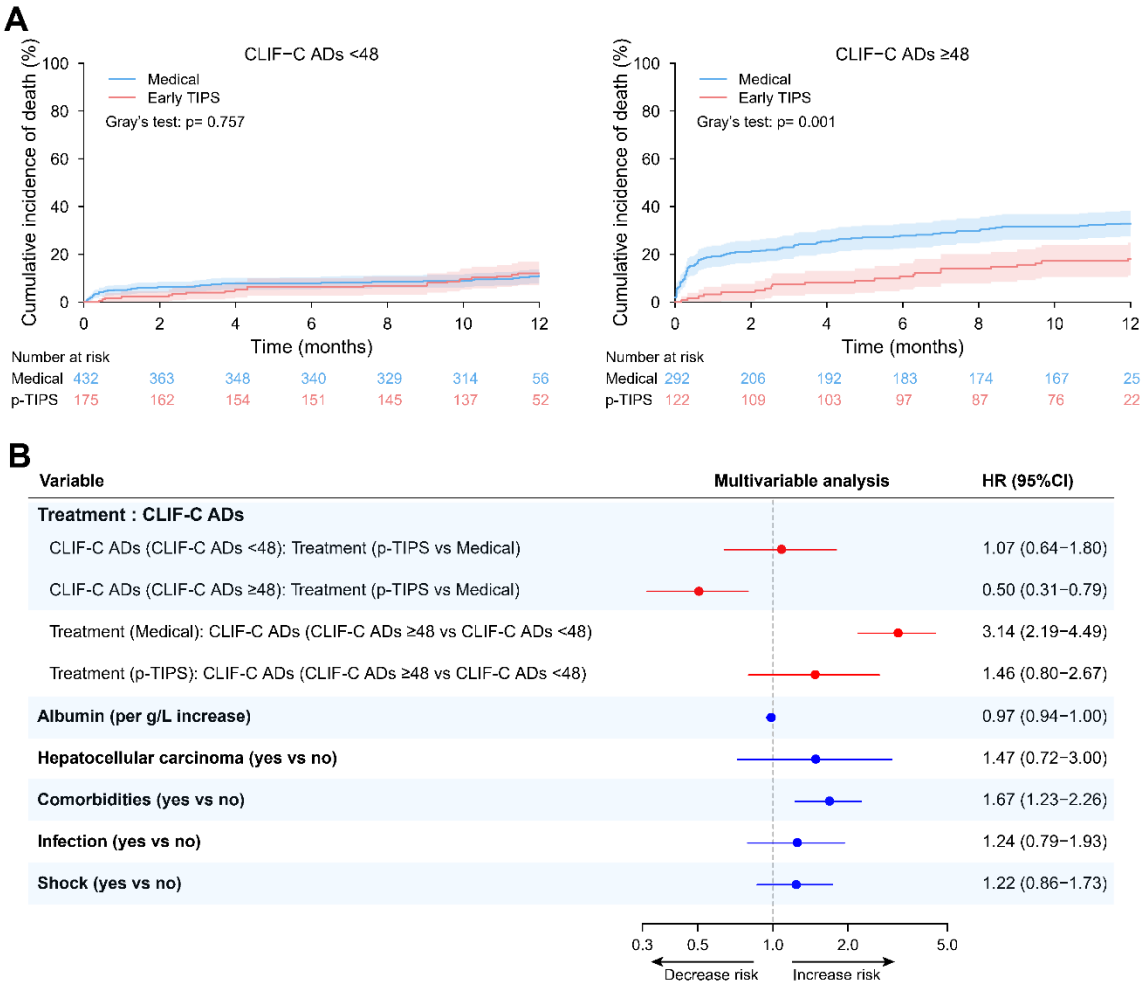


Fig. S2: Effect of pre-emptive TIPS on mortality stratified according to CLIF-C ADs 48 classification rule

Independent effect (hazard ratio with 95% confidence intervals) of pre-emptive TIPS versus medical treatment on 1-year mortality stratified by CLIF-C ADs 48 classification rule (low-/high-risk: CLIF-C ADs <48/>48), after adjusting for potential confounders in the competing risk multivariable models.

Abbreviations: CLIF-C AD score, chronic liver failure-consortium score for acute decompensation; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

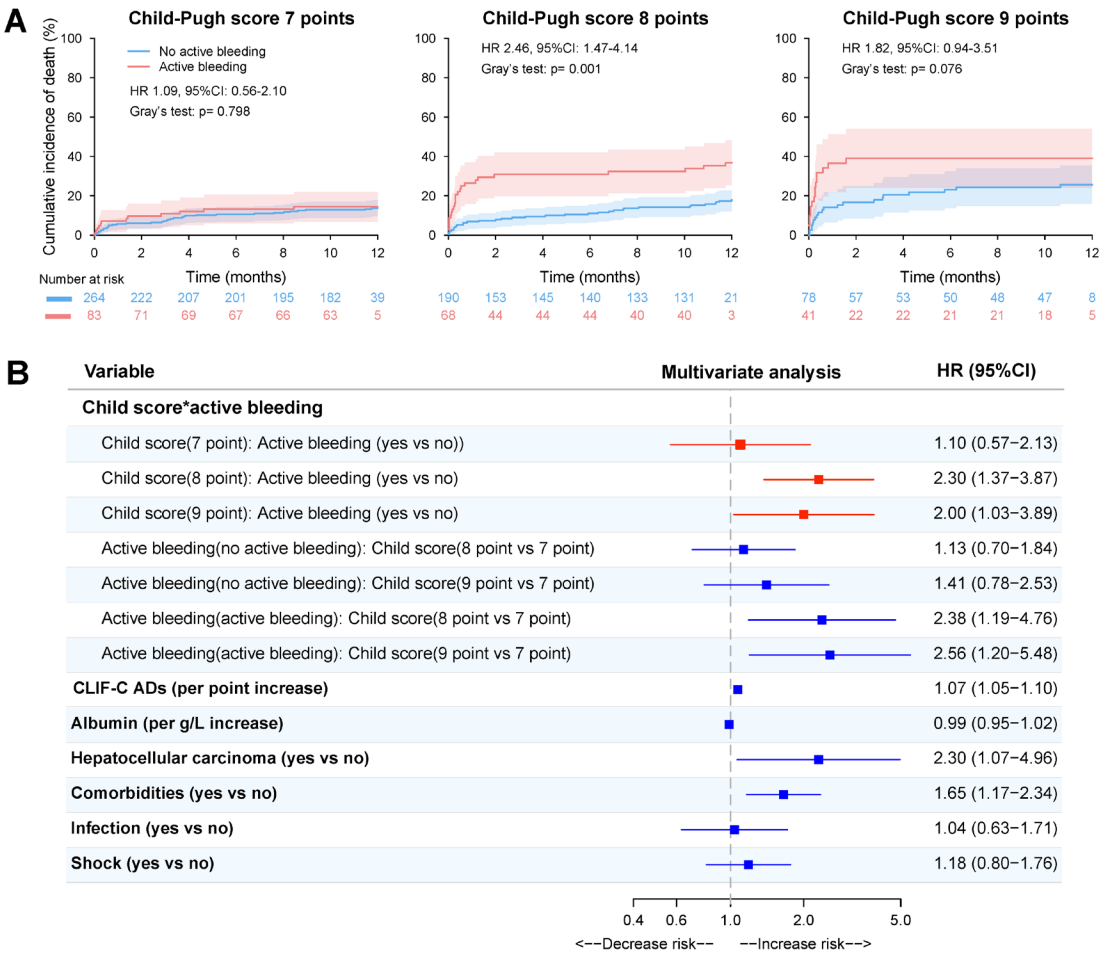


Fig. S3: Impact of active bleeding at index endoscopy on 1-year mortality in cirrhotic patients with different Child-Pugh B score who were treated with drug and endoscopy.

(A) Cumulative incidence of death at 1 year and **(B)** adjusted hazard ratios stratified according to presence of active bleeding at index endoscopy in patients with different Child-Pugh B score not receiving pre-emptive TIPS based on competing risk approach (the Fine and Gray method) with liver transplantation being the competing events.

Abbreviations: CLIF-C ADs, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

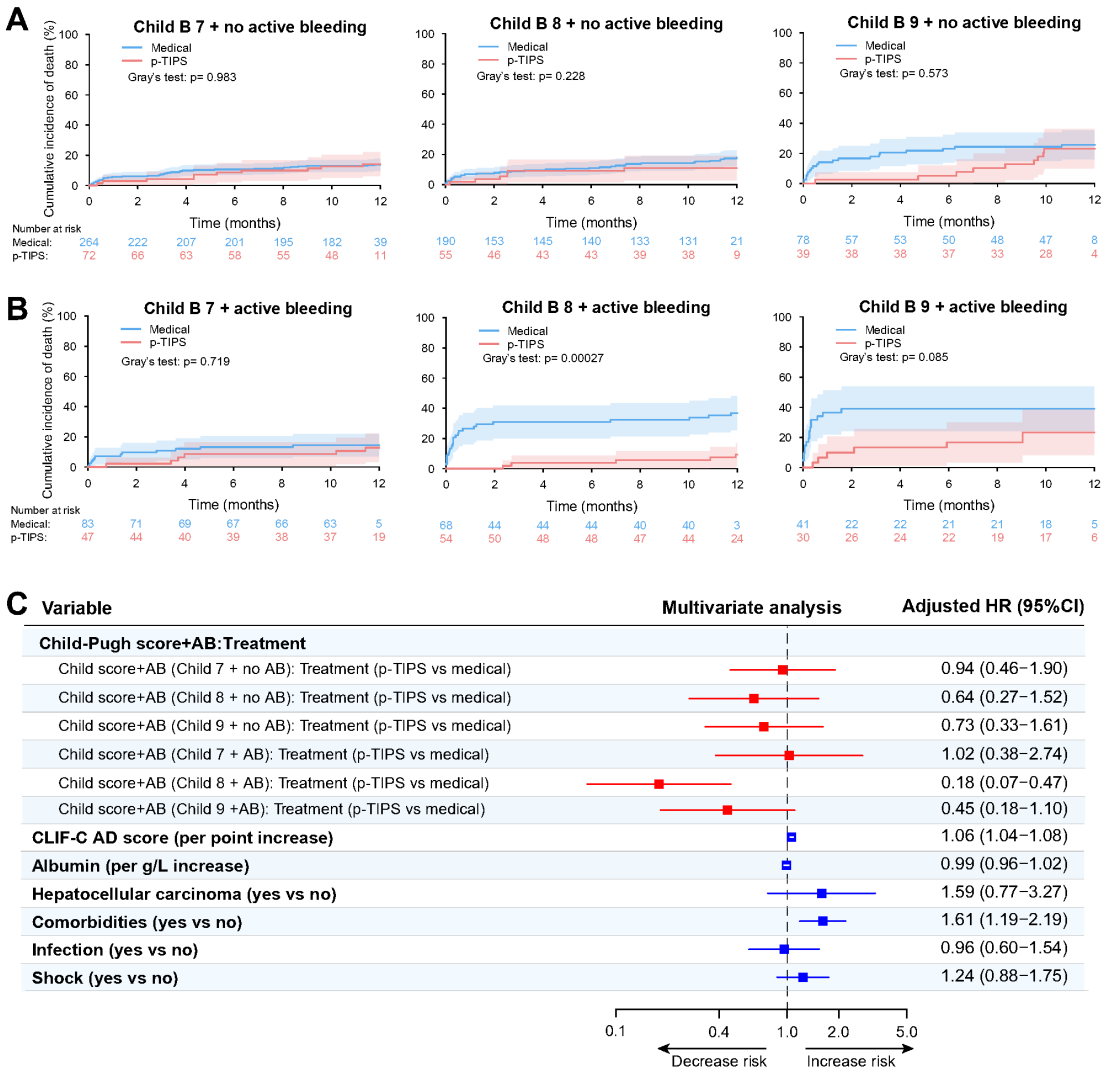


Fig. S4: Effect of pre-emptive TIPS on mortality stratified according to active bleeding at index endoscopy and different Child-Pugh B scores.

Cumulative incidence of death at 1 year in pre-emptive TIPS group versus medical group stratified according to different Child-Pugh B scores in patients **(A)** without active bleeding at index endoscopy and **(B)** with active bleeding at index endoscopy. **(C)** Independent effect (hazard ratio with 95% confidence intervals) of pre-emptive TIPS versus medical treatment on 1-year mortality stratified by active bleeding and different Child-Pugh B scores, after adjusting for potential confounders in the competing risk multivariable models.

Abbreviations: AB, active bleeding; CLIF-C AD score, chronic liver failure-consortium score for acute decompensation; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

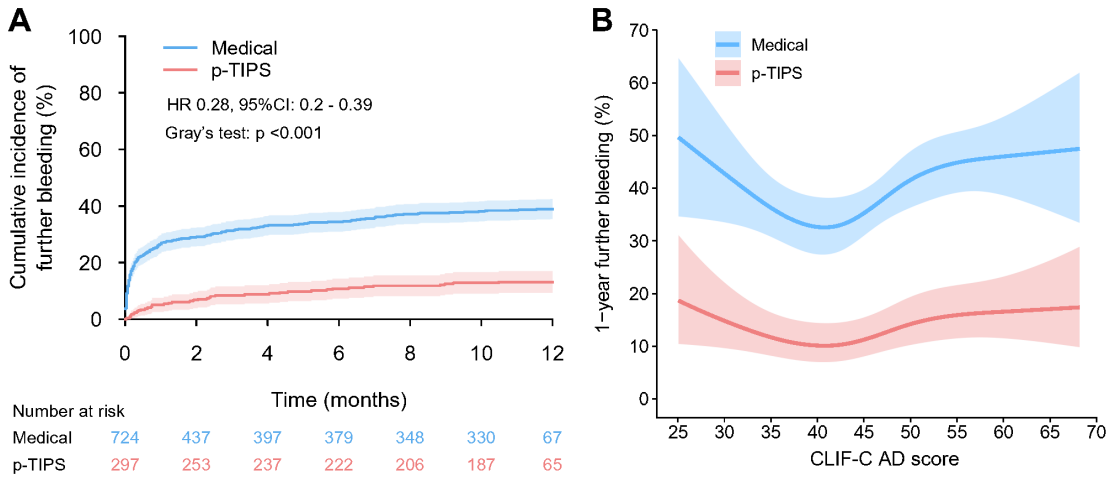


Fig. S5: Competing risks analyses for further bleeding in entire cohort and the relationship between the mortality rate and CLIF-C AD scores stratified by treatment groups.

(A) Cumulative incidence of further bleeding in pre-emptive TIPS versus medical groups based on competing risk approach (the Fine and Gray method) with death and liver transplantation being the competing events. **(B)** Probability of further bleeding within 1 year in relation to CLIF-C AD score stratified by treatment groups. Restricted cubic splines were generated using logistic regression models adjusted for propensity score. The colored bands indicate 95% confidence intervals.

Note: Further bleeding was defined as a composite outcome of failure to control acute bleeding or rebleeding.

Abbreviations: CLIF-C AD score, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

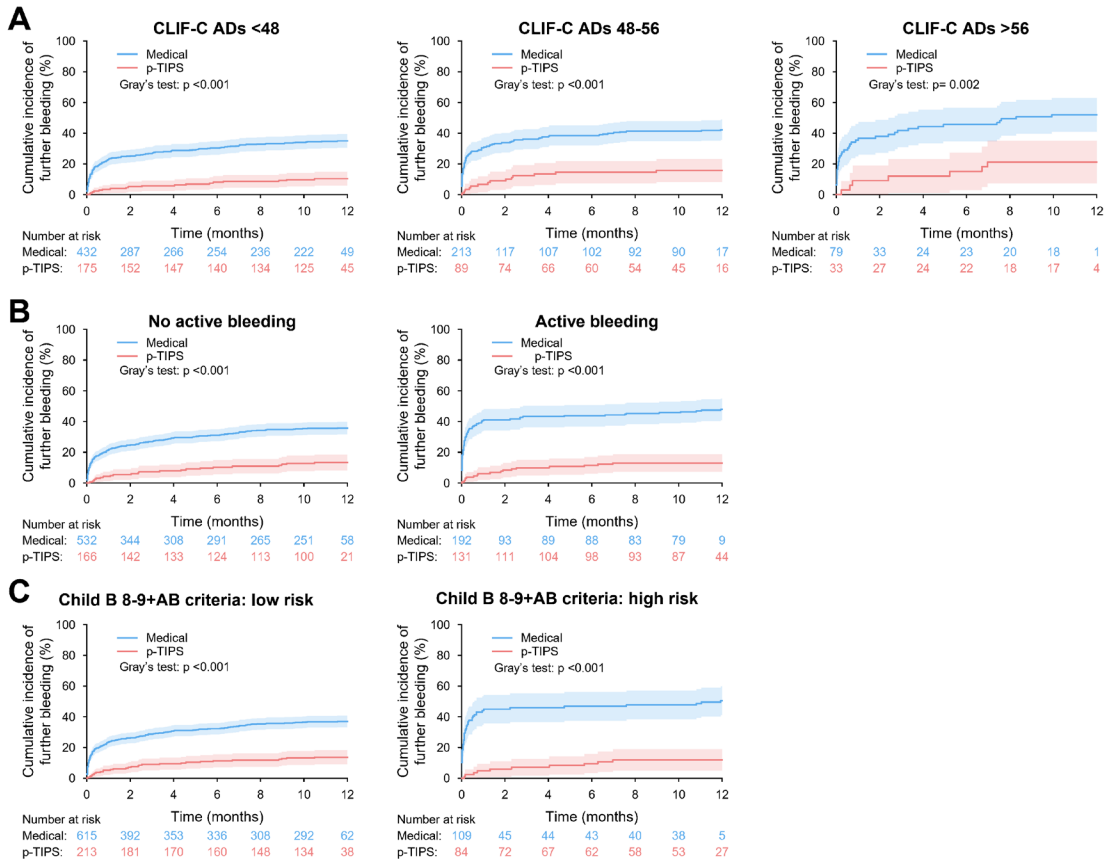


Fig. S6: Effect of pre-emptive TIPS versus drug plus endoscopic therapy on the further bleeding stratified by different risk stratification rules in Child-Pugh B patients

(A) Cumulative incidence of further bleeding in pre-emptive TIPS versus medical group stratified by CLIF-C ADs 48-56 grades, **(B)** active bleeding and **(C)** Child B 8-9+AB criteria based on competing risk approach (the Fine and Gray method) with death and liver transplantation being the competing events**.**

Note: Further bleeding was defined as a composite outcome of failure to control acute bleeding or rebleeding. Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: AB, active bleeding; CLIF-C ADs, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

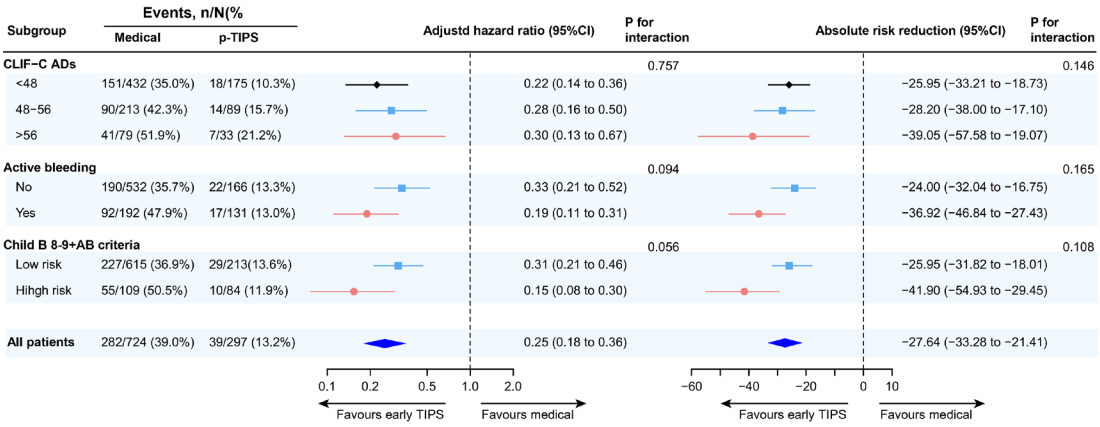


Fig. S7: **Forest showing the event rate, adjusted hazard ratios, and the absolute risk reduction for 1-year further bleeding stratified by different risk stratification rules.**

In the forest plot, the adjust hazard ratios and absolute risk reduction for the early group compared with the medical group are shown. Adjusted hazard ratios and absolute risk reduction with 95% confidence intervals (CI) indicate the effect of pre-emptive TIPS versus medical treatment (as reference) on further bleeding, which are derived from multivariable competing risk regression models, adjusted for propensity score within each risk category.

Note: Further bleeding was defined as a composite outcome of failure to control acute bleeding or rebleeding. Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: AB, active bleeding; CLIF-C ADs, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

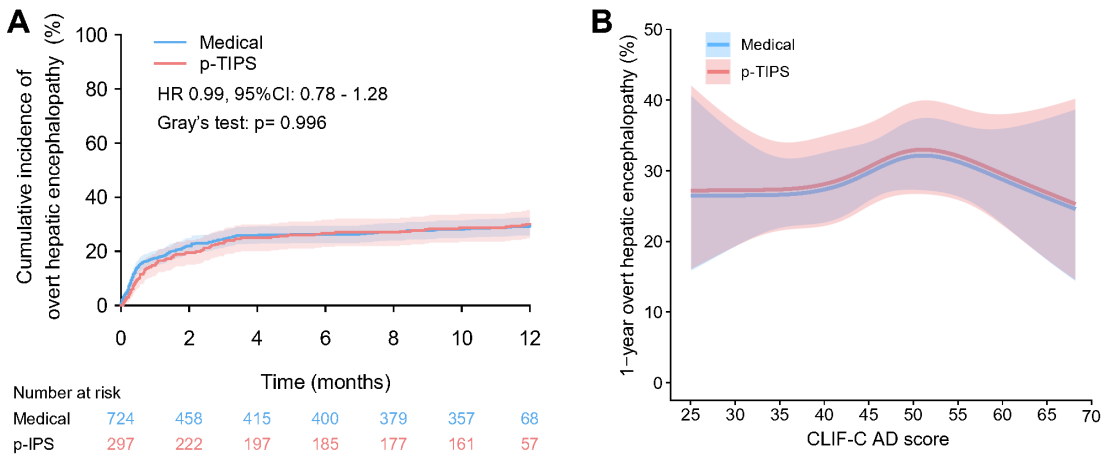


Fig. S8: Competing risks analyses for overt hepatic encephalopathy (OHE) in entire cohort and the relationship between the mortality rate and CLIF-C AD scores stratified by treatment groups.

(A) Cumulative incidence of OHE in pre-emptive TIPS versus medical groups based on competing risk approach (the Fine and Gray method) with death and liver transplantation being the competing events. (**B**) Probability of OHE within 1 year in relation to CLIF-C AD score stratified by treatment groups. Restricted cubic splines were generated using logistic regression models adjusted for propensity score. The colored bands indicate 95% confidence intervals.

Abbreviations: CLIF-C AD score, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

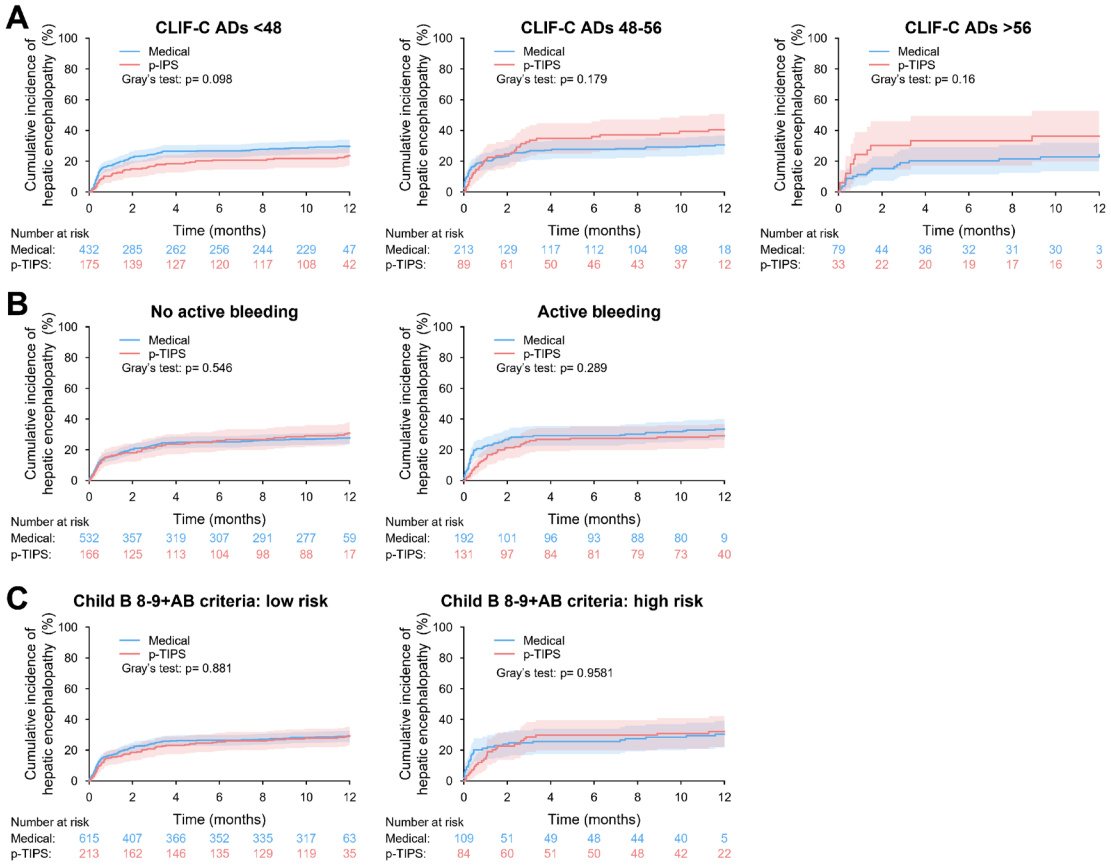


Fig. S9: Effect of pre-emptive TIPS versus drug plus endoscopic therapy on the overt hepatic encephalopathy (OHE) stratified by different risk stratification rules in Child-Pugh B patients

(A) Cumulative incidence of OHE in pre-emptive TIPS group versus medical group stratified by CLIF-C ADs 48-56 grades, **(B)** active bleeding and **(C)** Child B 8-9+AB criteria based on competing risk approach (the Fine and Gray method) with death and liver transplantation being the competing events**.**

Note: Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: AB, active bleeding; CLIF-C AD score, Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

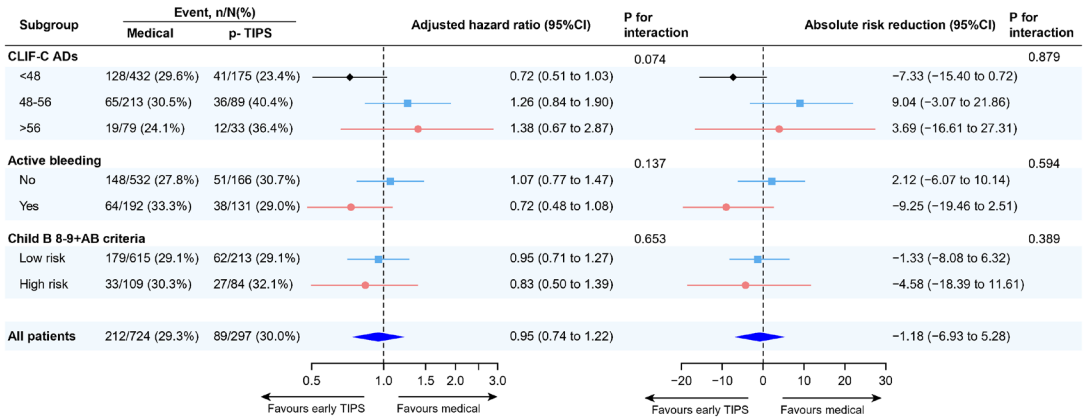


Fig. S10: **Forest showing the event rate, adjusted hazard ratios, and the absolute risk reduction for 1-year overt hepatic encephalopathy stratified by different risk stratification rules.**

In the forest plot, the adjust hazard ratios and absolute risk reduction for the early group compared with the medical group are shown. In the forest plot, the adjust hazard ratios and absolute risk reduction for the early group compared with the medical group are shown. Adjusted hazard ratios and absolute risk reduction with 95% confidence intervals (CI) indicate the effect of pre-emptive TIPS versus medical treatment (as reference) on overt hepatic encephalopathy, which are derived from multivariable competing risk regression models, adjusted for propensity score within each risk category.

Note: Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: AB, active bleeding; CLIF-C ADs, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

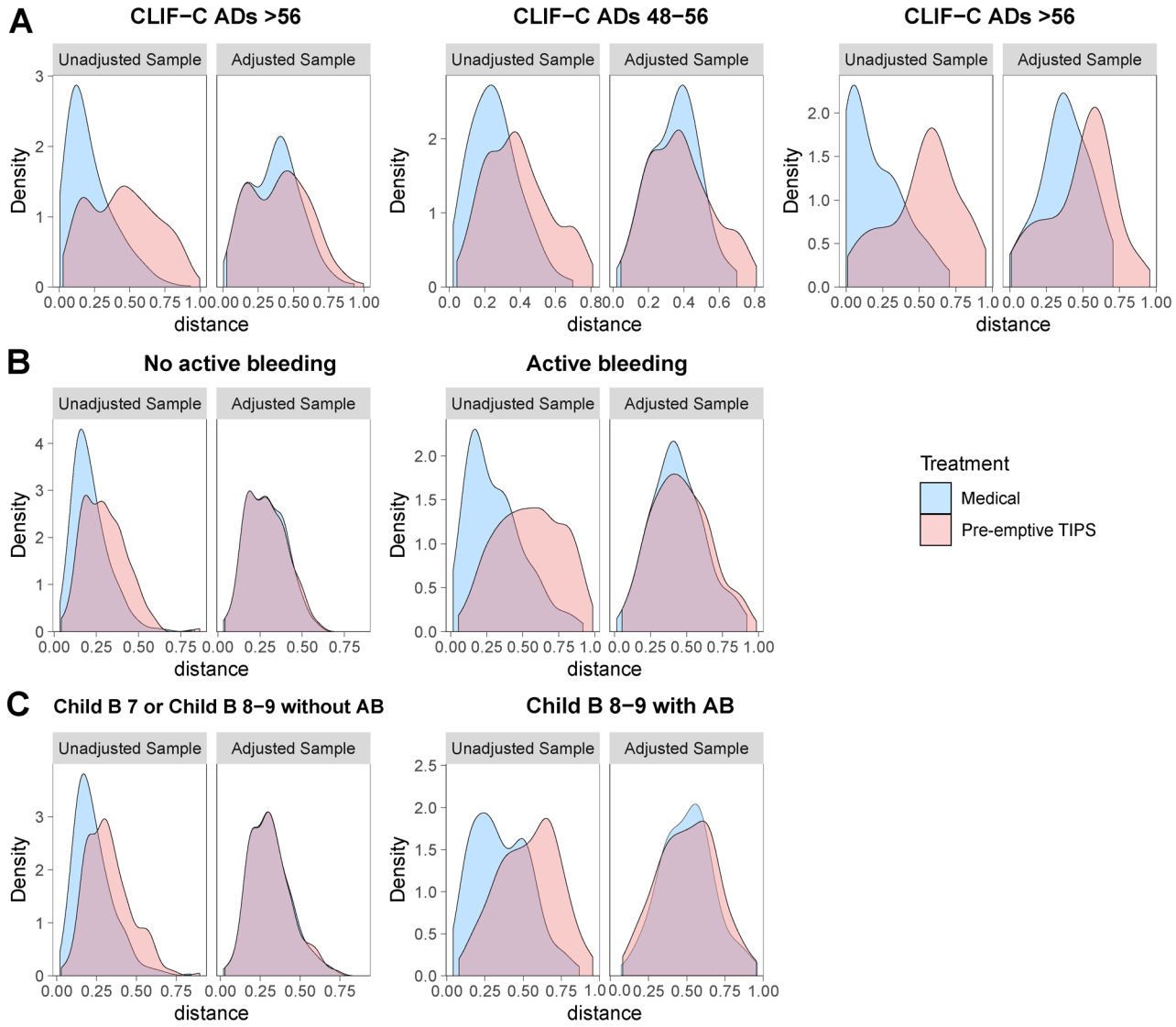


Fig. S11: Propensity score distribution in pre-emptive TIPS and medical group before and after matching stratified by different risk classification rules.

The density before matching on the left differ to a great degree. However, the density after matching on the right is very similar

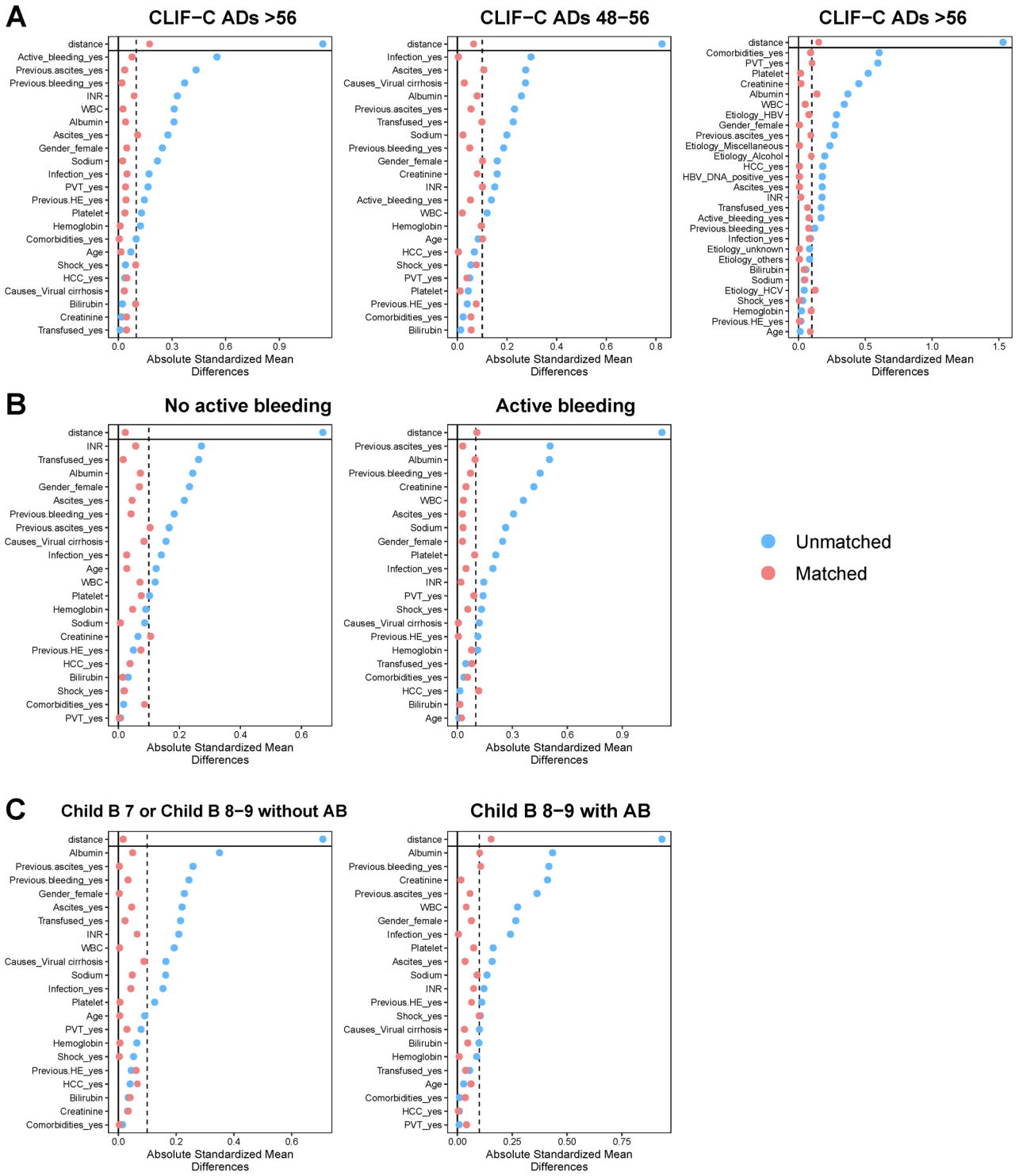


Fig. S12: **Assessment of balance before and after propensity matching between patients in pre-emptive TIPS and medical groups stratified by different risk classification rules.**

Balance of baseline characteristics between matched group was examined before and after matching using absolute standardized differences, with <10% considered good balance between groups. The standardized (mean) difference is a measure of distance between two group means in terms of one or more variables. In practice it is often used as a balance measure of individual covariates before and after

propensity score matching. As it is standardized, comparison across variables on different scales is possible.

Abbreviations: CLIF-C ADs, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; DBP, diastolic blood pressure; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HGB, Hemoglobin; MELD, Model for End-Stage Liver Disease; PVT, portal vein thrombosis; SBP, systolic blood pressure; WBC, white blood cell;

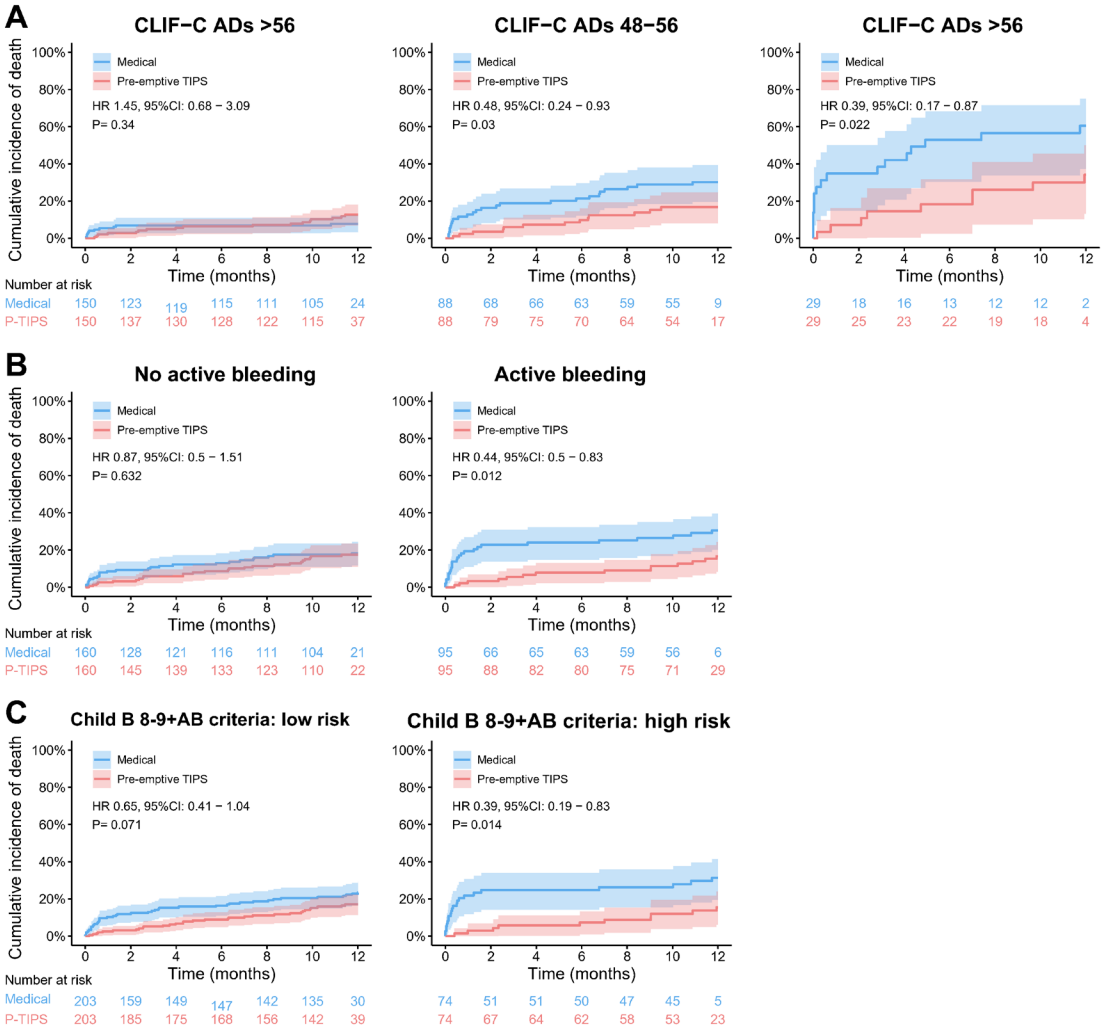


Fig. S13: Effect of pre-emptive TIPS versus drug plus endoscopic therapy on the mortality stratified by different risk classification rules in Child-Pugh B patients after propensity score matching.

Cumulative incidence of death in the pre-emptive TIPS group versus medical group stratified by (**A**) CLIF-C ADs 48-56 grades, (**B**) active bleeding and (**C**) Child B 8-9+AB criteria in Child-Pugh B patients after propensity score matching

Note: Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: AB, active bleeding; CLIF-C ADs, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

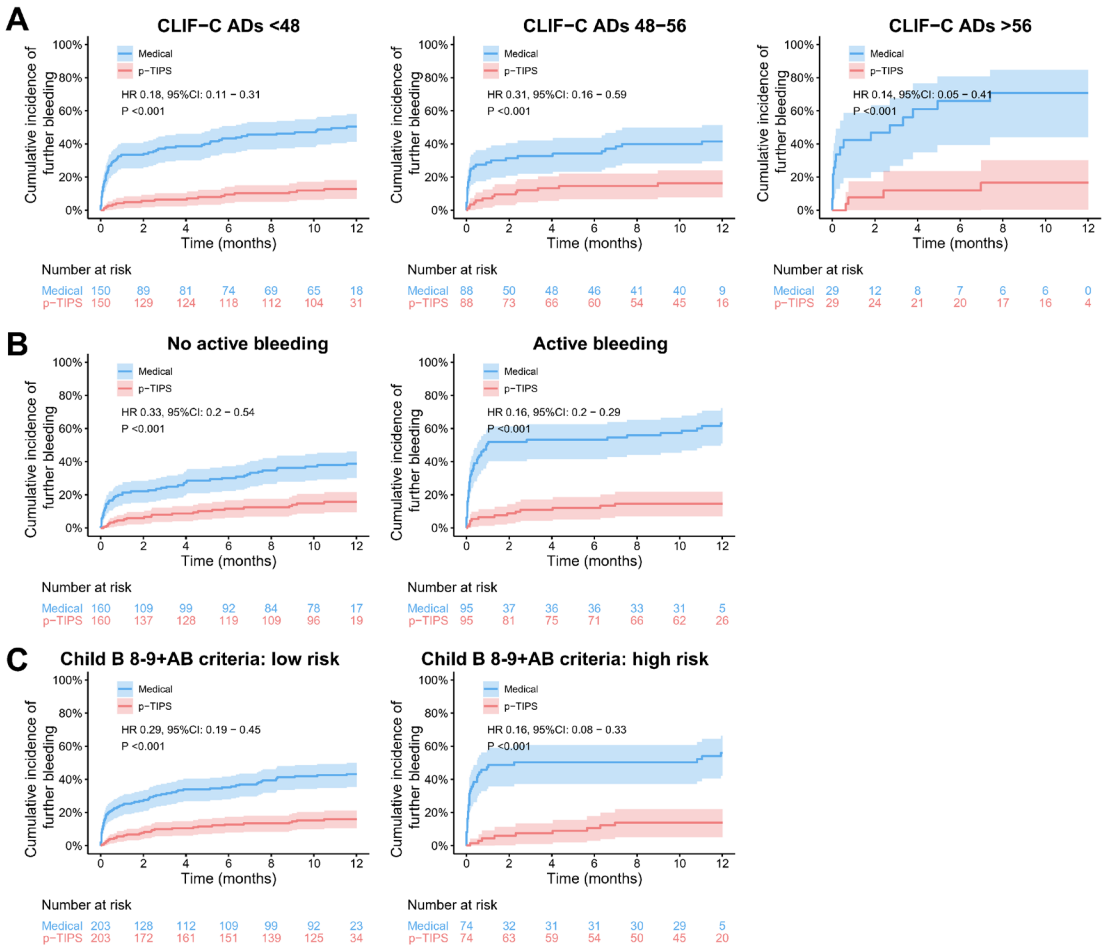


Fig. S14: Effect of pre-emptive TIPS versus drug plus endoscopic therapy on the further bleeding stratified by different risk classification rules in Child-Pugh B patients after propensity score matching.

Cumulative incidence of further bleeding in the pre-emptive TIPS group versus medical group stratified by (**A**) CLIF-C ADs 48-56 grades, (**B**) active bleeding and (**C**) Child B 8-9+AB criteria in Child-Pugh B patients after propensity score matching

Note: Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: AB, active bleeding; CLIF-C ADs, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

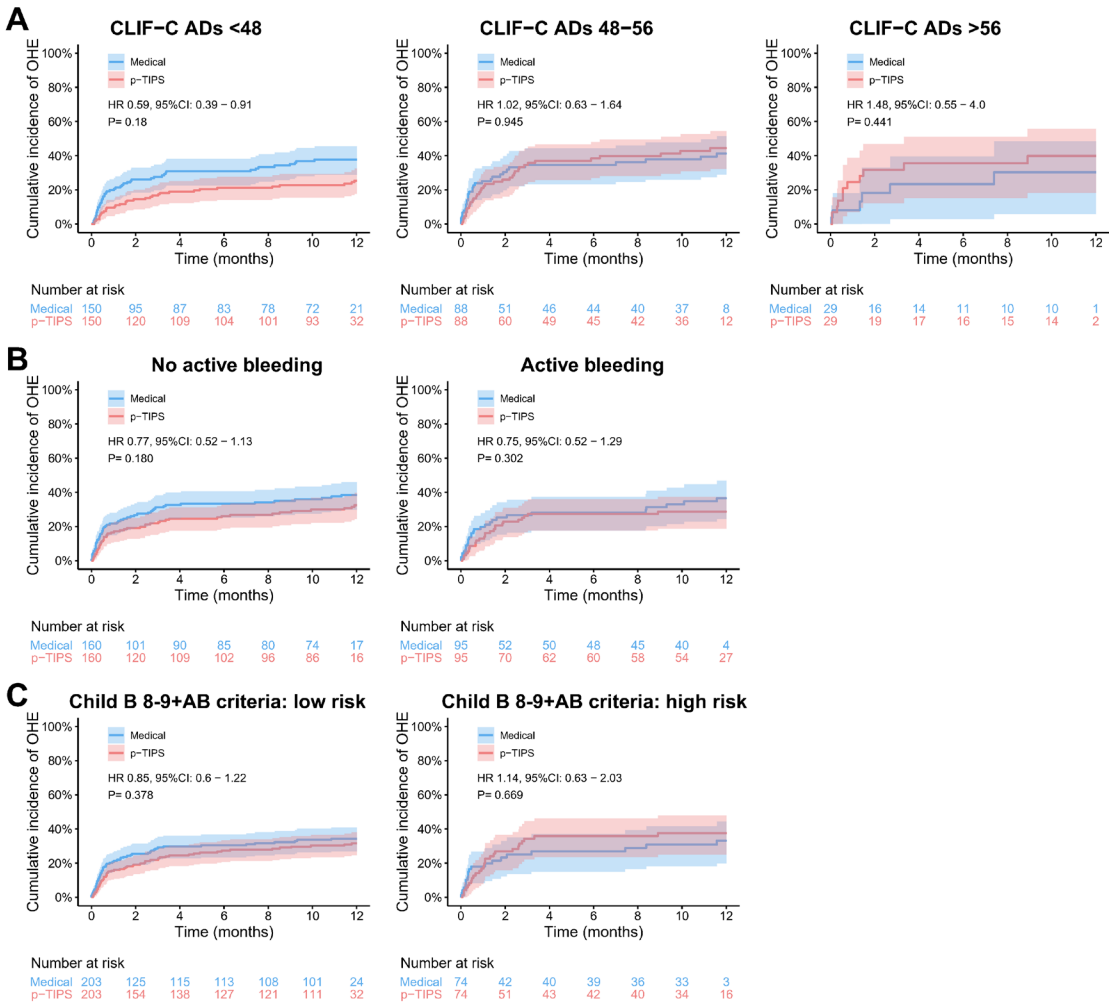


Fig. S15: Effect of pre-emptive TIPS versus drug plus endoscopic therapy on the overt hepatic encephalopathy stratified by different risk classification rules in Child-Pugh B patients after propensity score matching.

Cumulative incidence of overt hepatic encephalopathy (OHE) in the pre-emptive TIPS group versus medical group stratified by (**A**) CLIF-C ADs 48-56 grades, (**B**) active bleeding and (**C**) Child B 8-9+AB criteria in Child-Pugh B patients after propensity score matching

Note: Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: AB, active bleeding; CLIF-C ADs, European Foundation for the Study of Chronic Liver Failure Consortium Acute Decompensation score; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

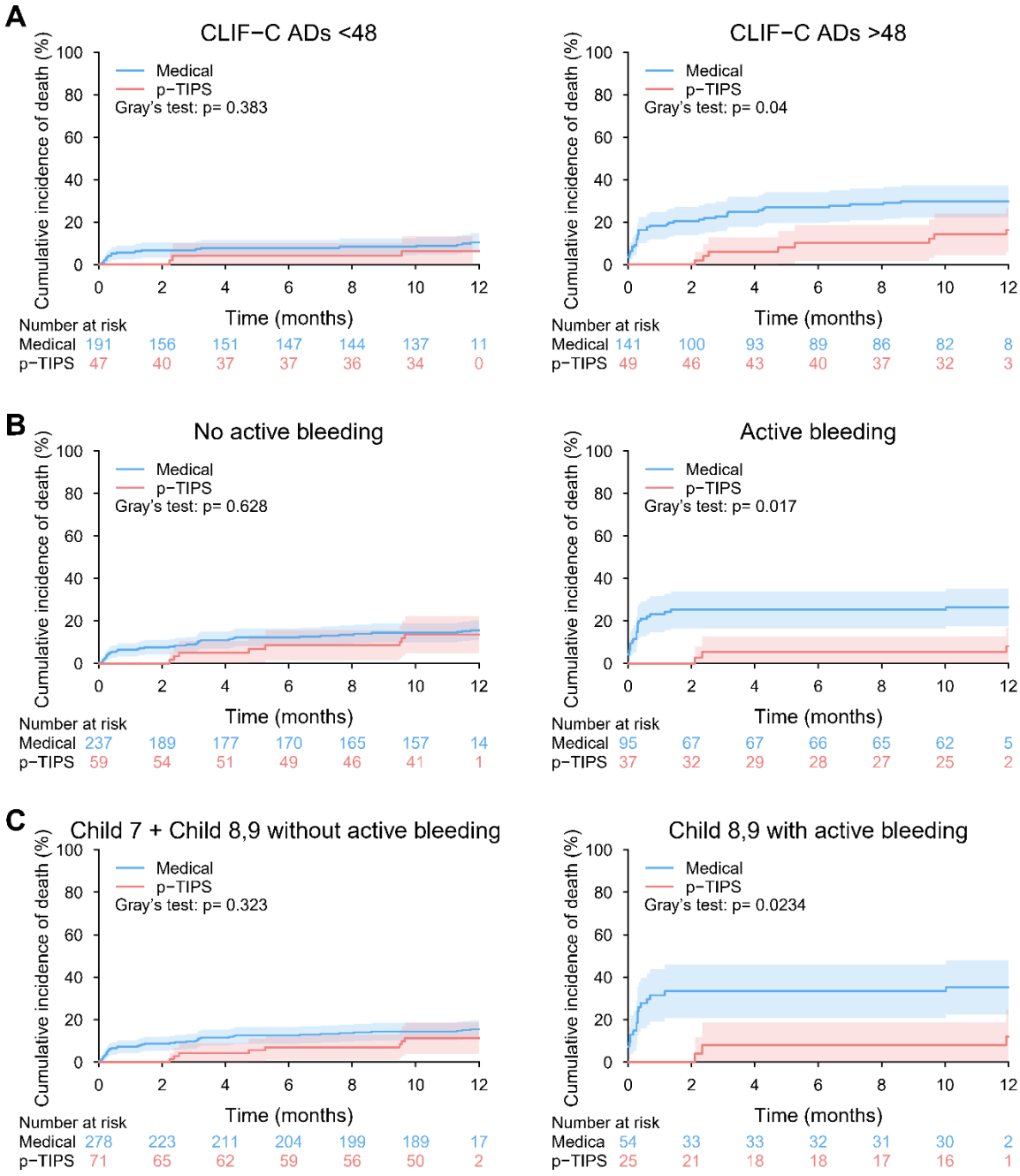


Fig. S16: Effect of pre-emptive TIPS versus drug plus endoscopic therapy on the mortality by different risk stratification rules in Child-Pugh B patients without previous bleeding

(A) Cumulative incidence of death in pre-emptive TIPS group versus medical group stratified by CLIF-C ADs 48 grade, **(B)** active bleeding and **(C)** Child B 8-9+AB criteria based on competing risk approach (the Fine and Gray method) with liver transplantation being the competing events**.**

Note: Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: CLIF-C ADs, chronic liver failure-consortium score for acute decompensation; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

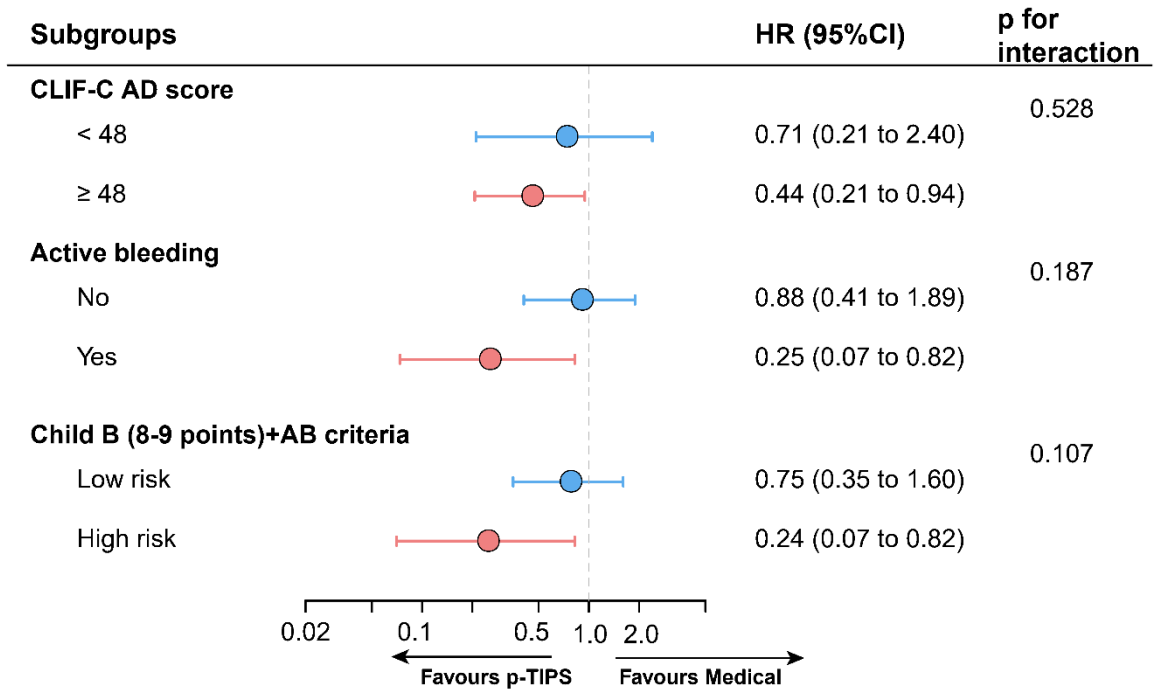
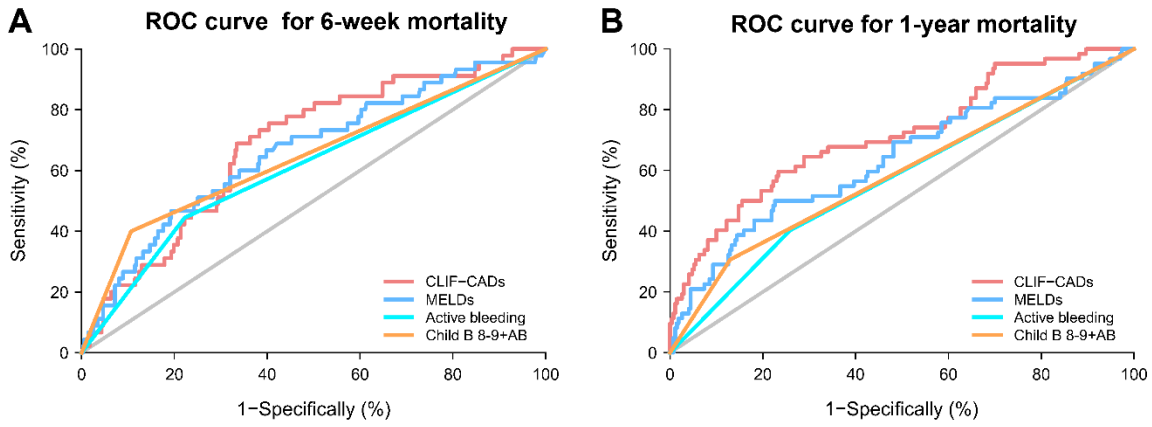


Fig. S17: Forest plot showing adjusted hazard ratios stratified by different risk stratification rules in Child-Pugh B patients without previous bleeding

Adjusted hazard ratios and absolute risk reduction with 95% confidence intervals (CI) indicate the effect of pre-emptive TIPS versus medical treatment (as reference) on the 1-year mortality, which are derived from multivariate competing risk regression models, adjusted for propensity score within each risk category.

Note: Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: CLIF-C ADs, chronic liver failure-consortium score for acute decompensation; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.



C **Discrimination of the evaluated risk stratification rules**

Models	6-week mortality		1-year mortality	
	C-for-risk	C-for-benefit	C-for-risk	C-for-benefit
CLIF-C ADs	0.684 (0.605 - 0.763)	0.638 (0.547 - 0.729)	0.717 (0.643 - 0.791)	0.645 (0.572 - 0.719)
MELD score	0.662 (0.574 - 0.751)	0.612 (0.514 - 0.709)	0.635 (0.552 - 0.718)	0.574 (0.505 - 0.643)
Active bleeding	0.611 (0.535 - 0.688)	0.603 (0.526 - 0.679)	0.572 (0.505 - 0.639)	0.547 (0.488 - 0.605)
Child B 8-9+AB	0.647 (0.573 - 0.721)	0.619 (0.542 - 0.696)	0.588 (0.527 - 0.650)	0.556 (0.501 - 0.611)

Fig. S18: Comparison of different risk stratification rules in patients without previous bleeding

The receiver operating characteristic curve (ROC) of the CLIF-C AD score, MELD score, active bleeding at endoscopy, and Child B 8-9+AB criteria for predicting (**A**) 6-week and (**B**) 1-year mortality. (**C**) Discrimination of the evaluated models. The concordance-statistic for benefit (c-for-benefit) is a variant of the conventional risk concordance-statistic (c-for-risk) designed to specifically calculate the ability for a model to discriminate between people having more treatment effect versus less benefit from a treatment (rather than just higher versus lower overall mortality risk). Note that the C-for-benefit statistic is in general much more conservative than the traditional concordance statistic, which only assesses the ability of a model to detect higher versus lower absolute mortality risk, not treatment effect.

Abbreviations: MELD, model for end-stage liver disease; CLIF-C ADs, chronic liver failure-consortium score for acute decompensation.

Table S1. Numbers of include patients in each participated center

Centers	Overall (n=1021)	Medical (n=724)	p-TIPS (n=297)
Xijing Hospital, Fourth Military Medical University, Xi'an	288 (28.2%)	147 (20.3%)	141 (47.5%)
First Affiliated Hospital of Nanchang University, Nanchang	303 (29.7%)	299 (41.3%)	4 (1.3%)
First Affiliated Hospital of Xi'an Jiaotong University, Xi'an	112 (11.0%)	81 (11.2%)	31 (10.4%)
Nanfang Hospital, Southern Medical University, Guangzhou	98 (9.6%)	61 (8.4%)	37 (12.5%)
Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing	45 (4.4%)	28 (3.9%)	17 (5.7%)
First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou	41 (4.0%)	30 (4.1%)	11 (3.7%)
Shandong Provincial Hospital affiliated to Shandong University, Jinan	33 (3.2%)	31 (4.3%)	2 (0.7%)
First Affiliated Hospital of Zhengzhou University, Zhengzhou	28 (2.7%)	5 (0.7%)	23 (7.7%)
Third Affiliated Hospital of Sun Yat-sen University, Guangzhou	27 (2.6%)	21 (2.9%)	6 (2.0%)
The First Affiliated Hospital of Soochow University, Suzhou	20 (2.0%)	8 (1.1%)	12 (4.0%)
Second Affiliated Hospital of Kunming Medical University, Kunming	14 (1.4%)	2 (0.3%)	12 (4.0%)
First Affiliated Hospital of Xinjiang Medical University, Urumqi	9 (0.9%)	8 (1.1%)	1 (0.3%)
Henan Provincial People's Hospital, Zhengzhou	3 (0.3%)	3 (0.4%)	0 (0.0%)

Table S2. Univariable and multivariable analysis of factors associated with 1-year further bleeding in the entire cohort (n=1021)

Variables	Univariable analysis		Multivariable analysis (model 1)		Multivariable analysis (model 2)		Multivariable analysis (model 3)	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Treatment (p-TIPS vs medical)	0.27 (0.19 to 0.38)	<0.001	0.24 (0.17 to 0.34)	<0.001	0.25 (0.18 to 0.35)	<0.001	0.24 (0.17 to 0.34)	<0.001
Age (per year increase)	1.01 (1.00 to 1.02)	0.091	1.01 (1.00 to 1.02)	0.013			1.01 (1.00 to 1.02)	0.014
Gender (female vs male)	0.80 (0.63 to 1.02)	0.077	0.89 (0.68 to 1.15)	0.366	0.94 (0.73 to 1.21)	0.622	0.90 (0.69 to 1.17)	0.423
MELD score (per point increase)	1.02 (0.98 to 1.05)	0.302	1.03 (1.00 to 1.06)	0.072				
CLIF-C ADs (per point increase)	1.02 (1.00 to 1.03)	0.015			1.01 (1.00 to 1.03)	0.057		
Active bleeding (yes vs no)	1.20 (0.95 to 1.52)	0.117	1.40 (1.10 to 1.78)	0.007	1.35 (1.06 to 1.71)	0.014	1.38 (1.08 to 1.76)	0.009
WBC (per 1×10^9cell/L increase)	1.01 (0.99 to 1.04)	0.214						
Platelet count (per 1×10^9/L increase)	1.002 (1.001 to 1.004)	0.022	1.002 (1.001 to 1.004)	0.009	1.002 (1.000 to 1.004)	0.051	1.002 (1.001 to 1.004)	0.010
INR (per unit increase)	1.02 (0.76 to 1.36)	0.898					1.19 (0.91 to 1.56)	0.210
Bilirubin (per mg/dL increase)	1.05 (0.98 to 1.13)	0.198					1.05 (0.98 to 1.12)	0.137
Serum albumin (per g/L increase)	0.97 (0.95 to 0.99)	0.01	1.00 (0.97 to 1.02)	0.803	1.00 (0.97 to 1.02)	0.879	1.00 (0.97 to 1.02)	0.708
Creatinine (per mg/dL increase)	1.23 (0.98 to 1.53)	0.07					1.14 (0.90 to 1.45)	0.268
Comorbidities‡ (yes vs no)	1.37 (1.07 to 1.74)	0.012	1.45 (1.11 to 1.88)	0.006	1.51 (1.17 to 1.94)	0.002	1.47 (1.13 to 1.91)	0.004
Portal vein thrombosis (yes vs no)	1.01 (0.75 to 1.36)	0.928	1.10 (0.81 to 1.48)	0.546	1.09 (0.81 to 1.47)	0.581	1.10 (0.81 to 1.49)	0.533
Hepatocellular carcinoma (yes vs no)	2.63 (1.67 to 4.15)	<0.001	2.60 (1.64 to 4.13)	<0.001	2.68 (1.69 to 4.24)	<0.001	2.64 (1.66 to 4.18)	<0.001
Infection admission (yes vs no)	1.23 (0.84 to 1.82)	0.286	1.04 (0.70 to 1.55)	0.849	0.93 (0.61 to 1.41)	0.734	1.03 (0.69 to 1.54)	0.894
Shock at admission* (yes vs no)	1.19 (0.90 to 1.57)	0.218	1.05 (0.79 to 1.39)	0.747	1.02 (0.77 to 1.35)	0.883	1.04 (0.78 to 1.38)	0.788
Blood transfusion (yes vs no)	2.12 (1.66 to 2.70)	<0.001	1.97 (1.53 to 2.54)	<0.001	1.97 (1.54 to 2.54)	<0.001	1.96 (1.52 to 2.53)	<0.001

Only variables with a p value <0.1 in the univariable analysis are shown. Variables selected into the univariable analysis were gender, age, etiology of cirrhosis, HBV-DNA or HCV-RNA detectable, MELD score, location of varices at index gastroscopy, grade of esophageal varices, ascites, hepatic encephalopathy, previous bleeding, hemoglobin, serum albumin, serum total bilirubin, INR, serum creatinine, commodities, portal vein thrombosis, hepatocellular carcinoma, heart rate at admission, infection at admission, shock at admission, transfusion requirement.

‡ Commodities include hypertension, coronary artery disease, and diabetes.

* Hypovolemic shock was defined as systolic blood pressure <100 mmHg and heart rate >100 bpm.

Abbreviations: CLIF-C ADs, Chronic Liver Failure Consortium Acute Decompensation score; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt; WBC, white blood cell.

Table S3: **Impact of pre-emptive TIPS (versus drug plus endoscopic therapy) on 1-year further bleeding according to different risk classification rules**

Risk classification	No. of patients (%)	Univariable Models Unadjusted Estimates			Multivariable Models Adjusted for the Baseline Predictive Variables †			
		HR (95%CI)	P value	P for interaction	HR (95%CI)	P value	P for interaction	Variables adjusted for
CLIF-C ADs 48-56				0.887			0.722	
<48	607 (59.4%)	0.24 (0.15 to 0.40)	< 0.001		0.20 (0.12 to 0.33)	<0.001		Active bleeding, PLT, HCC, PVT, blood transfusion
48-56	302 (29.6%)	0.29 (0.17 to 0.52)	< 0.001		0.28 (0.16 to 0.50)	<0.001		Active bleeding, INR, HCC, PVT, blood transfusion
>56	112 (11.0%)	0.27 (0.12 to 0.61)	0.0015		0.25 (0.11 to 0.57)	0.001		Active bleeding, PLT, HCC, PVT, blood transfusion
Active bleeding				0.175			0.133	
No	698 (68.4%)	0.31 (0.20 to 0.48)	<0.001		0.30 (0.19 to 0.48)	<0.001		HCC, PVT, comorbidities, blood transfusion
Yes	323 (31.6%)	0.19 (0.12 to 0.33)	<0.001		0.18 (0.11 to 0.31)	<0.001		WBC, PLT, HCC, PVT, blood transfusion
Child B 8-9+AB criteria ‡				0.088			0.078	
Low risk	828 (81.1%)	0.30 (0.21 to 0.45)	<0.001		0.28 (0.19 to 0.42)	<0.001		HCC, PVT, comorbidities, blood transfusion
High risk	193 (18.9%)	0.16 (0.08 to 0.31)	<0.001		0.17 (0.08 to 0.33)	<0.001		WBC, PLT, HCC, PVT, blood transfusion

† We adjusted these variables on the basis of their associations with the outcomes of interest or a change in effect estimates of more than 10%.

‡ **Child B 8-9+AB criteria:** Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: CLIF-C ADs, Chronic Liver Failure Consortium Acute Decompensation score; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HCC; hepatocellular carcinoma; INR, international normalized ratio; PLT, platelet count; PVT, portal vein thrombosis; WBC, white blood cell.

HR, hazard ratio for the effect of pre-emptive TIPS versus medical treatment (as reference).

Table S4: Univariable and multivariable analysis of factors associated with 1-year overt hepatic encephalopathy in the entire cohort (n=1021)

	Univariable analysis		Multivariable analysis (model 1)		Multivariable analysis (model 2)		Multivariable analysis (model 3)	
Variables	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**
Treatment (p-TIPS vs medical)	0.91 (0.71 to 1.17)	0.481	0.87 (0.67 to 1.13)	0.289	0.88 (0.68 to 1.14)	0.326	0.86 (0.66 to 1.12)	0.266
Age (per year increase)	1.00 (0.99 to 1.01)	0.546	1.00 (0.99 to 1.01)	0.736			1.00 (0.99 to 1.01)	0.654
MELD score (per point increase)	1.03 (1.00 to 1.07)	0.049	1.04 (1.00 to 1.07)	0.037				
CLIF-C ADs (per point increase)	1.01 (1.00 to 1.03)	0.085			1.01 (1.00 to 1.02)	0.142		
Active bleeding (yes vs no)	1.20 (0.95 to 1.53)	0.129	1.22 (0.95 to 1.56)	0.118	1.21 (0.94 to 1.54)	0.137	1.22 (0.95 to 1.56)	0.124
HE at admission (yes vs no)	1.56 (0.91 to 2.67)	0.104	1.68 (0.97 to 2.89)	0.062	1.65 (0.96 to 2.84)	0.071	1.67 (0.96 to 2.88)	0.068
INR (per unit increase)	1.22 (0.93 to 1.59)	0.146					1.22 (0.93 to 1.60)	0.143
Bilirubin (per mg/dL increase)	0.98 (0.89 to 1.07)	0.628			0.98 (0.89 to 1.08)	0.673	0.98 (0.89 to 1.08)	0.658
Serum albumin (per g/L increase)	0.98 (0.96 to 1.00)	0.072	0.98 (0.96 to 1.01)	0.134	0.99 (0.96 to 1.01)	0.257	0.98 (0.96 to 1.01)	0.176
Creatinine (per mg/dL increase)	1.13 (0.87 to 1.45)	0.366					1.13 (0.88 to 1.45)	0.352
Sodium (per mmol/L increase)	0.99 (0.97 to 1.01)	0.505					0.99 (0.97 to 1.01)	0.406
Hepatocellular carcinoma (yes vs no)	1.73 (1.01 to 2.97)	0.044	1.76 (1.03 to 3.01)	0.040	1.70 (1.00 to 2.92)	0.052	1.74 (1.01 to 2.98)	0.044
Shock at admission† (yes vs no)	1.27 (0.96 to 1.68)	0.097	1.22 (0.91 to 1.62)	0.183	1.24 (0.93 to 1.65)	0.144	1.22 (0.92 to 1.63)	0.170

Only variables with a p value <0.1 in the univariable analysis are shown. Variables selected into the univariable analysis were gender, age, etiology of cirrhosis, HBV-DNA detectable, MELD score, location of varices at index gastroscopy, grade of esophageal varices, ascites, hepatic encephalopathy, previous bleeding, hemoglobin, serum albumin, serum total bilirubin, INR, serum creatinine, commodities, portal vein thrombosis, hepatocellular carcinoma, heart rate at admission, infection at admission, shock at admission and transfusion requirement.

† Hypovolemic shock was defined as systolic blood pressure <100 mmHg and heart rate >100 beat per minute.

Abbreviations: CLIF-C ADs, Chronic Liver Failure Consortium Acute Decompensation score; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; p-TIPS, pre-emptive transjugular intrahepatic portosystemic shunt.

Table S5. Impact of pre-emptive TIPS (versus drug plus endoscopic therapy) on overt hepatic encephalopathy according to different risk classification rules in entire cohort (n=1021)

Risk classification	No. of patients (%)	Univariable Models Unadjusted Estimates			Multivariable Models Adjusted for the Baseline Predictive Variables			
		HR (95%CI)	P value	P for interaction	HR (95%CI)	P value	P for interaction	Variables adjusted for †
CLIF-C ADs 48-56				0.083			0.094	
<48	607 (59.4%)	0.71 (0.50 to 1.01)	0.053		0.70 (0.47 to 1.02)	0.064		Age, INR, bilirubin, albumin, creatinine, shock
48-56	302 (29.6%)	1.23 (0.82 to 1.84)	0.326		1.16 (0.76 to 1.78)	0.479		Age, WBC, active bleeding, bilirubin, HCC, shock, PLT
>56	112 (11.0%)	1.30 (0.63 to 2.68)	0.474		1.12 (0.53 to 2.36)	0.771		Age, WBC, INR, bilirubin, albumin, creatinine
Active bleeding				0.127			0.117	
No	698 (68.4%)	1.04 (0.75 to 1.42)	0.828		1.01 (0.73 to 1.41)	0.941		Age, WBC, INR, bilirubin, albumin, creatinine, shock, PVT
Yes	323 (31.6%)	0.70 (0.47 to 1.04)	0.076		0.69 (0.45 to 1.07)	0.095		INR, bilirubin, creatinine, HCC, shock
Child B 8-9+AB criteria‡				0.685			0.622	
Low risk	828 (81.1%)	0.92 (0.69 to 1.22)	0.554		0.90 (0.66 to 1.22)	0.481		Age, WBC, INR, bilirubin, albumin, creatinine, shock, PVT
High risk	193 (18.9%)	0.81 (0.49 to 1.35)	0.423		0.79 (0.47 to 1.34)	0.790		Age, creatinine, HCC, bilirubin, shock

† We adjusted these variables on the basis of their associations with the outcomes of interest or a change in effect estimates of more than 10%.

‡ Child B 8-9+AB criteria: Low risk: Child-Pugh B without active bleeding and Child-Pugh B 7 points with active bleeding; High risk: Child-Pugh B 8-9 points with active bleeding at endoscopy.

Abbreviations: CLIF-C ADs, Chronic Liver Failure Consortium Acute Decompensation score; HCC; hepatocellular carcinoma; INR, international normalized ratio; PLT, platelet count; PVT, portal vein thrombosis; WBC, white blood cell. HR, hazard ratio for the effect of pre-emptive TIPS versus medical treatment (as reference).