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Mortality after transjugular intrahepatic portosystemic shunt in older adult cirrhotic patients: a validated prediction model

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ABSTRACT

Background & Aims: Implantation of a transjugular intrahepatic portosystemic shunt (TIPS) improves survival in cirrhotic patients with refractory ascites and portal hypertensive bleeding. However, the indication for TIPS in older adult patients (≥70 years) is debated and a specific prediction model developed in this particular setting is lacking. The aim of this study was to develop and validate a multivariable model for an accurate prediction of mortality in older adults. **Approach & Results:** We prospectively enrolled 411 consecutive patients observed at 4 referral centers with *de novo* TIPS implantation for refractory ascites or secondary prophylaxis of variceal bleeding (derivation cohort) and an external cohort of 415 patients with similar indications for TIPS (validation cohort). Older adult patients in the two cohorts were 99 and 76 respectively. A cause-specific Cox competing risks model was used to predict liver-related mortality, with orthotopic liver transplant and death for extrahepatic causes as competing events. Age, alcoholic etiology, creatinine levels and international normalized ratio in the overall cohort, and creatinine and sodium levels in older adults were independent risk factors for liver-related death by multivariable analysis.

Conclusions: After TIPS implantation, mortality is increased by ageing, but TIPS placement should not be precluded in patients older than 70 years. In older adults, creatinine and sodium levels are useful predictors for decision making. Further efforts to update the prediction model with larger sample size are warranted.

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List of abbreviations: TIPS, transjugular intrahepatic portosystemic shunt; RA, refractory ascites; OLT, orthotopic liver transplantation; MELD, model for end-stage liver disease; FIPS, Freiburg index of post-TIPS survival; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; GFR, glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration; PSPG, portosystemic pressure gradient; SD, standard deviation; IQR, interquantile range; CIF, cumulative incidence function; ExPeCT, Elderly Patients Calculator TIPS; INR, international normalized ratio; MICE, multivariable imputation by chained equations; AUROC, area under the receiver operating characteristic curve; AUD, alcohol use disorder; AUC, area under the ROC curve; CI, confidence intervals.

Transjugular intrahepatic portosystemic shunt (TIPS) represents a well-established intervention for the treatment of portal hypertension-related complications of cirrhosis, improving survival in patients with refractory ascites (RA) and portal hypertensive bleeding [1-3]. Patients who receive TIPS may experience further decompensating events, needing orthotopic liver transplantation (OLT). Nevertheless, indications to TIPS placement have extended over time, including older adult patients with comorbidities. Different scores, such as the Child-Pugh score, the model for end-stage liver disease (MELD) score, and the recently published Freiburg index of post-TIPS survival (FIPS) have been proposed to identify patients with a high risk of mortality [4-6]. However, these scores do not take into account the technical improvements achieved during the last decades, such as the introduction of self-expandable covered stents, the technique of TIPS underdilation or the use of controlled-expansion devices [2,7,8]. Moreover, they were developed without considering OLT and extrahepatic death as events competing with liver-related death and were not specifically derived and validated in older adults. Finally, the discriminative accuracy remains the main focus in the evaluation of performance, whereas calibration often receives less attention [9].

The aims of this prospective multicenter study were to derive and validate a model able to predict liver-related mortality after TIPS placement for RA or secondary prophylaxis of variceal bleeding in a population of older adult patients.

Methods

Study design and patients

Patients with cirrhosis of any etiology receiving TIPS for RA or for secondary prophylaxis of variceal bleeding consecutively observed between October 2010 and March 2021 at 4 Italian tertiary referral centers (University Hospitals of Florence, Modena, Padua, and Rome) with high expertise in TIPS placement were prospectively enrolled as derivation cohort. A cohort of patients receiving TIPS for the same indications between January 2007 and December 2019 at the Istituto Mediterraneo per i Trapianti e Terapie ad Alta

Specializzazione (ISMETT), Palermo (Italy) were included as validation cohort. In both derivation and validation cohorts, all patients underwent TIPS placement using Viatorr covered stent grafts (Gore, Flagstaff, Ariz). Additional characteristics of the devices used in this study are reported in Supplementary Methods. Patients aged 70 years or older were defined as the 'older adult' group. Inclusion criteria were: a) diagnosis of cirrhosis according to clinical history, histology or imaging; b) TIPS placed to prevent recurrence of variceal bleeding or to treat RA. Exclusion criteria were: a) emergency TIPS placed in the setting of acute variceal bleeding as preemptive or rescue TIPS; b) non-cirrhotic portal hypertension; c) hepatocellular carcinoma (HCC) outside of Milan criteria. Absolute contraindications to TIPS were: 1) severe liver failure (Child-Pugh >11, serum bilirubin >5mg/dL, MELD >18); 2) severe organic renal failure (serum creatinine >3mg/dL); 3) heart failure; 4) severe porto-pulmonary hypertension (mean pulmonary artery pressure >45 mm Hg at right heart catheterization); 5) recurrent or persistent overt hepatic encephalopathy (HE) grade ≥2 (West-Heaven scale) despite adequate treatment; 6) uncontrolled sepsis.

For derivation and validation cohorts, patient data were recorded at the time of TIPS placement in an anonymized Excel case report form shared by the participating centers, as part of a multicenter Italian survey (RI-TIPS, Italian Registry of TIPS), which included demographic and clinical data, etiology of cirrhosis, previous history of hepatic encephalopathy (HE), biochemistry (serum bilirubin, albumin, creatinine, sodium, international normalized ratio [INR], platelet count, glomerular filtration rate [GFR], calculated according to Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), Child-Pugh, MELD and MELD-Na score, indication to TIPS placement (RA or secondary prophylaxis of variceal bleeding), porto-systemic pressure gradient (PSPG) before and after TIPS placement, and TIPS dilation diameter. Under-dilated TIPS was defined as a balloon dilation diameter ≤7 mm. The etiology of cirrhosis was established according to the evaluation of the treating clinician at the time of inclusion in the study.

The RI-TIPS survey was approved by Ethical Committee of the University of Florence and by ethical committees of all participating centers. It complied with the ethical principles reported in the Declaration of Helsinki. All patients gave consent to provide their data at the time of TIPS placement.

Follow-up and outcomes

All patients were followed-up as outpatients every 6 months until the end of study, or when clinically indicated (recurrence of portal hypertension complications, TIPS dysfunction or other events). Scheduled control visits included physical examination and blood tests. At each visit, all patients were carefully assessed for overt HE by physical examination. HE was graded according to international guidelines [10,11]. Doppler ultrasonography of TIPS was performed 2 weeks and 3 months after TIPS placement and every 6 months thereafter.

The primary outcome was liver-related death, defined as caused by liver failure (including cases precipitated by infections), portal hypertensive bleeding, hepatorenal syndrome, or HCC. OLT and death for extrahepatic causes were considered as competing events. In the older adult group, the only competing event was death for extrahepatic causes.

Secondary outcomes included: 1) ascites recurrence at 6 months after TIPS placement in patients with RA; 2) variceal bleeding recurrence at any time in patients receiving TIPS for secondary prophylaxis of variceal bleeding; 3) TIPS dysfunction; and 4) the incidence of at least one episode of HE grade 2 or higher.

Statistical analysis

Data for continuous variables are expressed as mean (standard deviation, SD) or median (interquartile range, IQR). Data for categorical variables are expressed as frequency (percentage).

Probability of liver-related death was evaluated by competing risks survival analysis, represented by cumulative incidence function (CIF) [12], with OLT and death for extrahepatic causes considered as competing events. Transplant-free survival was computed by Kaplan-Meier method as supplementary analysis and it was defined as the time from inclusion in the study to liver transplant or death from any cause.

All prediction models were developed and validated according to TRIPOD statements [13] (Supplementary Table S1).

Cox cause-specific model was fitted in order to estimate the effect of covariates on CIFs for liver-related mortality [12]. To estimate the baseline hazard function, the methods proposed by Ozenne et al. [14] were employed, using the function predictCox from the R package riskRegression. Two prediction models were developed: the first in the overall cohort and the second in older adults. These prediction models have been translated into a webapp freely available to the public (ExPeCT, Elderly Patients Calculator TIPS, https://promisepa.shinyapps.io/TIPS/).

Covariates were entered in the multivariable analysis by a stepwise forward selection. We pre-defined a subgroup analysis according to TIPS indication (RA and secondary prophylaxis of variceal bleeding). Variables screened were age, sex, etiology of cirrhosis, bilirubin, albumin, INR, creatinine, sodium, platelet count, indication to TIPS (RA versus secondary prophylaxis of variceal bleeding) and TIPS dilation diameter. For all these variables, missing data were imputed according to Van Buuren et al. [15], by using the Multivariable Imputations by Chained Equations (MICE) algorithm. Covariates in the final model with a p-value <0.05 were considered statistically significant. Composite covariates (i.e. Child-Pugh class, MELD) were not included in the multivariable model to avoid collinearity with the individual score items. According to TRIPOD guidelines [13], results are presented as beta coefficients, standard error and p values. Details on sample size calculation are reported in Supplementary Materials.

Risks factors for liver-related mortality identified by competing risks multivariable analysis were used to generate a prediction model. The predicted probability of dying for liver-related causes after TIPS placement was computed for hypothetical patients identified by a combination of prognostic factors.

External validation was performed in a cohort of patients consecutively enrolled at ISMETT (Palermo). The performance of the two prediction models (overall cohort model and older adults model) was assessed by discrimination and calibration.

Discrimination of the models was assessed by the area under the receiver operating characteristic curve (AUROC) and by Harrell's c-index. To estimate the ROC curves in the presence of censoring and different timepoints, we used the function risksetROC from the R package risksetROC. This function plots ROC based on incident/dynamic definition by Heagerty et al. [16]. AUROCs of the models obtained in the derivation cohort were compared with those provided by the recently published FIPS score [6].

Calibration was evaluated by two approaches. The first, according to Crowson et al [17], evaluated 'calibration in the large' and calibration slope. 'Calibration in the large' compares the event rate with the average predicted risk by the estimation of a model intercept, which has target value of 0, with negative values suggesting overestimation and positive values suggesting underestimation. The calibration slope has a target value of 1 with values <1 suggesting that estimated risks are too extreme (overfitting), while values >1 suggest that estimated risks are not extreme enough (underfitting). The second approach, based on Gerds et al. [18], evaluated calibration plots of predicted versus observed 1- and 2-year event rates.

All analyses were performed in R core Team (version 4.0.3).

Results

Baseline characteristics

Baseline characteristics of the 411 patients in the derivation cohort, stratified according to age (higher or lower than of 70 years) are shown in Table 1. Missing data of baseline characteristics of the derivation cohort are reported in Supplementary Table S2. Mean age was 59 years in patients younger than 70 years and 74 years in older adults. Age distribution of older adults (n=99) is shown in Supplementary Figure S1 and 38% of patients were older than 74 years. Alcohol use disorder (AUD) was the most common etiology (37%), followed by viral infection (30%). At the time of TIPS placement, AUD was present as a main or concomitant etiology of liver disease in 181 patients, out of whom 145 (80.1%) were abstinent, while 36 (19.9%) had an active alcohol consumption. Most of patients were in Child-Pugh class B (71%) and the

mean MELD score was 12. The indication for TIPS was RA in 221 (54%) patients and secondary prophylaxis of variceal bleeding in 190 (46%) patients. Compared to younger patients, older adults had significantly higher prevalence of viral etiology (41%) and lower prevalence of AUD (18%). In terms of liver function, older adult patients had a significantly less advanced liver disease as showed by INR levels and higher prevalence of Child-Pugh class A (26%). As expected, older adults had significantly higher creatinine levels, when compared to younger patients. Indications for TIPS placement were not significantly different according to age. In older adult patients, median TIPS dilation diameter was significantly lower and the prevalence of under-dilated TIPS (≤7 mm) was significantly higher compared to patients younger than 70 years.

Follow-up events

During a median follow-up time of 19.6 months (IQR 32 months), 99 out of 411 patients (24%) died for liver-related causes, 49 (12%) patients underwent OLT and 17 patients (4%) died for extrahepatic causes. Among 99 older adults, 44 (44%) died for liver-related causes, 7 (7%) patients died for extrahepatic causes and no one underwent OLT. In the overall cohort, the probabilities of liver-related death at 1-, 2- and 3-years were 13%, 17% and 24%, respectively (Figure 1). Probability of liver-related death was higher in older adult patients (19%, 30% and 41% at 1, 2 and 3 years, respectively) compared to patients younger than 70 years (12%, 14% and 21% at 1, 2 and 3 years, respectively).

In the overall cohort, cumulative probabilities of OLT were 7% at 1 year and 12% at 2 and 3 years. Cumulative probabilities of extrahepatic death were 3% at 1 and 2 years and 5% at 3 years (Supplementary Figure S2). Cumulative incidence of extrahepatic death between older adult patients and patients younger than 70 years are shown in Supplementary Figure S3. Only one older patient died after TIPS for cardiac decompensation. Transplant-free survival (i.e. considering OLT as death) was not significantly different between patients younger than 70 years and older adult patients (p=0.07, Figure 2). Of note, survival curves clearly diverged after 5 years of follow-up.

Within three months after TIPS placement, ascites resolved in 148 out of 221 patients (67.0%, 95% CI 56.6-78.7%). The 6-month rate of ascites recurrence was 18.2%, 95% CI 12.3-25.4%. No significant differences between patients younger than 70 years and older adult patients (20.8% versus 7.1%, respectively, p=0.09) were observed. Among patients who placed TIPS for secondary prophylaxis of variceal bleeding, only 6 (3.2%, 95%CI 1.2-6.8%) experienced bleeding recurrence. Shunt dysfunction occurred in 12 out of 99 older adult patients (12.1%), and in 61 out of 312 patients younger than 70 years (19.5%) (p=0.09).

Liver-related mortality in the overall derivation cohort

Age, alcoholic etiology, creatinine levels and INR were independently associated with a higher risk of liver-related death, by multivariable analysis (Table 2). When age and creatinine were replaced by GFR, INR was the only independent predictor of death (Supplementary Table S3). The overall Harrell's c-index was 0.66 (95% CI 0.59-0.73). Areas under the ROC curve (AUC) of the model at 1-, 2- and 3-years are shown in Supplementary Figure S4. When AUCs of our prediction model were compared with those of the FIPS score a significantly better performance was observed in all comparisons (1-year 0.68 vs. 0.56, p=0.017; 2-year 0.69 vs. 0.56, p=0.002; 3-year 0.67 vs. 0.56, p=0.030).

The predicted probabilities of liver-related death according to risk factors for mortality (i.e. age, etiology of cirrhosis, creatinine levels, and INR) in four different patient profiles are shown in Figure 3. Probabilities of liver-related death at 1-, 2- and 3-year after TIPS placement were 4%, 6% and 9% in a young patient (50-years old) with favorable profile (viral etiology, creatinine 1 mg/dL, INR 1), 11%, 16% and 23% in an older adult (75-years old) with favorable profile, 56%, 70% and 83% in a young patient (50-years old) with unfavorable profile (alcoholic etiology, creatinine 2 mg/dL, INR 2), and 89%, 96% and 99% in an older adult (75-years old) with unfavorable profile.

Liver-related mortality in older adult patients of the derivation cohort

Creatinine (beta 1.07, standard error 0.37, p=0.004) and sodium levels (beta -0.08, standard error 0.033, p=0.022) were the two only independent predictors associated with liver-related mortality in older adult

patients, by multivariable analysis (Table 2). GFR was not significantly associated with liver-related mortality by univariate analysis.

The overall Harrell's c-index was 0.61 (95% CI 0.50-0.72). One-, 2- and 3-year AUCs of the model are shown in Supplementary Figure S5. When AUCs of our prediction model were compared with those of the FIPS score (1-year AUC 0.58, 2-year AUC 0.58 and 3-year AUC 0. 58), no significant differences were found (1-year p=0.36, 2-year p=0.72, 3-year p=0.60).

Figure 4 shows the predicted probabilities of liver-related death according to predictors of mortality (creatinine and sodium levels) in three different patient profiles in older adult patients in the derivation cohort. In patients with favorable profile (creatinine 1.2 mg/dL and sodium 140 mEq/L), probabilities of liver-related death were 14%, 26% and 34% at 1, 2 and 3 years, respectively. In patients with intermediate profile (creatinine 2 mg/dL and sodium 135 mEq/L), liver-related mortality was 40%, 63% and 75% at 1, 2 and 3 years, respectively. In patients with unfavorable profile (creatinine 2.5 mg/dL and sodium 130 mEq/L), liver-related mortality was 71%, 91% and 96% at 1, 2 and 3 years, respectively.

Liver-related mortality according to the indication for TIPS placement in the derivation cohort

Baseline characteristics of patients according to the indication for TIPS placement in the derivation cohort are shown in Supplementary Table S4. Cumulative probabilities of liver-related death are shown in Supplementary Figure S6.

In patients receiving TIPS for RA, age and INR were independently associated with liver-related mortality by multivariable analysis (Table 3). Harrell's c-index was 0.63 (95% CI 0.53-0.73). AUCs are shown in Supplementary Figure S7. Probabilities of liver-related death according to different risk profiles is showed in Supplementary Figure S8.

In patients undergoing TIPS for secondary prophylaxis of variceal bleeding, age, alcoholic etiology and INR were independently associated with liver-related mortality by multivariable analysis (Table 3). Harrell's c-

index was 0.67 (95% CI 0.57-0.78). AUCs are shown in Supplementary Figure S9. Probabilities of liver-related death according to different risk profiles is showed in Supplementary Figure S10.

External validation of the models for liver-related mortality according to the indication for TIPS placement is reported in Supplementary Methods, Supplementary Figure S7 and Supplementary Figure S9.

Hepatic encephalopathy after TIPS

After TIPS placement, 192 patients (46.7%) developed at least one episode of grade ≥2 HE. The median time to HE development was 42 days (IQR 150 days). The rate of HE occurrence, as well as the median time to HE development were not significantly different between older adults and patients younger than 70 years (51.5% vs 45.2%, respectively, p=0.48. 60 days versus 33 days, respectively, p=0.44).

Shunt reduction for HE was required in 4 out of 99 older adult patients (4.0%) and in 5 out of 312 patients younger than 70 years (1.6%, p=0.15).

Creatinine levels and TIPS diameter were significantly associated with the risk of HE after TIPS by multivariable analysis (Supplementary Table S5).

External validation of the model for liver-related mortality

A. Overall cohort

Baseline characteristics of patients in the validation cohort (n=415) are shown in Supplementary Table S6. Mean age was 63 years and viral etiology was the most prevalent (54%). Most of patients were in Child-Pugh class B (64%) and mean MELD score was 13. The most frequent indication to TIPS placement was RA in 74% of patients. Supplementary Table S7 compares baseline characteristics between validation and derivation cohorts. Comparisons according to TIPS indication are reported in Supplementary Table S8 for RA and in Supplementary Table S9 for secondary prophylaxis of variceal bleeding. Baseline characteristics of

patients according to the indication for TIPS placement in the validation cohort are shown in Supplementary Table S10.

Probabilities of liver-related death, OLT and extrahepatic death are reported in Supplementary Figure S11. Performance measures of the overall cohort model are reported in Supplementary Materials, Supplementary Figure S4 and in Supplementary Figure S12. We did not find any differences in liver-related death as well as in HE according to the type of stent graft in both derivation and in validation cohorts.

B. Older adults

Mean age was 73 years in older adults (n=76). Distribution of age in older adults is shown in Supplementary Figure S13 and 33% of patients were older than 74 years. It is important to underline that mean age of older adults was not significantly different between derivation and validation cohorts. In contrast, older adults in the validation cohort had a higher prevalence of type 2 diabetes and of HCV infection as etiology of liver disease. Moreover, they had significantly more advanced liver disease in terms of Child-Pugh class and MELD score compared to older adults in the derivation cohort (Supplementary Table S11).

Discrimination. Harrell's c-index was 0.57 (95% CI 0.46-0.71). The AUC of the model derived in older adult patients was 0.58 at 1-, 2- and 3-years (Supplementary Figure S5), that were identical to those of the FIPS score (0.58 at 1-, 2- and 3-year).

Calibration. One year observed event-rate was 23.1% and 1-year average predicted risk was 24.8%. 2-year observed event-rate was 31.9% and 2-year average predicted risk was 39.5%. Calibration intercept was -0.63 (95% CI -1.07; -0.25), suggesting overestimation of the risk of liver-related death. Calibration slope was 0.15 (95% CI -0.37; 0.69), indicating that estimated risks are too extreme (overfitting). Calibration curves at 1 and 2 years are shown in Figure 5.

Discussion

Updated clinical guidelines strongly recommend TIPS placement as an effective treatment for portal hypertension-related events in patients with cirrhosis and refractory ascites or previous variceal bleeding. In these patients, TIPS significantly improves survival by reducing the risk of further decompensating events and by improving nutritional status [1-3,19,20]. In contrast, the indication to TIPS placement in older adult patients represents an unsolved medical need because of the lack of data on the potential benefit of the procedure in this selected population. Differently from patients younger than 70 years, older adult patients cannot receive OLT in case of further decompensating events after TIPS placement. Moreover, the benefit of TIPS could be reduced by death for non-hepatic causes as competing risk.

In this prospective multicenter study including more than 800 patients with cirrhosis undergoing TIPS for refractory ascites or secondary prophylaxis of variceal bleeding, we found that age, together with alcoholic etiology, creatinine levels and INR were independent risk factors for liver-related death in the overall population, by a validated multivariable competing risks model. Age had a negative impact on liver-related mortality also after stratifying according to the indications to TIPS placement (refractory ascites or recurrent variceal bleeding). Thus, older adult patients should be carefully selected according to a specifically derived prediction model in order to identify the optimal patient profile before TIPS. Our analyses indicate that in older adult patients (older than 70 years), creatinine and sodium levels are able to predict the risk of liver-related death, allowing the clinician to identify candidates to TIPS placement with a favorable risk profile. Moreover, our results suggest that age *per se* cannot be an absolute contraindication to TIPS.

AUD is associated with a significantly higher risk of liver-related death compared to viral etiology. It is well known that highly effective antiviral treatments improve survival by reducing the risk of further decompensation also in patients with more advanced liver disease [21,22]. Although it has been shown that long-term alcohol abstinence could decrease portal hypertension, improving survival, unfortunately it cannot be reached in all patients [23,24]. Future changes in the prevalence of different etiologies of liver disease, with a decrease in viral causes and an increase in metabolic and alcoholic etiologies, may limit the

accuracy of our prediction model. INR represents a well-known surrogate marker of the severity of liver disease and it is included not only in Child-Pugh and MELD score, but also in diagnostic criteria for acute-on-chronic liver failure. Creatinine levels were another independent risk factor for liver-related death not only in the overall cohort but also in older adult patients, underlining the importance of the assessment of kidney function when selecting patients for TIPS placement. Interestingly, the probability of liver-related death was significantly lower in older adult patients with normal creatinine and INR, compared to young patients with elevated creatinine and INR. We did not find an independent association between bilirubin levels and liver-related mortality, probably because patients who underwent TIPS were selected only when liver function was sufficiently preserved and no rescue or preemptive TIPS were included in the study. Indeed, in our study, older adult patients displayed signs of less advanced liver disease compared to younger patients in terms of INR and Child-Pugh class, probably reflecting a more careful selection by physicians when managing older adults.

Multivariable analyses did not confirm the indication for TIPS placement as a significant predictor of liver-related death. Nevertheless, considering the significant differences between patients who underwent TIPS for refractory ascites or secondary prophylaxis of variceal bleeding, we developed two different prediction rules for liver-related death according to the different indications for TIPS. Similarly to the overall cohort, age and INR were independent prognostic factors for liver-related mortality in both TIPS indications, while alcoholic etiology was confirmed as a significant risk factor for liver-related death only in patients with recurrent variceal bleeding.

Although our model did not identify the under-dilation of TIPS (i.e. a diameter ≤7) as a significant risk factor for liver-related death, it should be noted that placement of a small-diameter TIPS was significantly more frequent in older adult than in young patients. It is interesting to underline that a small TIPS diameter was independently associated with a reduced risk of HE occurrence after TIPS. These results are in line with those of a previous prospective non-randomized study [7] and provide further evidence supporting the effectiveness and safety of under-dilated TIPS, especially in older adult patients. Further studies specifically designed to evaluate under-dilated TIPS in this population are needed to confirm these findings. Along

these lines, the possibility that an under-dilated TIPS undergoes passive dilatation to its nominal diameter is still a matter of debate. A previous study [7] has shown that the diameter of the shunt remains substantially stable. However, further data are warranted to confirm the stability of diameter over time and its correlation with clinical outcomes.

For the first time, to the best of our knowledge, we built a prediction score (ExPeCT) specifically derived and validated in older adult patients, based on serum levels of sodium and creatinine. Although previous studies tried to evaluate the safety and the feasibility of TIPS in older adult patients [25,26], different age thresholds (i.e. older than 60 or 65 years) were used. Moreover, they did not evaluate survival as primary outcome, nor did they report a competing risk analysis [25], or they were performed only in the setting of refractory ascites with a short follow-up [26]. Differently from creatinine, sodium levels were an independent risk factor for liver-related mortality only in older adults. Of note, older adult patients with normal creatinine and sodium levels have a survival probability of about 70% after 3 years from TIPS placement. Conversely, older adult patients with creatinine of 2.5 mg/dL and sodium levels of 130 mEq/L showed a worse outcome, with a risk of liver-related death of about 70% after 1 year. These results suggest that older adult patients with preserved renal function and normal sodium levels could obtain a survival outcome after TIPS placement similar to younger patients. Moreover, the occurrence of HE and/or recurrence of ascites or bleeding was not significantly different comparing the two groups of patients according to age. Although the results of this study indicate that age is not an absolute contraindication to TIPS placement in an older adult, a careful multidisciplinary evaluation of risks, benefits, and quality of life of patients and their caregivers related to the occurrence of post-TIPS complications (such as HE and cardiac decompensation) should have a considerable relevance in the decision process.

Some limitations of this study should be acknowledged. First, the lack of a control group treated with standard of care precludes the assessment of a possible survival benefit of TIPS in older adults. However, consistently with the aim of our study, risks and benefits of TIPS placement were compared between older and non-older adults. Second, although creatinine levels resulted an independent prognostic factor for liver-related death in the overall cohort and in older adult patients, we were not able to discriminate

between functional (i.e. related to portal hypertension) and organic (i.e. related to parenchymal nephropathy) causes of renal impairment. This could be relevant as functional renal impairment related to advanced liver disease may potentially be improved by TIPS placement, differently from parenchymal nephropathy. Third, it should be underlined that this prediction model developed in tertiary care centers should be used with caution in older adult patients with cirrhosis treated in less-experienced centers. Fourth, although our prediction models were externally validated, the model performance was far from ideal. Similar performance, both for discrimination and calibration, was recently reported for MELD and FIPS scores [6, 9]. It should be acknowledged that our prediction model overestimates the 2-year risk of liver-related death in older adults. This could result in a more conservative selection of patients in the older adult population. The miscalibration observed in our models may be related to the small sample size of the older adult cohort and to differences between the derivation and validation cohorts [27]. Additional causes of poor calibration may be dependent on heterogeneity in terms of patient characteristics, event rates, and treatment policy, as demonstrated by the lack of under-dilated TIPS placed in our validation cohort. Although strong calibration is desirable for decision making, it may be unrealistic in many real-world clinical settings [28]. Further efforts are needed to improve the performance of prediction models for survival after TIPS, including novel variables related to systemic inflammation, as well as new cardiovascular parameters, as recently proposed [29]. Finally, updating data for recalibration in different external validation cohorts is warranted.

In conclusion, our results indicate that in older adult patients with cirrhosis receiving TIPS for refractory ascites or secondary prophylaxis of variceal bleeding, an externally validated prediction model including creatinine and sodium is able to predict liver-related mortality after TIPS placement. TIPS placement should not be precluded to carefully selected patients older than 70 years.

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Author names in bold designate shared co-first authorship.

Figure Legend

Figure 1. Probability of liver-related death in 411 patients of the derivation cohort undergoing TIPS placement stratified according to age (≥ 70 years versus < 70 years).

Figure 2: Transplant-free survival in 411 patients undergoing TIPS placement in the overall population and stratified according to age (≥ versus <70 years). Overall population dashed line, patients <70 years light grey line and patients ≥70 years dark grey line.

Figure 3. Predicted probabilities of liver-related death according to predictors of mortality (age, etiology of cirrhosis, creatinine levels, and INR) in four different patient profiles in the overall derivation cohort. A: non older adult (60-years old) with favorable profile (viral etiology, creatinine 1 mg/dL, INR 1). B: older adult (75-years old) with favorable profile (viral etiology, creatinine 1 mg/dL, INR 1). C: non older adult (60-years old) with unfavorable profile (alcoholic etiology, creatinine 2 mg/dL, INR 2). D: older adult (75-years old) with unfavorable profile (alcoholic etiology, creatinine 2 mg/dL, INR 2).

Figure 4. Predicted probabilities of liver-related death according to predictors of mortality (creatinine and sodium levels) in three different patient profiles in older adult patients in the derivation cohort. A (favorable profile): creatinine 1.2 mg/dL, sodium 140 mEq/L. B (intermediate profile): creatinine 2 mg/dL, sodium 135 mEq/L. C (unfavorable): creatinine 2.5 mg/dL, sodium 130 mEq/L.

Figure 5. One- and 2-year calibration curves on validation data for older adult model. The circle compares event rate (observed proportion) with average predicted risk (predicted probability). The grey line

represents perfect calibration. The average predicted risk is higher than event rate, demonstrating that the prediction model overestimates the risk of liver-related death.

Table 1. Baseline characteristics of 411 patients (derivation cohort) with TIPS placement for refractory ascites or secondary prophylaxis of variceal bleeding according to age (<70 years or ≥70 years).

Variables	Overall (N=411)	Age <70 years (N=312)	Age ≥70 years (N=99)	*p*-value*
Age at TIPS placement (years)	63±8.2	59±5.6	74±3.3	<0.001
Male sex (%)	297 (72.3)	228 (73.1)	69 (69.7)	0.60
Etiology of cirrhosis (%)				
Alcohol alone	148 (36.0)	130 (41.7)	18 (18.2)	<0.001
HCV alone	95 (23.1)	57 (18.3)	38 (38.4)	<0.001
NASH alone	73 (17.8)	56 (17.9)	17 (17.2)	0.50
HBV alone	16 (3.9)	13 (4.2)	3 (3.0)	0.53
Concomitant etiologies:				
HCV+alcohol	18 (4.4)	15 (4.8)	3 (3.0)	0.63
HBV+alcohol	4 (1.0)	4 (1.3)	0 (0.0)	0.76
NASH+alcohol	11 (2.7)	9 (2.9)	2 (2.0)	0.78
Others**	44 (10.7)	27 (8.7)	17 (17.2)	0.03
Comorbidities (%)				
Diabetes	48 (11.7)	35 (11.2)	13 (13.1)	0.08
CKD	50 (12.2)	33 (10.6)	17 (17.1)	0.18
CHD	24 (5.8)	17 (5.4)	7 (7.1)	0.83
COPD	24 (5.8)	19 (6.1)	5 (5.1)	0.79
Albumin (g/dL)	3.33±0.57	3.32±0.58	3.36±0.55	0.56

Bilirubin (mg/dL)	1.38±0.8	1.41±0.81	1.27±0.75	0.11
INR	1.31±0.19	1.32±0.2	1.26±0.18	0.01
Creatinine (mg/dL)	1.07±0.47	1.04±0.45	1.19±0.53	0.02
Sodium (mEq/L)	137±5	136±5	137±5	0.07
Platelet count (10^9/L)	105±75	107±83	98±46	0.19
HE before TIPS (%)	68 (16.5)	60 (19.2)	8 (8.1)	0.02
Child-Pugh score	7.5±1.4	7.6±1.4	7.3±1.3	0.08
Child-Pugh class (%)				0.02
A	88 (21.4)	62 (19.8)	26 (26.3)	
B	292 (71.0)	222 (71.2)	70 (70.7)	
C	31 (7.5)	28 (9.0)	3 (3.0)	
MELD score	12.1±3.6	12.1±3.4	12.3±4.1	0.59
MELD-Na score	13.8±4.5	13.9±4.4	13.5±4.6	0.48
Indication to TIPS placement (%)				0.27
- Refractory ascites	221 (53.8)	172 (55.3)	49 (49.5)	
- Variceal bleeding	190 (46.3)	140 (44.9)	50 (50.5)	
PSPG before TIPS (mm Hg)	21.5±5.1	21.3±5.1	21.9±5.0	0.34
PSPG after TIPS (mm Hg)	10.7±4.4	10.7±4.4	10.4±4.4	0.5
TIPS dilation (median, IQR) (mm)	8 (2)	8 (2)	6.5 (2)	0.01
6 mm	170 (41.4)	122 (39.1)	48 (48.5)	0.04
7 mm	35 (8.5)	23 (7.4)	12 (12.1)	
8 mm	122 (29.7)	97 (31.1)	25 (25.3)	
10 mm	84 (20.4)	70 (22.4)	14 (14.1)	
Underdilated TIPS (%)	205 (49.9)	145 (46.5)	60 (60.6)	0.04

*p-values refer to the comparison between patients younger vs older than 70 years.

** Others etiologies included: autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, cryptogenic cirrhosis.

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as absolute number (percentage) for categorical variables.

TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; PSPG, porto-systemic pressure gradient.

Table 2. Predictors of liver-related death by multivariable competing risks analysis in the derivation cohort of patients undergoing TIPS: overall cohort and older adult cohort (≥70 years).

Overall cohort (N=411)			
Variable	**Beta**	**Standard error**	**p-value**
Age (years)	0.07	0.013	<0.001
Alcoholic etiology*	0.52	0.242	0.032
NASH etiology*	-0.21	0.314	0.513
Creatinine (mg/dL)	0.59	0.214	0.006
INR	0.24	0.055	<0.001
Older adult cohort (N=99)			
Variable	**Beta**	**Standard error**	**p-value**
Creatinine (mg/dL)	1.07	0.369	0.004
Sodium (mEq/L)	-0.08	0.033	0.022

*Reference: viral etiology.

In the overall cohort (n=411), baseline survival was 0.89 at 1 year, 0.87 at 2 years and 0.85 at 3 years.

In the older adult cohort (n=99), baseline survival was 0.83 at 1 year, 0.70 at 2 years and 0.60 at 3 years.

TIPS, transjugular intrahepatic portosystemic shunt; NASH, non-alcoholic steatohepatitis; INR, international normalized ratio.

Table 3. Predictors of liver-related death by multivariable competing risks analysis in the derivation cohort of patients with TIPS placement according to indication (top: refractory ascites; bottom: secondary prophylaxis of variceal bleeding).

Refractory ascites as indication (N=221)			
Variable	**Beta**	**Standard error**	**p-value**
Age (years)	0.05	0.020	0.016
INR	0.22	0.070	0.007
Secondary prophylaxis of variceal bleeding as indication (N=190)			
Variable	**Beta**	**Standard error**	**p-value**
Age (years)	0.09	0.021	<0.001
Alcoholic etiology*	1.1	0.381	0.023
NASH etiology*	-0.21	0.452	0.650
INR	0.19	0.084	0.026

*Reference: viral etiology.

In the refractory ascites cohort (n=221), baseline survival was 0.87 at 1 year, 0.81 at 2 years and 0.73 at 3 years.

In the secondary prophylaxis of variceal bleeding cohort (n=190), baseline survival was 0.91 at 1 year, 0.88 at 2 years and 0.80 at 3 years.

INR, international normalized ratio; TIPS, transjugular intrahepatic portosystemic shunt; NASH, non-alcoholic steatohepatitis.

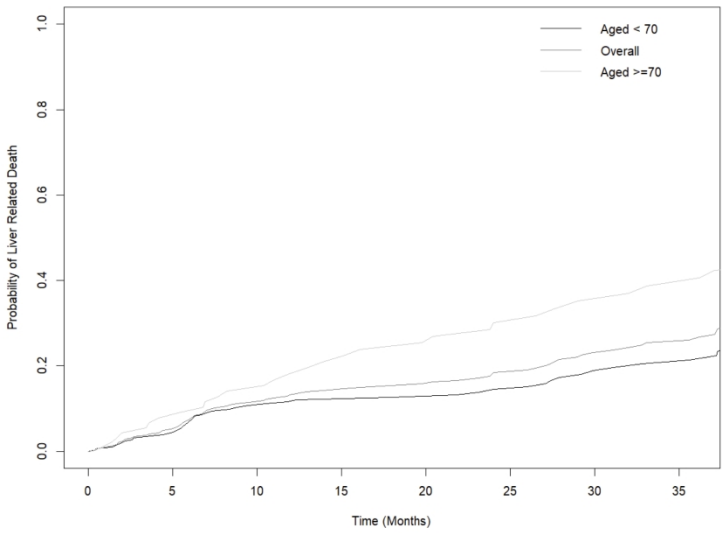

Figure 1. Probability of liver-related death in 411 patients of the derivation cohort undergoing TIPS placement stratified according to age (≥ 70 years versus < 70 years).

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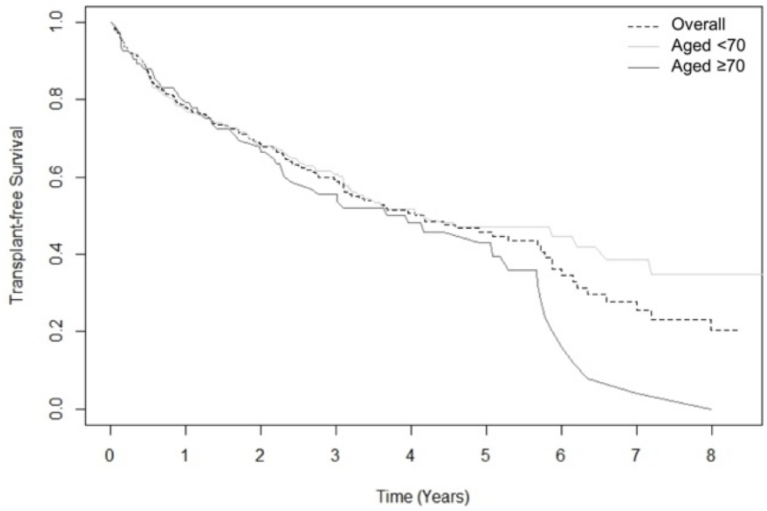

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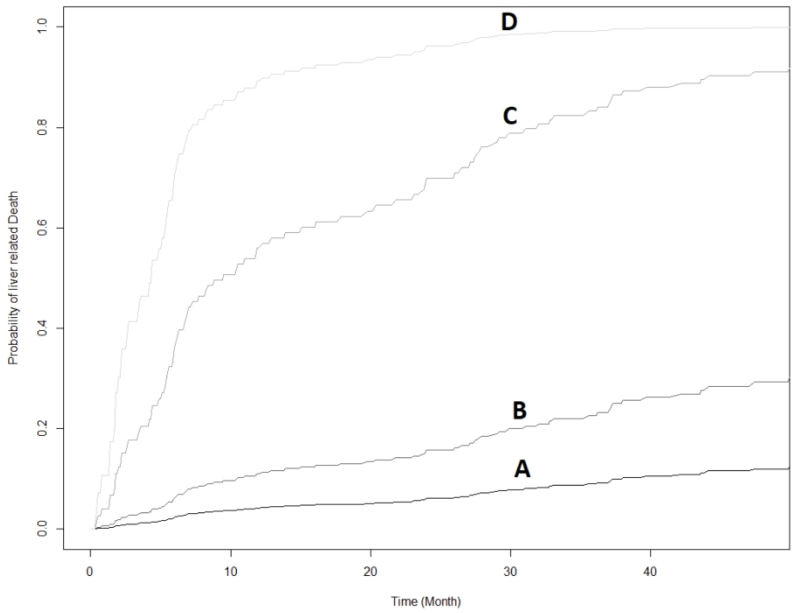

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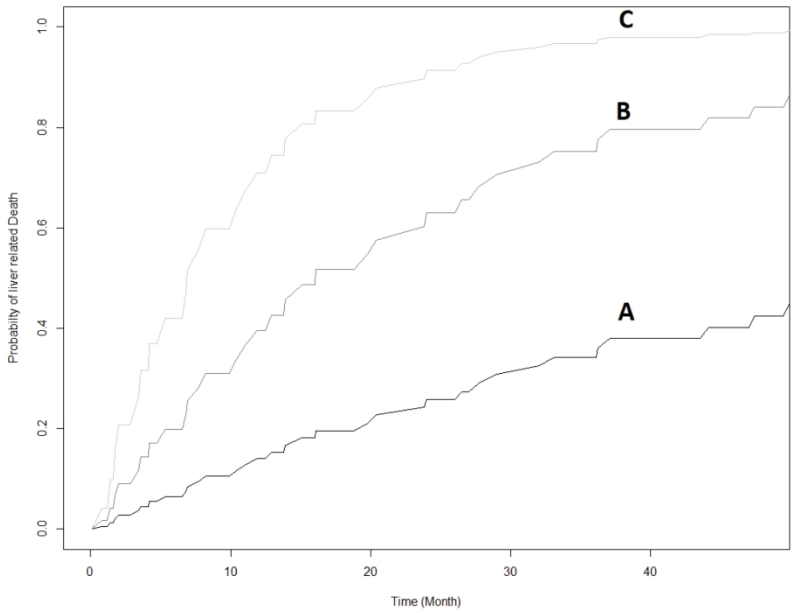

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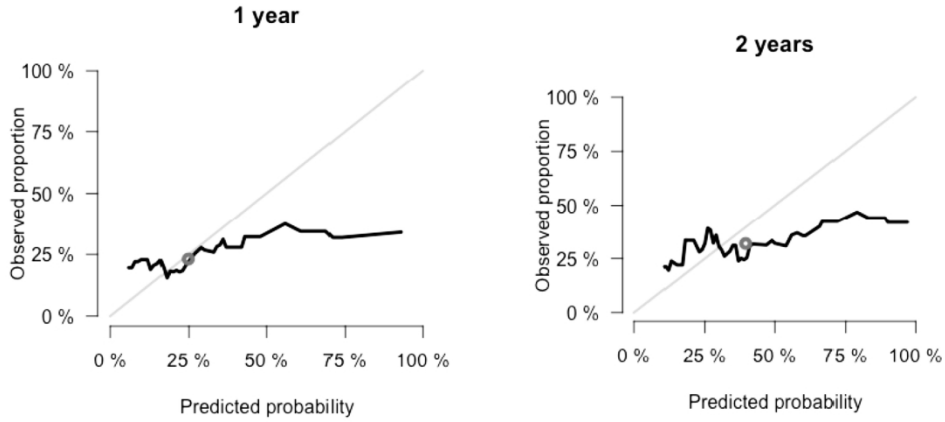

Figure 5. One- and 2-year calibration curves on validation data for older adult model. The circle compares event rate (observed proportion) with average predicted risk (predicted probability). The grey line represents perfect calibration. The average predicted risk is higher than event rate, demonstrating that the prediction model overestimates the risk of liver-related death.

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SUPPLEMENTARY MATERIALS

Methods

Additional characteristics of the devices used

In the derivation cohort 'underdilated TIPS' largely belonged to old-generation Viatorr covered 10-mm stent dilated to a diameter ≤7 mm. More recently, controlled-expansion stent grafts were used (9%), with the same initial approach (dilation to ≤7 mm).

In the validation cohort, from 2007 to 2016, 69% of patients received old generation 10-mm (diameter) Viatorr covered stent grafts, dilated to their nominal diameter. Since 2016, all patients (31%) received the new Viatorr controlled-expansion stent grafts, followed by 8-mm diameter balloon dilatation.

Sample size calculation

According to Riley et al. methods, we calculated the sample size needed to minimize potential model overfitting. We fixed the anticipated R^2_{CS} to 0.2 (for time-to-event outcomes) with shrinkage factor equal to 0.1 (thus S=0.9). Given that the number of candidate predictor parameters is 11 and an expected optimism of ≤0.05, a total of at least 438 participants are required.

Model Calibration on the validation cohort

Calibration was evaluated by two approaches.

The first approach, according to Crowson et al (REF 2016), evaluated 'calibration in the large', calibration slope, and overall calibration. 'Calibration in the large' compares the event rate with the average predicted risk by the estimation of a model intercept, which has target value of 0, with negative values suggesting overestimation and positive values suggesting underestimation.

The calibration slope evaluated the spread of the estimated risk and it has a target value of 1 with value <1 suggesting that estimated risks are too extreme (and values >1 suggesting the opposite).

Overall calibration is asymptotically equivalent to the Hosmer-Lemeshow test, for which a significant p-value means a poor overall calibration.

The second approach based on Gerds et al. (2014) evaluated calibration plots of predicted risk of 1- and 2-year liver-related death versus 1- and 2-year observed event rates.

First approach

The first calibration approach was performed according to Crowson et al. (2016, and 2017 Erratum). The advantage of following this approach is the possibility of quantifying the magnitude of miscalibration, according to different aspects of model calibration: 'calibration in the large', calibration slope and overall calibration. Note that this approach was developed for assessing the calibration of a PH Cox model while, technically, we estimated a cause-specific Cox model. Accordingly, we approximated the cumulative incidence function of liver related deaths, estimated by the Aalen-Johansen method on the basis of a competing-risks cause-specific Cox model, to the estimated probability of liver related deaths (i.e. 1-survival), using the Breslow estimator of survival in a PH Cox model.

'Calibration in the large', calibration slope, and overall calibration were assessed by estimating three different Poisson models with offset.

Calibration in-the-large for overall cohort model

Calibration in the large is the assessment of calibration of average predicted versus observed risk. Intercept test (Calibration in the large) constrains the intercept to be 0. The exponential of the intercept estimates the ratio between the observed event in the validation set and the number predicted by the derivation set model.

The estimated calibration intercept is 0.6 and it is statistically different from 0. This should be 0, and the reported 95% C.I. does not contain it. The ratio between observed events and the predicted ones is equal to 1.82, suggesting underestimation of the risk.

```
> p2<-log(predict(fit, ism, type="expected")+1e-10) ## adding 1e-10 helps to avoid zeroes
> fit1<-glm(status2 ~offset(p2), family=poisson, data= ism)
> coef(fit1)
(Intercept)
   0.600443
> confint(fit1)
    2.5 %    97.5 %
0.4281798 0.7633427
```

Calibration in-the-large for older adult model

The intercept coefficient is -0.63 and it is statistically different from 0. The ratio between observed events and the predicted ones is equal to 0.59, suggesting overestimation of the risk.

```
#cox_70 is the model fitted on the corresponding derivation subgroup
> coef(cox_70)
   creatina       sodio
 1.01171651 -0.07888738

> p70<-log(predict(cox_70, d_is70, type="expected")+1e-10)
> fit1_70<-glm(status2 ~offset(p70), family=poisson, data=d_is70)
> coef(fit1_70)
(Intercept)
 -0.6300424
> confint(fit1_70)
     2.5 %     97.5 %
-1.0685964 -0.2474352
```

Calibration slope test for overall cohort model

In the slope test, the slope is constrained to be 1. A slope <1 suggests estimated risks to be extreme, thus a larger estimated risk for patients at high risks, and lower for patients at low risk (overfitting). A slope >1 suggests the opposite, i.e. that risk estimates are too moderate (underfitting).

Calibration slope is 0.06 (see the estimated coefficient of p2). This should be 1, but the 95% C.I. does not contain it, suggesting that estimated risks are too extreme, i.e. too high for patients who are at high risk and too low for patients who are at low risk (overfitting).

```
lp<-predict(fit, newdata=ism, type="lp")
logbase <- p2-lp
fit2 <- glm(status2 ~ lp + offset(logbase), family= poisson, data=ism)
coef(fit2)[2]
         p2
0.05956327
> confint(fit2)[2,]
       2.5 %       97.5 %
-0.003394874  0.146545913
```

Calibration slope for older adult model

Calibration slope is 0.15 and the 95% C.I. does not contain 1, suggesting that estimated risks are too extreme, i.e. too high for patients who are at high risk and too low for patients who are at low risk (overfitting).

```
lp70<-predict(cox_70, newdata=d_is70, type="lp")
logbase70 <- p70-lp70
fit2_70 <- glm(status2 ~ lp70 + offset(logbase70), family= poisson, data=d_is70)
coef(fit2_70)[2]
     lp70
0.1504983
confint(fit2_70)[2,]
     2.5 %     97.5 %
-0.3745711  0.6889973
```

Goodness-of-fit test for calibration (overall calibration)

Overall calibration is based on the estimation of a poisson model without intercept and with regression parameters given by groups based on deciles of the model linear predictor. The goodness-of-fit test for H0: beta_1=beta_2=…=beta_10=0, vs H1: at least one beta_k $\neq$ 0, k=1,…,10, is asymptotically equivalent to the Hosmer-Lemeshow test. We used the Wald test for this, which is asymptotically equivalent to the score test suggested in Crowson et al. (2016).

Goodness-of-fit test for overall cohort model (overall calibration)

Goodness-of-fit test for calibration of model 1 is significant (p=0.002), meaning that, overall, there is a poor calibration.

```
#Object "fit" is the model fitted (model 1) on the whole derivation cohort, while "ism" is the whole
#validation data set. Moreover, "cox_70" is the model fitted (model 2) on the subgroup derivation
#cohort of patients with age>=70 years, while "d_is2" is the corresponding subgroup of patients in
#the validation data set

groupb <- cut(lp, c(-Inf, quantile(lp,(1:9)/10), Inf))

fit3 <- glm(status2 ~-1+groupb+offset(p2), family= poisson, data=ism)

#overall wald test

library(mdscore)

> wald.test(fit3,terms=9)

$W

[1] 9.163522

$pvalue

[1] 0.00246887
```

Goodness-of-fit test for older adult model (overall calibration)

Goodness-of-fit test for calibration of model 2 is significant (p=0.002), meaning that, overall, there is a poor calibration.

```
group70 <- cut(lp70, c(-Inf, quantile(lp70,(1:9)/10), Inf))

fit3_70 <- glm(status2 ~-1+group70+offset(p70), family= poisson, data=d_is70)

wald.test(fit3_70,terms=9)

$W

[1] 9.810698

$pvalue
```

```
[1] 0.001734996
```

Second approach

The second approach, based on Gerds et al. (2014), is aimed to assess calibration plots of event rate (observed proportion) with average predicted risks. According to this method, the observed proportion at predicted risk value 'p' is obtained based on the subjects whose predicted risk is inside a nearest neighborhood around the value 'p'. The larger the bandwidth the more subjects are included in the current neighborhood. The algorithm to create such calibration plots is implemented in the R package riskRegression (Gerds and Kattan, 2021). We used the internal 'nne' algorithm which automatically selects the optimal bandwidth parameter to estimate the density function of the predicted risk. An average point of predicted vs actual risk, corresponding to the so-called calibration in the large, was also over-imposed to the plots by selecting the bandwidth parameter equal to 1.

The calibration plots of the predicted risk of liver related deaths by the cause-specific Cox models versus the observed proportion at 1 and 2-year intervals, using the validation cohort, are showed in the Supplementary Figure S13 for the overall cohort model in Figure 5 for the older adult model. The circle compares the average predicted risks to the observed risk for liver related death (calibration in the large).

For the overall cohort model, at 1 year, event-rate was 20% and average predicted risks was 13%. At 2-year, event-rate was 27% and average predicted risks was 18%.

For the older adult model, at 1 year, event-rate was 23% and average predicted risks was 24.8%. At 2-year, event-rate was 32% and average predicted risks was 39.5%.

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Crowson CS, Atkinson EJ, Therneau TM. Erratum to - Assessing calibration of prognostic risk scores. Stat Methods Med Res.2017;26:1992–1993.

Gerds TA, Andersen PK, Kattan MW. Calibration plots for risk prediction models in the presence of competing risks. Statistics in Medicine. 2014;33:3191-3203.

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Results

Liver-related mortality according to the indication for TIPS placement

Baseline characteristics of patients according to the indication for TIPS placement in the derivation cohort are shown in Supplementary Table S4. Compared to patients with secondary prophylaxis of variceal bleeding as indication, patients with RA had a significantly higher prevalence of alcoholic etiology and lower prevalence of non-alcoholic steatohepatitis etiology. As expected, patients with RA had a significantly more advanced liver disease, as shown by significantly higher creatinine levels, significantly lower sodium levels and significantly higher Child-Pugh, MELD and MELD-Na scores. Conversely, platelet count was significantly lower in patients with secondary prophylaxis of variceal bleeding as indication.

Among 221 patients undergoing TIPS for RA, 45 patients (20.4%) died for liver-related causes, 30 patients (13.6%) underwent OLT and 11 patients (5.0%) died for extrahepatic causes. Among 190 patients undergoing TIPS for secondary prophylaxis of variceal bleeding, 45 patients (23.7%) died for liver-related causes, 15 patients (7.9%) underwent OLT and 5 patients (2.6%) died for extrahepatic causes**.** Cumulative probabilities

of liver-related death were higher in patients undergoing TIPS for RA (14%, 20% and 29% at 1, 2 and 3 years, respectively) than in those receiving TIPS for secondary prophylaxis of variceal bleeding (11%, 15% and 25% at 1, 2, and 3 years) (Supplementary Figure S6).

In patients receiving TIPS for RA, age and INR were independently associated with liver-related mortality by multivariable analysis (Table 3). Harrell's c-index was 0.63 (95% CI 0.53-0.73). AUCs were 0.63 at 1 year and 0.64 at 2 and 3 years (Supplementary Figure S7). In the external validation cohort, Harrell's c-index was 0.59 (95% CI 0.51-0.67) and AUCs were 0.63 at 1 year and 0.62 at 2 and 3 years (Supplementary Figure S7). Probabilities of liver-related death according to different risk profiles is showed in Supplementary Figure S8.

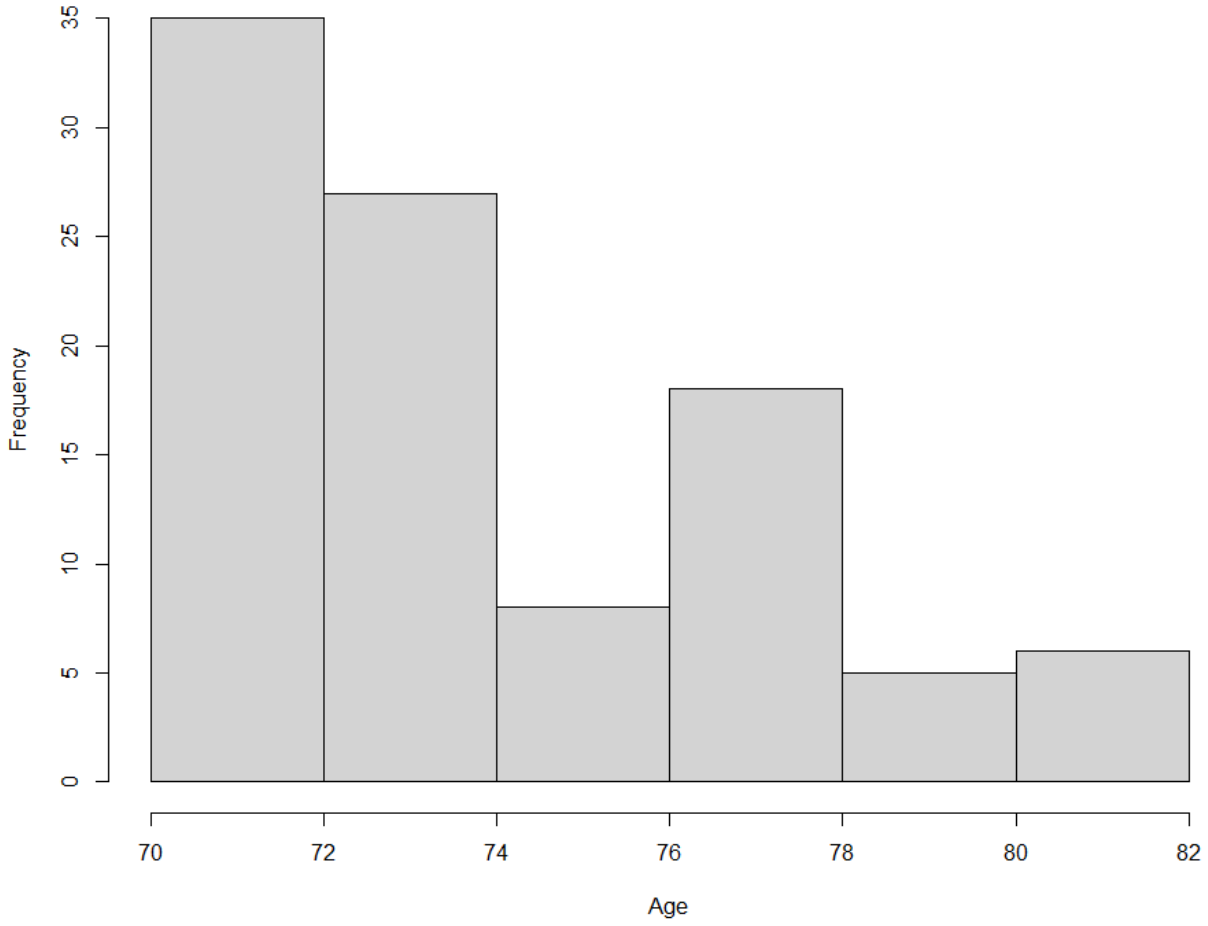
In patients undergoing TIPS for secondary prophylaxis of variceal bleeding, age, alcoholic etiology and INR were independently associated with liver-related mortality by multivariable analysis (Table 3). Harrell c-index was 0.67 (95% CI 0.57-0.78). AUCs were 0.70 at 1 and 2 years and 0.68 at 3 years (Supplementary Figure S9). In the external validation cohort, Harrell's c-index was 0.63 (95% CI 0.49-0.77). AUCs were 0.63 at 1 and 2 years and 0.64 at 3 years (Supplementary Figure S9). Probabilities of liver-related death according to different risk profiles is showed in Supplementary Figure S10**.**

Performance of the overall cohort model in the validation cohort

Discrimination. Overall Harrell's c-index was 0.66 (95% CI 0.61-0.71). One-, 2- and 3-year AUCs of the model derived in the overall cohort are showed in Supplementary Figure S4 and they are similar to those of FIPS score (1-year AUC 0.64, 2-year AUC 0.64 and 3-year AUC 0.64)**.**

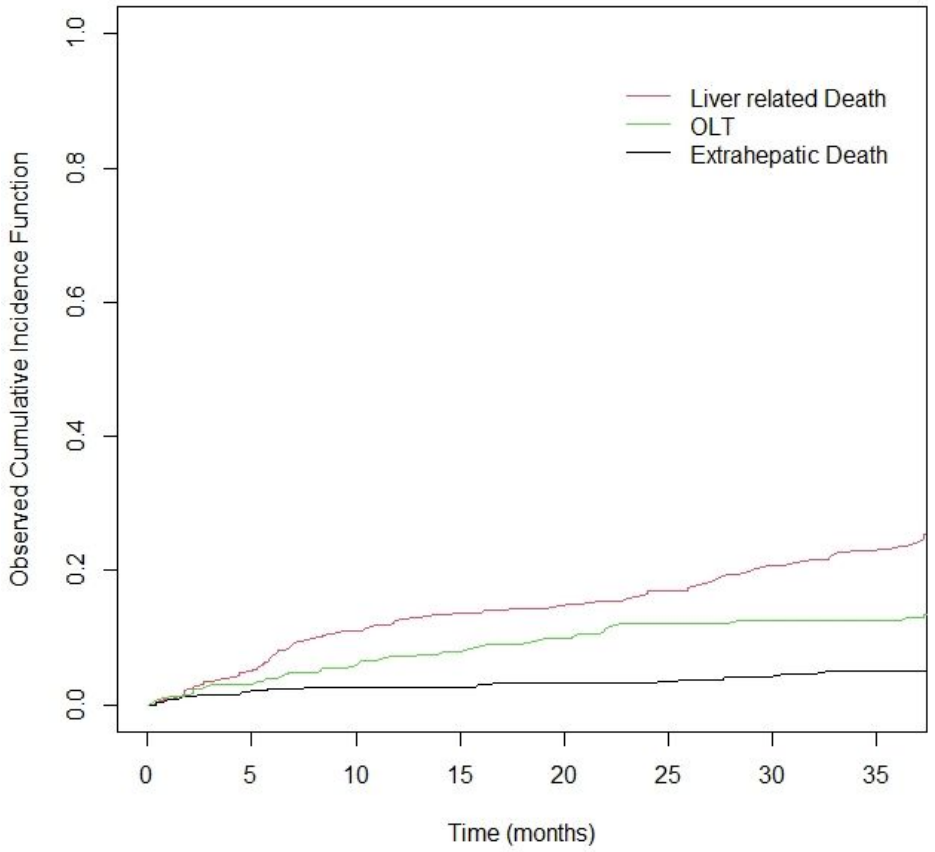
Calibration. One-year event-rate was 20% and 1-year average predicted risk was 13%. Two-year event-rate was 27% and 2-year average predicted risk was 18%. Calibration intercept was 0.60 (95% CI 0.42;0.75), suggesting underestimation of the risk of liver-related death. Calibration slope was 0.06 (95% CI -0.01;0.14), suggesting that estimated risks are too extreme (overfitting). Calibration plots at 1 and 2 years are showed in Supplementary Figure S13 (panel A).

Supplementary Figure S1. Frequency distribution of age in 99 older adults (age ≥70 years) undergoing TIPS placement for refractory ascites or for secondary prophylaxis of variceal bleeding in the derivation cohort.

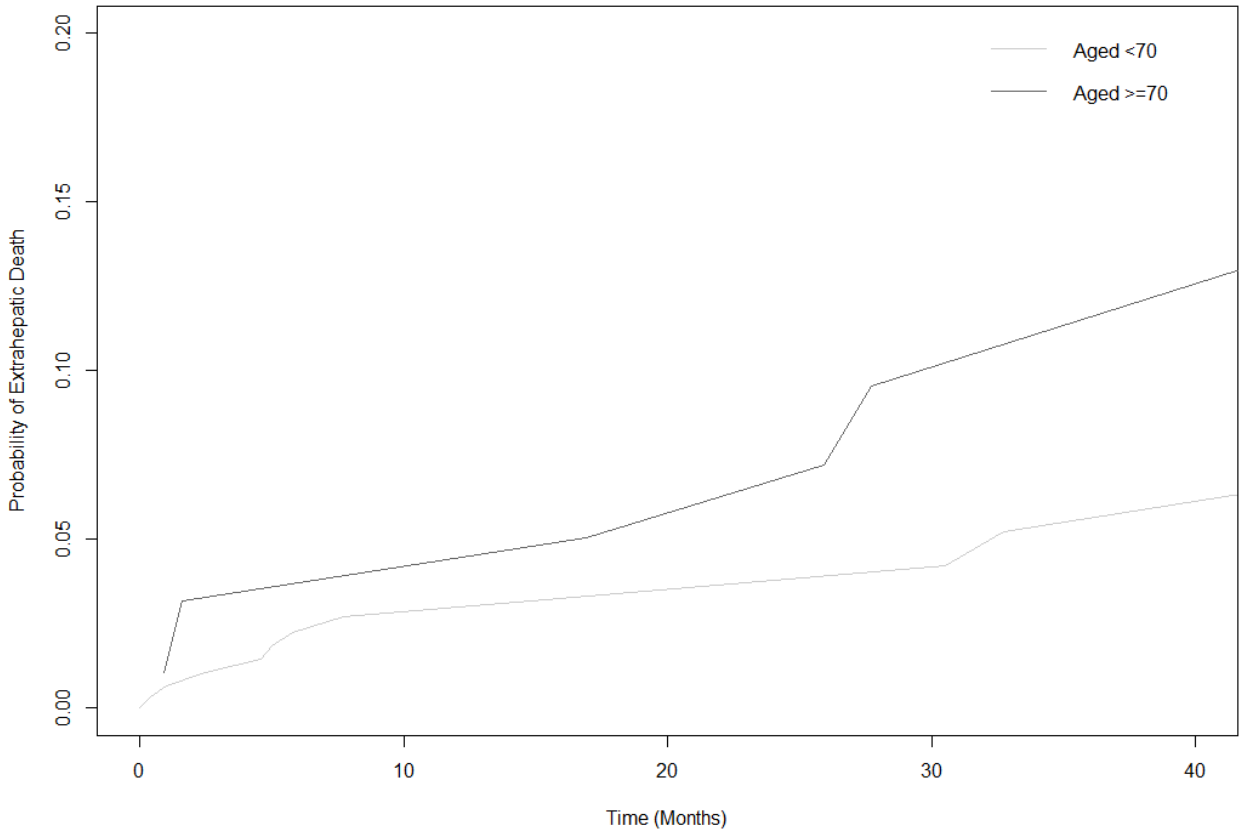


Supplementary Figure S2. Cumulative incidence functions for liver-related mortality, OLT and extrahepatic mortality in 411 patients undergoing TIPS placement for refractory ascites or for secondary prophylaxis of variceal bleeding in the derivation cohort.

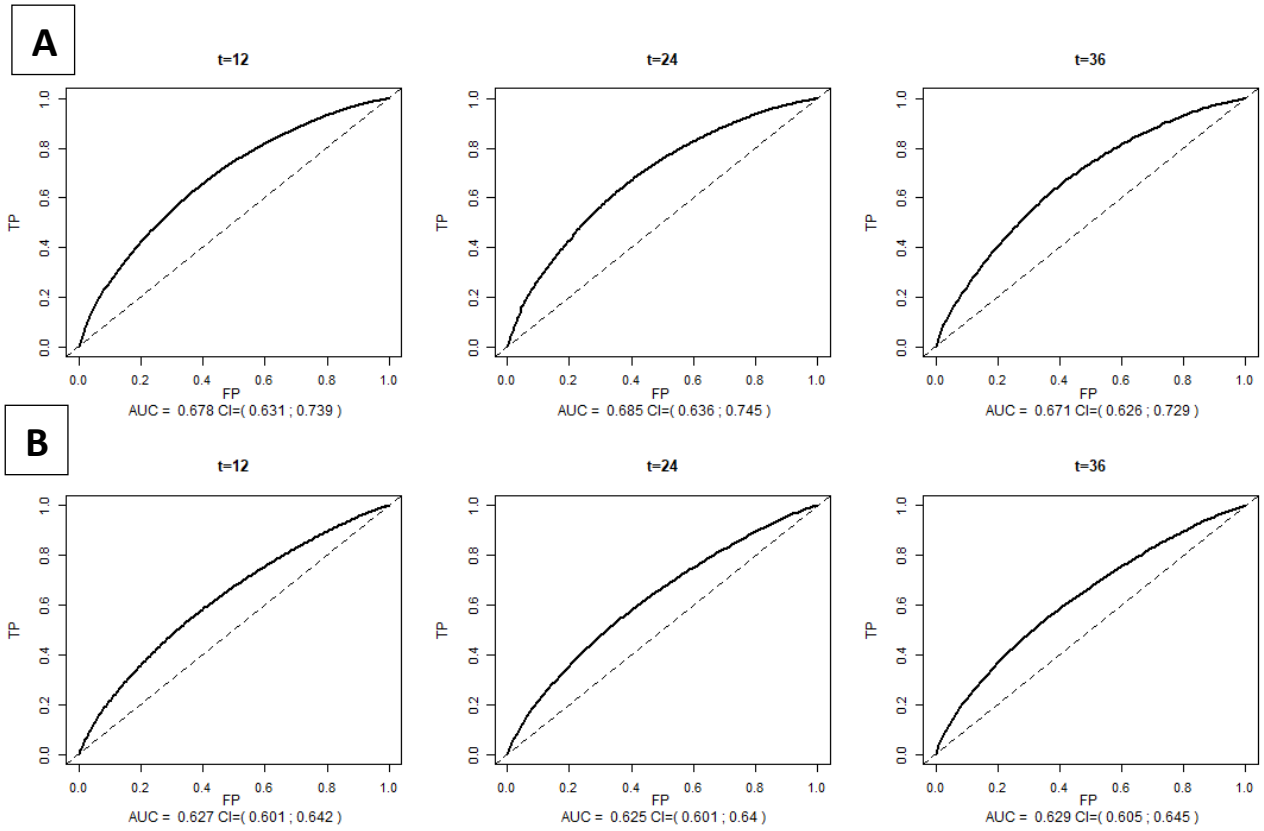
OLT, orthotropic liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt.



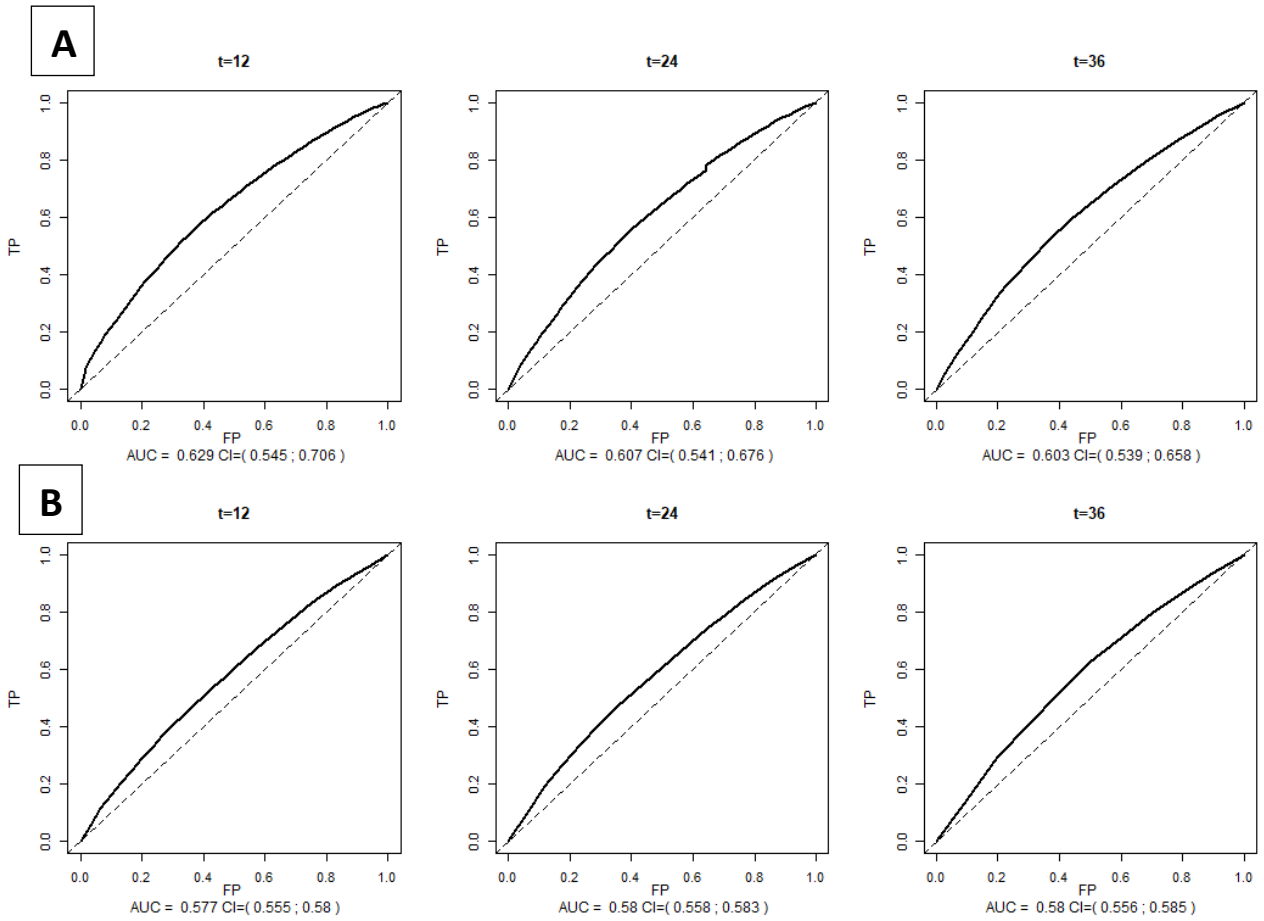
Supplementary Figure S3. Cumulative incidence functions for extrahepatic mortality in 411 patients undergoing TIPS placement for refractory ascites or for secondary prophylaxis of variceal bleeding in the derivation cohort, stratified according to age (≥70 years versus <70 years).



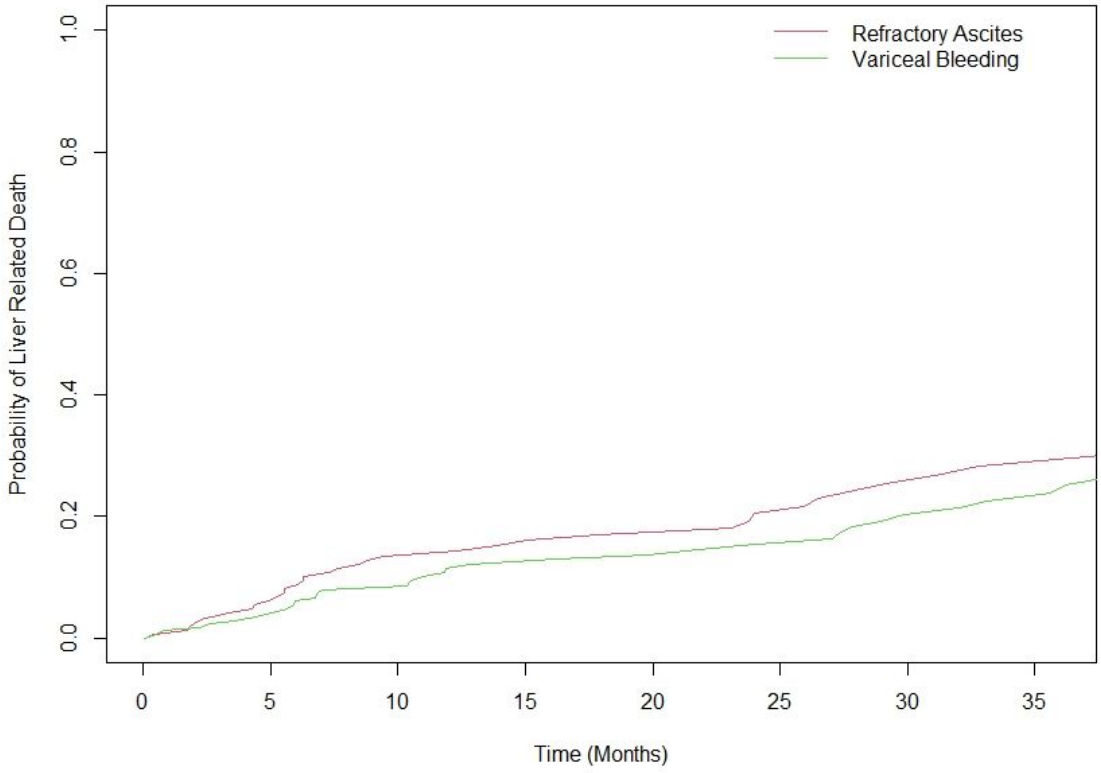
Supplementary Figure S4. Discrimination of the model predicting liver-related mortality in patients undergoing TIPS placement by 12-, 24- and 36-month area under the curve (AUC) and 95% confidence intervals (CI) is showed in the derivation (panel A) and validation (panel B) cohorts.



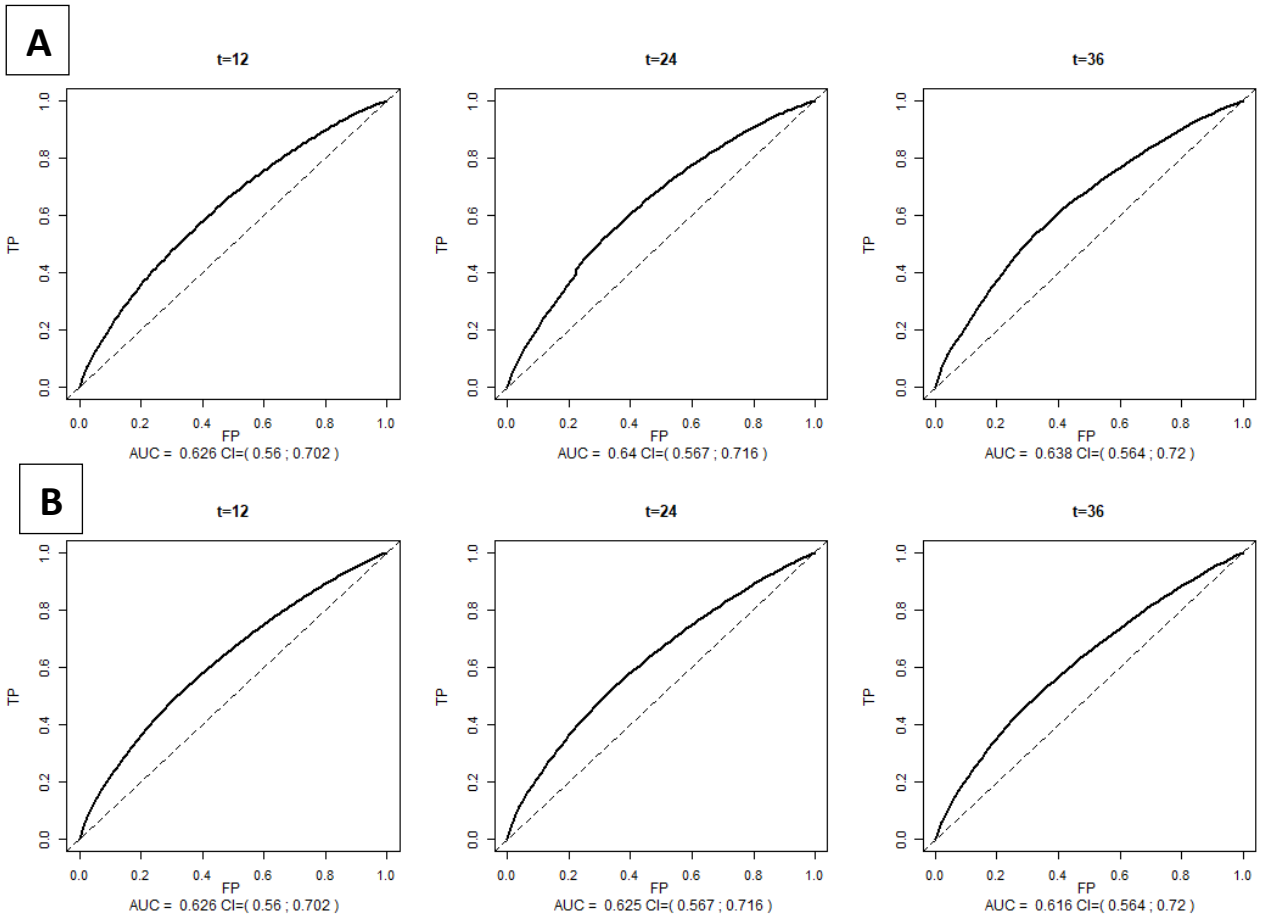
Supplementary Figure S5. Discrimination of the model predicting liver-related mortality in patients older than 70 years undergoing TIPS placement by 12-, 24- and 36-month area under the curve (AUC) and 95% confidence intervals (CI) is showed in the derivation (panel A) and validation (panel B) cohorts.



Supplementary Figure S6. Cumulative incidence functions for liver-related mortality in patients undergoing TIPS placement stratified according to indication in the derivation cohort: refractory ascites (red curve) and secondary prophylaxis of variceal bleeding (green curve).

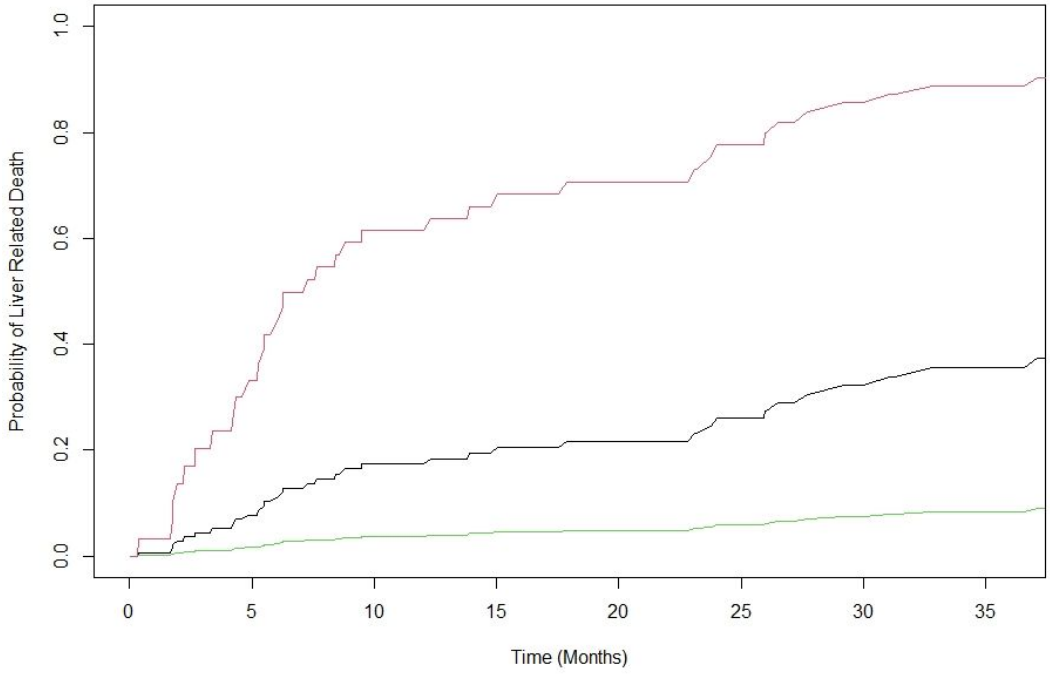


Supplementary Figure S7. Discrimination of the model predicting liver-related mortality in patients undergoing TIPS placement for refractory ascites by 12-, 24- and 36-month area under the curve (AUC) and 95% confidence intervals (CI) is showed in the derivation (panel A) and validation (panel B) cohorts.

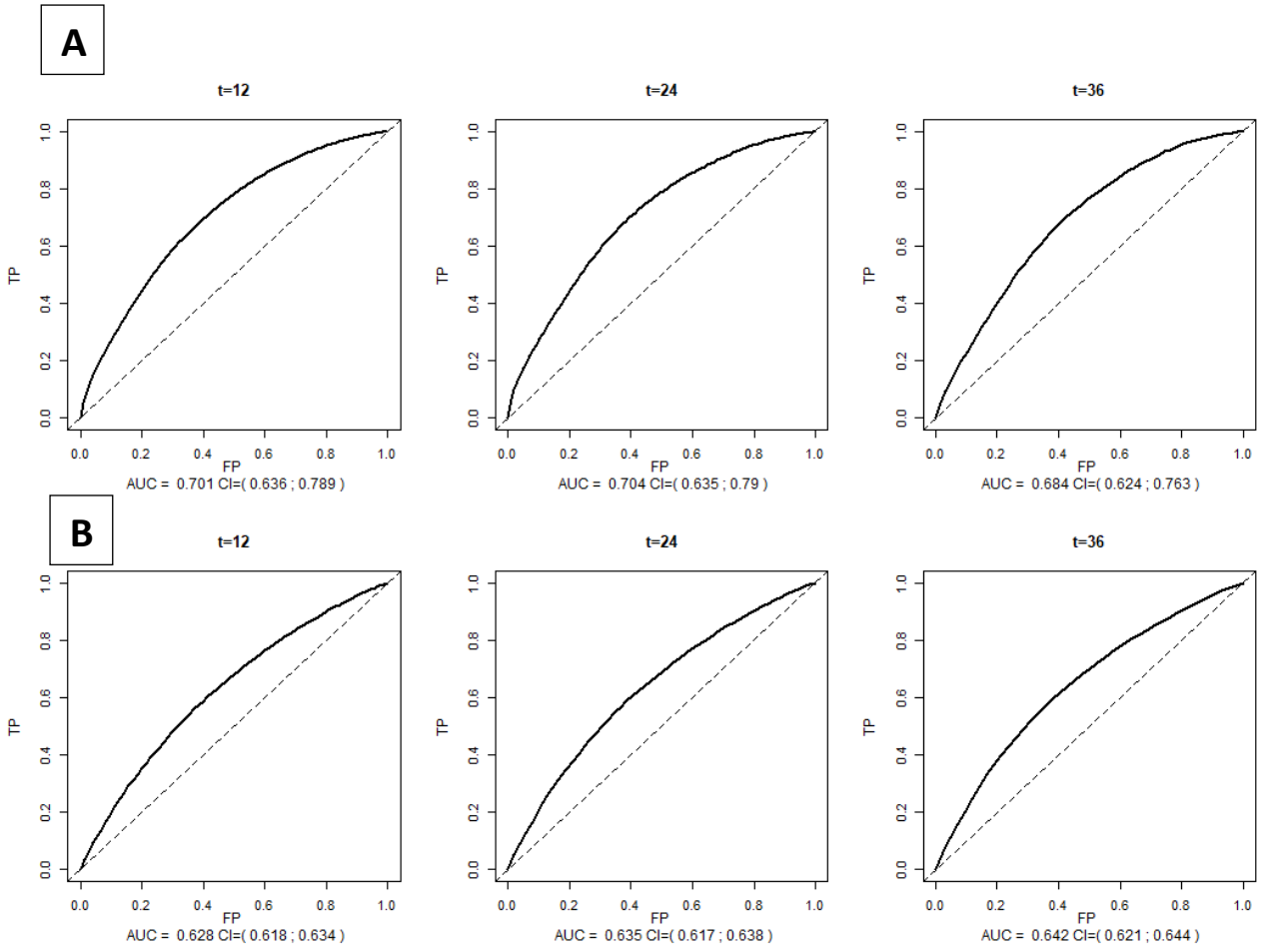


Supplementary Figure S8. Predicted probabilities of liver-related mortality according to predictors of mortality (age, INR) in three different patient profiles in patients undergoing TIPS placement for refractory ascites in the derivation cohort. Green curve (favorable profile): 50-year old, INR 1. Grey curve (intermediate profile): 60-year old, INR 1.5. Red curve (unfavorable profile): 70-year old, INR 2.

TIPS, transjugular intrahepatic portosystemic shunt; INR, international normalized ratio.

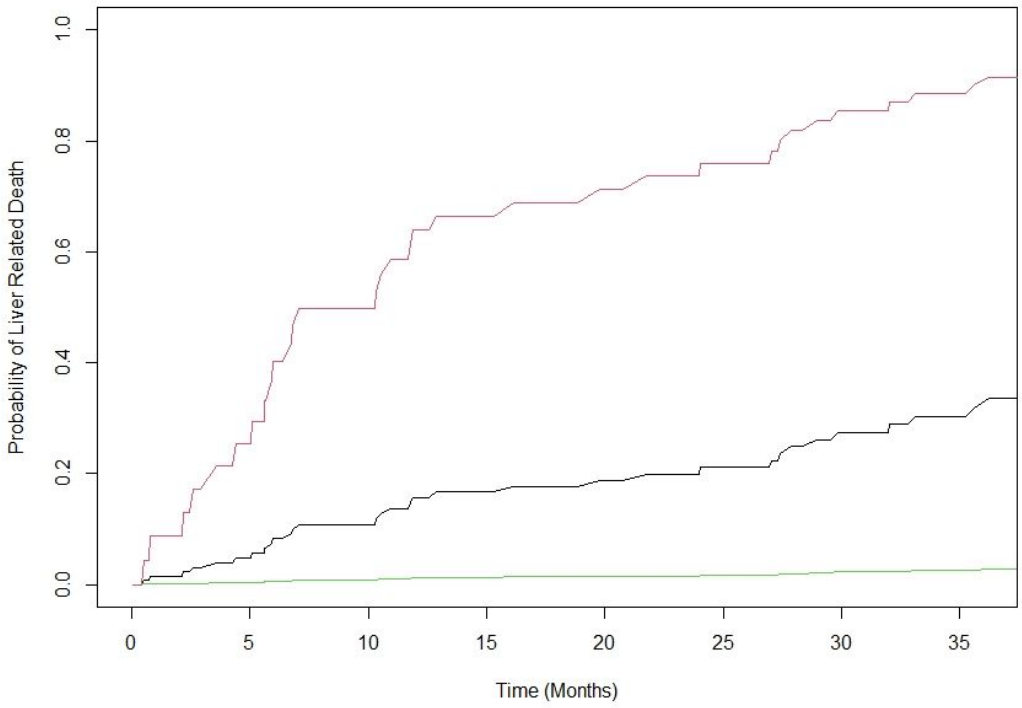


Supplementary Figure S9. Discrimination of the model predicting liver-related mortality in patients undergoing TIPS placement for secondary prophylaxis of variceal bleeding by 12-, 24- and 36-month area under the curve (AUC) and 95% confidence intervals (CI) is shown in the derivation (panel A) and validation (panel B) cohorts.



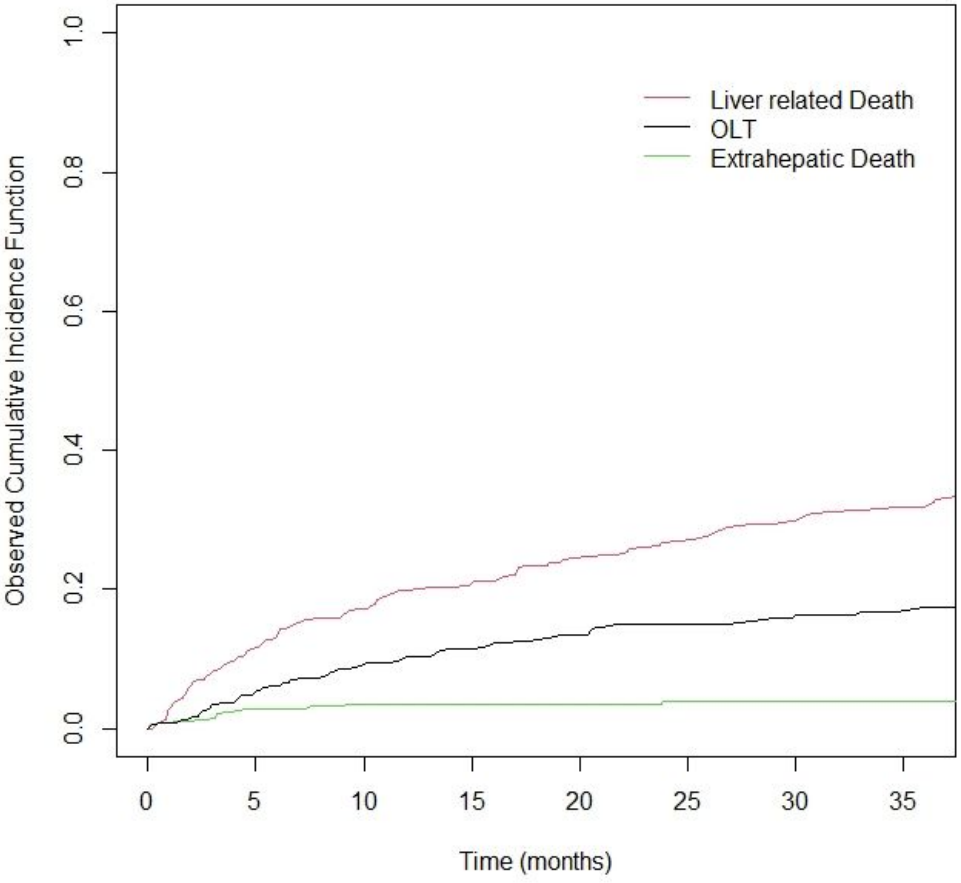
Supplementary Figure S10. Predicted probabilities of liver-related death according to predictors of mortality (age, etiology, INR) in three different patient profiles in patients undergoing TIPS placement for secondary prophylaxis of variceal bleeding in the derivation cohort. Green curve (favorable profile): 50-year old, viral etiology, INR 1. Grey curve (intermediate profile): 60-year old, alcoholic etiology, INR 1.5. Red curve (unfavorable profile): 70-year old, alcoholic etiology, INR 2.

TIPS, transjugular intrahepatic portosystemic shunt; INR, international normalized ratio.

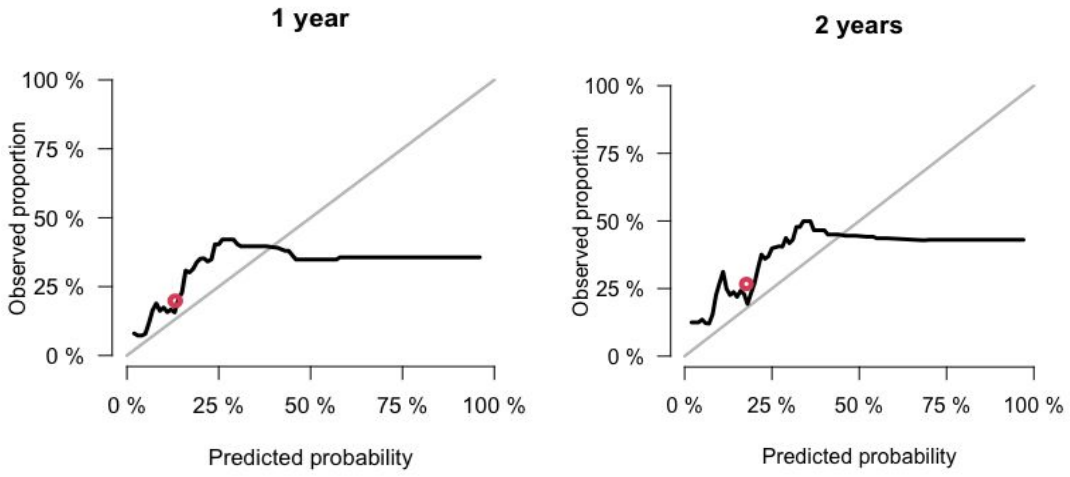


Supplementary Figure S11. Cumulative incidence functions for liver-related mortality, OLT and extrahepatic mortality in 415 patients undergoing TIPS placement for refractory ascites or for secondary prophylaxis of variceal bleeding in the validation cohort.

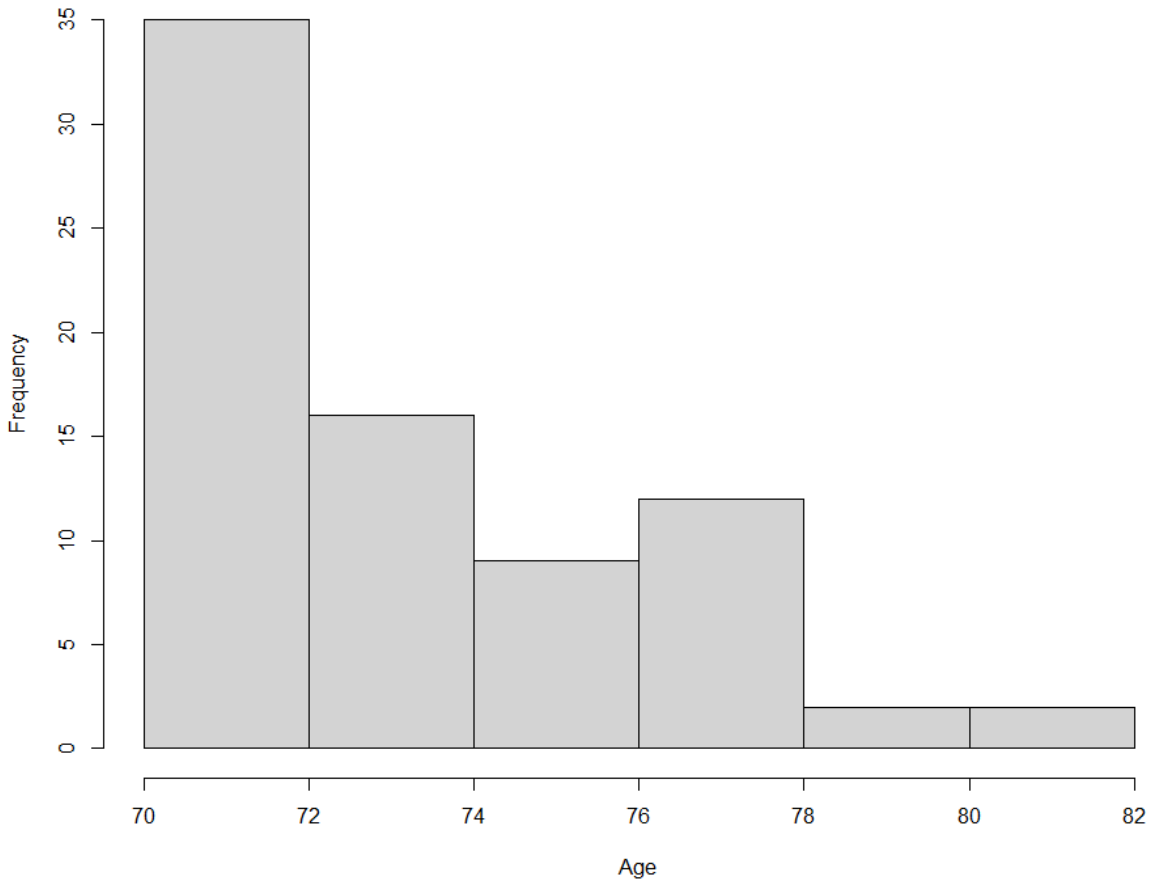
OLT, orthotopic liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt.



Supplementary Figure S12. One- and 2-year calibration curves on validation data for overall cohort model. The circle compares event rate (observed proportion) with average predicted risk (predicted probability). The grey line represents perfect calibration.



Supplementary Figure S13. Frequency distribution of age in 76 older adults (age ≥70 years) undergoing TIPS placement for refractory ascites or for secondary prophylaxis of variceal bleeding in the validation cohort.



Supplementary Table S1. TRIPOD Checklist for Prediction Model Development and Validation.

Section/Topic			Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2,3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4,5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4,5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4,5
	5b	D;V	Describe eligibility criteria for participants.	5
	5c	D;V	Give details of treatments received, if relevant.	5, supplementary materials page 1
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	7
Sample size	8	D;V	Explain how the study size was arrived at.	7, supplementary materials page 1
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7
	10c	V	For validation, describe how the predictions were calculated.	7,8
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	-
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	7
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	5, supplementary materials page 1
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8,9
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8,9, Table 1, Supplementary Tables S2, S4, S6-S11
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Supplementary Tables S7-S9, S11
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	9
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	-
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	10-12, Tables 2-3
	15b	D	Explain how to the use the prediction model.	7
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	10-13, Supplementary Figures S4, S5, S7, S9
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	-
Discussion				

Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16,17
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	14-16
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	14-17
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	14-17
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	7
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	1

Supplementary Table S2. Missing data in baseline characteristics of derivation cohort.

Variables	Missing data (%)
Age at TIPS placement	0
Male sex	0
Comorbidities	13
Etiology of cirrhosis	0.5
Albumin	3
Bilirubin	4
INR	4
Creatinine	2
Sodium	2
Platelet count	14
HE before TIPS	15
Child-Pugh score	3
Indication to TIPS placement	0
PSPG before TIPS	3
PSPG after TIPS	4
TIPS dilation diameter	2

TIPS, transjugular intrahepatic portosystemic shunt; INR, international normalized ratio; HE, hepatic encephalopathy; PSPG, porto-systemic pressure gradient.

Supplementary Table S3. Multivariable competing risks model for liver-related death including glomerular filtration rate (GFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula in the overall derivation cohort.

Overall cohort (N=411)			
Variable	**Beta**	**Standard error**	**p-value**
Alcoholic etiology*	0.20	0.370	0.37
NASH etiology*	-0.18	0.570	0.21
GFR	-0.01	0.004	0.11
INR	1.42	0.010	<0.001

NASH, non-alcoholic steatohepatitis. GFR, glomerular filtration rate. INR, international normalized ratio.

One-, 2- and 3-year AUC: 0.59 (95% CI 0.54-0.65).

Supplementary Table S4. Baseline characteristics of patients with TIPS placement according to the indication (refractory ascites or secondary prophylaxis of variceal bleeding) in the derivation cohort.

Variables	Refractory ascites (N=221)	Secondary prophylaxis of variceal bleeding (N=190)	*p*-value
Age at TIPS placement (years)	62.7±7.9	63.1±8.5	0.71
Male sex (%)	161 (72.8)	136 (71.6)	0.38
Etiology of cirrhosis (%)			
Alcohol alone	94 (42.5)	54 (28.4)	0.01
HCV alone	52 (23.5)	43 (22.6)	1
NASH alone	28 (12.7)	45 (23.7)	0.003
HBV alone	9 (4.1)	7 (3.7)	1
Concomitant etiologies:			
HCV+alcohol	8 (3.6)	10 (5.2)	0.52
HBV+alcohol	4 (18.1)	0 (0.0)	0.32
NASH+alcohol	6 (2.7)	5 (2.3)	0.77
Others	21 (9.5)	23 (12.1)	0.10
Comorbidities			
Diabetes	30 (13.6)	18 (9.5)	0.33
CKD	33 (14.9)	17 (8.9)	0.11
CHD	8 (3.6)	16 (8.4)	0.05
COPD	13 (5.9)	11 (5.8)	1
Albumin (g/dL)	3.3±0.54	3.2±0.62	0.46
Bilirubin (mg/dL)	1.40±0.78	1.36±0.82	0.61

INR	1.30±0.20	1.31±0.20	0.66
Creatinine (mg/dL)	1.17±0.49	0.97±0.43	<0.001
Sodium (mEq/L)	135±5	138±4	<0.001
Platelet count (10^9/L)	119±89	88±48	<0.001
HE before TIPS (%)	44 (20.0)	24 (12.6)	0.04
Child-Pugh score	8.1±1.0	6.9±1.5	<0.001
Child-Pugh class (%)			<0.001
A	0 (0.0)	88 (46.3)	
B	203 (91.9)	89 (46.8)	
C	18 (8.1)	13 (6.8)	
MELD score	12.7±3.7	11.5±3.3	<0.001
MELD-Na score	14.9±4.5	12.5±4.1	<0.001
PSPG before TIPS placement (mm Hg)	21.4±5.2	21.5±4.9	0.87
PSPG after TIPS placement (mm Hg)	11.1±4.5	10.0±4.2	0.02
TIPS dilation (median, IQR) (mm)	7 (2)	8 (2)	0.05
Underdilated TIPS (%)	115 (52.0)	90 (47.3)	0.16

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as absolute number (percentage) for categorical variables.

TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; PSPG, porto-systemic pressure gradient.

Supplementary Table S5. Risk factors for the development of hepatic encephalopathy after TIPS placement for refractory ascites or secondary prophylaxis of variceal bleeding in the derivation cohort by multivariable Cox regression analysis.

Variable	Beta	Hazard Ratio	95% Confidence Interval	*p*-value
Creatinine (mg/dL)	0.27	1.31	1.01-1.70	0.045
TIPS diameter ≤7 mm	-0.37	0.69	0.53-0.91	0.008

TIPS, transjugular intrahepatic portosystemic shunt.

Supplementary Table S6. Baseline characteristics of 415 patients with TIPS placement for refractory ascites or secondary prophylaxis of variceal bleeding in the validation cohort according to age (<70 years or ≥70 years).

Variables	Overall (N=415)	Age <70 years (N=339)	Age ≥70 years (N=76)	*p*-value
Age at TIPS placement (years)	63±6.9	60.6±5.0	73.5±3.1	<0.001
Male sex (%)	265 (64)	225 (66)	40 (53)	0.03
Etiology of cirrhosis (%)				
Alcohol	76 (18)	70 (20)	6 (8)	0.01
HCV	188 (46)	147 (44)	41 (54)	0.03
NASH	44 (11)	31 (9)	13 (17)	0.07
HBV	35 (8)	31 (9)	4 (5)	0.38
Others	70 (17)	58 (17)	12 (16)	0.90
Comorbidities				
Diabetes	84 (20)	63 (19)	21 (28)	0.57
CKD	24 (6)	18 (5)	6 (8)	0.90
CHD	12 (3)	10 (3)	2 (3)	0.90
COPD	14 (3)	13 (4)	1 (1)	0.28
Albumin (g/dL)	2.93±0.57	2.95±0.55	2.86±0.65	0.28
Bilirubin (mg/dL)	1.78±1.3	1.84±1.34	1.52±1.10	0.02
INR	1.28±0.25	1.28±0.25	1.28±0.25	1

Creatinine (mg/dL)	1.19±0.55	1.16±0.54	1.36±0.56	0.01
Sodium (mEq/L)	136±5	136±5	136±5	1
Platelet count (10^9/L)	95±59	95±61	94±47	0.89
Child-Pugh score	8.4±1.6	8.4±1.6	8.2±1.5	0.63
Child-Pugh class (%)				0.10
A	33 (8)	27 (8.5)	6 (8)	
B	278 (71)	218 (68.5)	60 (79)	
C	82 (21)	73 (23)	10 (13)	
MELD score	13±4	12.8±4.2	13.3±4.0	0.33
Indication to TIPS placement (%)				
- Refractory ascites	306 (74)	249 (73)	57 (75)	0.89
- Variceal bleeding	109 (26)	90 (27)	19 (25)	
PSPG before TIPS placement (mm Hg)	17.0±4.9	17.2±5.0	16.1±4.4	0.07
PSPG after TIPS placement (mm Hg)	6.9±3.0	7.1±3.0	6.2±2.7	0.028
TIPS dilation (median, IQR) (mm)	8 (2)	8 (2)	8 (2)	0.54
8 mm	238 (57.3)	192 (56.6)	46 (60.5)	0.54
10 mm	177 (42.7)	147 (43.4)	30 (39.5)	

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as absolute number (percentage) for categorical variables.

TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; PSPG, porto-systemic pressure gradient.

Supplementary Table S7. Baseline characteristics of patients with TIPS placement for refractory ascites or secondary prophylaxis of variceal bleeding in the derivation and in the validation cohort.

Variables	Derivation cohort (N=411)	Validation cohort (N=415)	*p*-value
Age at TIPS placement (years)	63±8.2	63±6.9	0.84
Male sex (%)	297 (72.3)	265 (64)	0.01
Etiology of cirrhosis (%)			
Alcohol	148 (36.0)	76 (18)	<0.001
HCV	95 (23.1)	188 (46)	<0.001
NASH	73 (17.8)	44 (11)	<0.001
HBV	16 (3.9)	35 (8)	0.01
Others	44 (10.7)	70 (17)	0.01
Comorbidities			
Diabetes	48 (11.7)	84 (20)	0.02
CKD	50 (12.2)	24 (15)	0.82
CHD	24 (5.8)	12 (8)	0.85
COPD	24 (5.8)	14 (9)	0.50
Albumin (g/dL)	3.33±0.57	2.93±0.57	<0.001
Bilirubin (mg/dL)	1.38±0.8	1.78±1.3	<0.001
INR	1.31±0.19	1.28±0.25	0.09
Creatinine (mg/dL)	1.07±0.47	1.19±0.55	0.001

Sodium (mEq/L)	137±5	136±5	0.05
Platelet count (10^9/L)	105±75	95±59	0.08
Child-Pugh score	7.5±1.4	8.4±1.6	<0.001
Child-Pugh class (%)			<0.001
A	88 (21.4)	33 (8)	
B	292 (71.0)	278 (71)	
C	31 (7.5)	82 (21)	
MELD score	12.1±3.6	13±4	<0.001
Indication to TIPS placement (%)			0.002
- Refractory ascites	221 (53.8)	306 (74)	
- Variceal bleeding	190 (46.3)	109 (26)	
PSPG before TIPS placement (mm Hg)	21.5±5.1	17.0±4.9	<0.001
PSPG after TIPS placement (mm Hg)	10.7±4.4	6.9±3.0	<0.001
TIPS dilation (mm)			<0.001
6 mm	170 (41.4)	0 (0)	
7 mm	35 (8.5)	0 (0)	
8 mm	122 (29.7)	238 (57.3)	
10 mm	84 (20.4)	177 (42.7)	

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as absolute number (percentage) for categorical variables.

TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; MELD, model for end-stage liver disease; PSPG, porto-systemic pressure gradient.

Supplementary Table S8. Baseline characteristics of patients with TIPS placement for refractory ascites in derivation and validation cohorts.

Variables	Refractory ascites Derivation cohort (N=221)	Refractory ascites Validation cohort (N=306)	*p*-value
Age at TIPS placement (years)	62.7±7.9	63±6.9	0.18
Male sex (%)	161 (72.8)	200 (65)	0.18
Etiology of cirrhosis (%)			
Alcohol	94 (42.5)	63 (21)	<0.001
HCV	52 (23.5)	130 (43)	<0.001
NASH	28 (12.7)	38 (12)	0.60
HBV	9 (4.1)	26 (9)	0.22
Others	21 (9.5)	48 (16)	0.05
Comorbidities			
Diabetes	30 (13.6)	71 (23)	<0.001
CKD	33 (14.9)	22 (7)	0.78
CHD	8 (3.6)	10 (3)	0.23
COPD	13 (5.9)	11 (4)	0.09
Albumin (g/dL)	3.3±0.54	2.98±0.56	<0.001
Bilirubin (mg/dL)	1.40±0.78	1.86±1.31	<0.001
INR	1.30±0.20	1.29±0.24	0.47
Creatinine (mg/dL)	1.17±0.49	1.26±0.57	0.05
Sodium (mEq/L)	135±5	135±4.6	0.14

Platelet count (10^9/L)	119±89	97±60	0.003
Child-Pugh score	8.1±1.0	8.7 (1.4)	<0.001
Child-Pugh class (%)			<0.001
A	0 (0.0)	0 (0)	
B	203 (91.9)	230 (75)	
C	18 (8.1)	76 (25)	
MELD score	12.7±3.7	13.4±4.1	0.006
PSPG before TIPS placement (mm Hg)	21.4±5.2	17.0±4.7	<0.001
PSPG after TIPS placement (mm Hg)	11.1±4.5	7.0±2.9	<0.001
TIPS dilation (mm)	7 (2)	8 (2)	<0.001
Underdilated TIPS (%)	115 (52.0)	0 (0.0)	<0.001

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as absolute number (percentage) for categorical variables.

TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; HE, hepatic encephalopathy; MELD, model for end-stage liver disease, PSPG, porto-systemic pressure gradient.

Supplementary Table S9. Baseline characteristics of patients with TIPS placement for secondary prophylaxis of variceal bleeding in derivation and validation cohorts.

Variables	Secondary prophylaxis of variceal bleeding Derivation cohort (N=190)	Secondary prophylaxis of variceal bleeding Validation cohort (N=109)	*p*-value
Age at TIPS placement (years)	63.1±8.5	62±6.7	0.24
Male sex (%)	136 (71.6)	65 (60)	0.05
Etiology of cirrhosis (%)			
Alcohol	54 (28.4)	13 (12)	0.001
HCV	43 (22.6)	58 (53)	<0.001
NASH	45 (23.7)	6 (6)	<0.001
HBV	7 (3.7)	9 (8)	0.25
Others	23 (12.1)	22 (20)	0.01
Comorbidities			
Diabetes	18 (9.5)	13 (12)	<0.001
CKD	17 (8.9)	2 (2)	0.75
CHD	16 (8.4)	2 (2)	0.88
COPD	11 (5.8)	3 (3)	0.82
Albumin (g/dL)	3.2±0.62	2.82±0.58	<0.001
Bilirubin (mg/dL)	1.36±0.82	1.50±1.23	0.13
INR	1.31±0.20	1.28±0.27	0.14

Creatinine (mg/dL)	0.97±0.43	1.00±0.44	0.53
Sodium (mEq/L)	138±4	139±5.1	0.19
Platelet count (10^9/L)	88±48	88±54	0.93
Child-Pugh score	6.9±1.5	7.5 (1.6)	0.009
Child-Pugh class (%)			0.46
A	88 (46.3)	33 (32)	
B	89 (46.8)	62 (58)	
C	13 (6.8)	11 (10)	
MELD score	11.5±3.3	11.6±4.1	0.89
PSPG before TIPS placement (mm Hg)	21.5±4.9	17.0±5.4	<0.001
PSPG after TIPS placement (mm Hg)	10.0±4.2	6.6±3.2	<0.001
TIPS dilation (mm)	8 (2)	8 (2)	1
Underdilated TIPS (%)	90 (47.3)	0 (0.0)	<0.001

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as absolute number (percentage) for categorical variables.

TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; HE, hepatic encephalopathy; MELD, model for end-stage liver disease, PSPG, porto-systemic pressure gradient.

Supplementary Table S10. Baseline characteristics of patients with TIPS placement according to the indication (refractory ascites or secondary prophylaxis of variceal bleeding) in the validation cohort.

Variables	Refractory ascites (N=306)	Secondary prophylaxis of variceal bleeding (N=109)	*p*-value
Age at TIPS placement (years)	63±6.9	62±6.7	0.14
Male sex (%)	200 (65)	65 (60)	0.29
Etiology of cirrhosis (%)			
Alcohol	63 (21)	13 (12)	0.07
HCV	130 (43)	58 (53)	0.06
NASH	38 (12)	6 (6)	0.07
HBV	26 (9)	9 (8)	1
Others	48 (16)	22 (20)	0.34
Comorbidities			
Diabetes	71 (23)	13 (12)	0.001
CKD	22 (7)	2 (2)	0.24
CHD	10 (3)	2 (2)	1
COPD	11 (4)	3 (3)	1
Albumin (g/dL)	2.98±0.56	2.82±0.58	0.02
Bilirubin (mg/dL)	1.86±1.31	1.50±1.23	0.04
INR	1.29±0.24	1.28±0.27	0.78
Creatinine (mg/dL)	1.26±0.57	1.00±0.44	<0.001

Sodium (mEq/L)	135±4.6	139±5.1	<0.001
Platelet count (10^9/L)	97±60	88±54	0.14
HE (%)	111 (38)	22 (21)	0.001
Child-Pugh score	8.7 (1.4)	7.5 (1.6)	<0.001
Child-Pugh class (%)			<0.001
A	0 (0)	33 (32)	
B	230 (75)	62 (58)	
C	76 (25)	11 (10)	
MELD score	13.4±4.1	11.6±4.1	<0.001
PSPG before TIPS placement (mm Hg)	17.0±4.7	17.0±5.4	0.99
PSPG after TIPS placement (mm Hg)	7.0±2.9	6.6±3.2	0.16
TIPS dilation (median, IQR) (mm)	8 (2)	8 (2)	0.57
8 mm	178 (58.2)	60 (55.0)	0.57
10 mm	128 (41.8)	49 (45.0)	

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as absolute number (percentage) for categorical variables.

TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; HE, hepatic encephalopathy; MELD, model for end-stage liver disease, PSPG, porto-systemic pressure gradient.

Supplementary Table S11. Baseline characteristics of older adult patients with TIPS placement for refractory ascites or secondary prophylaxis of variceal bleeding in the derivation and in the validation cohort.

Variables	Age ≥70 years Derivation cohort (N=99)	Age ≥70 years Validation cohort (N=76)	*p*-value
Age at TIPS placement (years)	74±3.3	73.5±3.1	0.15
Male sex (%)	69 (69.7)	40 (52.6)	0.03
Etiology of cirrhosis (%)			
Alcohol	18 (18.2)	6 (8)	0.08
HCV	38 (38.4)	41 (54)	<0.001
NASH	17 (17.2)	13 (17)	1
HBV	3 (3.0)	4 (5)	0.72
Others	17 (17.2)	12 (16)	0.80
Comorbidities			
Diabetes	48 (11.7)	84 (20)	0.02
CKD	50 (12.2)	24 (15)	0.82
CHD	24 (5.8)	12 (8)	0.85
COPD	24 (5.8)	14 (9)	0.50
Albumin (g/dL)	3.36±0.55	2.86±0.65	<0.001
Bilirubin (mg/dL)	1.27±0.75	1.52±1.10	0.08
INR	1.26±0.18	1.28±0.25	0.75
Creatinine (mg/dL)	1.19±0.53	1.36±0.56	0.05

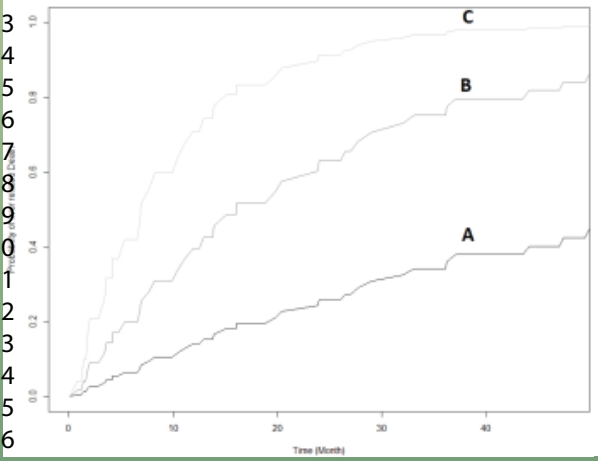
Sodium (mEq/L)	137±5	136±5	0.07
Platelet count (10^9/L)	98±46	94±47	0.63
Child-Pugh score	7.3±1.3	8.2±1.5	<0.001
Child-Pugh class (%)			<0.001
A	26 (26.3)	6 (8)	
B	70 (70.7)	60 (79)	
C	3 (3.0)	10 (13)	
MELD score	12.3±4.1	13.3±4.0	0.03
Indication to TIPS placement (%)			<0.001
- Refractory ascites	49 (49.5)	57 (75)	
- Variceal bleeding	50 (50.5)	19 (25)	
PSPG before TIPS placement (mm Hg)	21.9±5.0	16.1±4.4	<0.001
PSPG after TIPS placement (mm Hg)	10.4±4.4	6.2±2.7	<0.001
TIPS dilation (mm)	6.5 (2)	8 (2)	<0.001
6 mm	48 (48.5)	0 (0.0)	
7 mm	12 (12.1)	0 (0.0)	
8 mm	25 (25.3)	46 (60.5)	
10 mm	14 (14.1)	30 (39.5)	

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as absolute number (percentage) for categorical variables.

TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CHD, chronic heart disease; COPD, chronic obstructive pulmonary disease; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; MELD, model for end-stage liver disease; PSPG, porto-systemic pressure gradient.

Mortality after TIPS in older adult cirrhotic patients

Indication for TIPS in older adult patients (≥70 years) is debated and a specific prediction model in this setting is lacking



Predicted probabilities of liver-related death in three different older adult patient profiles:

- ✓ **A** favorable - creatinine 1.2 mg/dL, sodium 140 mEq/L
- ✓ **B** intermediate - creatinine 2 mg/dL, sodium 135 mEq/L
- ✓ **C** unfavorable - creatinine 2.5 mg/dL, sodium 130 mEq/L

We developed a prediction model (Elderly Patients Calculator TIPS, ExPeCT) to be applied to older adult patients to be candidate to TIPS:

https://promisepa.shinyapps.io/TIPS

Creatinine and sodium levels allow to predict 1-, 2- or 3-year mortality following TIPS

ExPeCT is useful to identify patients with a post-derivative favorable outcome
TIPS should not be precluded to carefully selected patients older than 70 years

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