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A novel score predicts mortality after transjugular intrahepatic portosystemic shunt: MOTS - Modified TIPS Score

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Abstract

Background and aims: The high risk for severe shunting-related post-interventional complications demands a stringent selection of candidates for transjugular intrahepatic portosystemic shunt (TIPS). We aimed to develop a simple and reliable tool to accurately predict early post-TIPS mortality.

Methods: 144 cases of TIPS implantation were retrospectively analysed. Using univariate and multivariate Cox regression analysis of factors predicting mortality within 90 days after TIPS, a score integrating urea, international normalized ratio (INR) and bilirubin was developed. The Modified TIPS-Score (MOTS) ranges from 0 to 3 points: INR >1.6, urea >71 mg/dl and bilirubin >2.2 mg/dl account for one point each. Additionally, MOTS was tested in an external validation cohort ($n = 187$) and its performance was compared to existing models.

Results: Modified TIPS-Score achieved a significant prognostic discrimination reflected by 90-day mortality of 8% in patients with MOTS 0–1 and 60% in patients with MOTS 2–3 ($p < .001$). Predictive performance (area under the curve) of MOTS was accurate ($c = 0.845$ [0.73–0.96], $p < .001$), also in patients with renal insufficiency ($c = 0.830$ [0.64–1.00], $p = .02$) and in patients with refractory ascites ($c = 0.949$ [0.88–1.00], $p < .001$), which are subgroups with particular room for improvement of post-TIPS mortality prediction. The results were reproducible in the validation cohort.

Conclusions: Modified TIPS-Score is a novel, practicable tool to predict post-TIPS mortality, that can significantly simplify clinical decision making. Its practical applicability should be further investigated.

KEYWORDS
hepatic encephalopathy, mortality, prediction, renal insufficiency, risk, transjugular intrahepatic portosystemic shunt

1 | INTRODUCTION

Since the first transjugular intrahepatic portosystemic shunt (TIPS) has been implanted in 1982, technical improvement, practical experience and scientific evidence have contributed to the current clinical value of this intervention.[1,2] During the last three decades, TIPS has evolved as an effective treatment of portal hypertension-related complications with beneficial effects on morbidity and mortality in selected patients.[3–7] However, severe shunting-related complications, such as refractory post-TIPS hepatic encephalopathy (HE) and acute chronic liver failure demand an optimal selection of candidates. Numerous models have been developed in order to identify patients who are at high risk for poor outcome and post-TIPS mortality.[8–12] The best-known example is the model of end-stage liver disease (MELD), which was initially published in 2000 as a model to predict 3-month survival after TIPS.[13] Besides its role as a severity-estimating tool of liver disease, MELD has also remained the primary tool to predict post-TIPS mortality compared to other models, such as Child-Pugh score, MELD-Na, Emory score, Platelet- Albumin-Bilirubin, CLIF-C AD and ACLF scores.[9,10,14] However, the suitability of MELD for some of its applications is controversial.[15,16] Creatinine is the most frequently criticized component of MELD as it may underestimate liver disease severity, especially in patients with sarcopenia and simultaneously overestimate disease severity in patients with non-liver related renal dysfunction.[17,18] In particular for the prediction of post-TIPS outcome, creatinine may bear the risk of overestimating mortality in patients with renal impairment and therefore impede optimal therapy, especially in patients with ascites and hepatorenal syndrome as renal function improves significantly after TIPS.[19–21] A model including creatinine, bilirubin, albumin and age, the Freiburg index of post-TIPS survival (FIPS), showing improved prognostic discrimination compared to established models, was recently published.[22] However, in two external validation cohorts, the superiority of FIPS over MELD and Child-Pugh scores could not be confirmed.[23,24] The present study aimed to develop a modified TIPS score (MOTS), based on MELD, the current gold standard of post-TIPS mortality prediction, that can be calculated from routine laboratory parameters without any technical help and is widely applicable.

Lay Summary

Transjugular intrahepatic portosystemic shunt (TIPS), an artificially created connection between the portal vein and a hepatic vein, can be helpful for selected patients with significant portal hypertension. The Modified TIPS score is a novel tool to estimate the risk of dying within 90 days after this intervention, thus supporting optimal patient selection.

2 | METHODS

2.1 | Training cohort and score development

In this retrospective study, we analysed all cases of TIPS placement performed between January 2004 and December 2017 at the Medical University Hospital of Graz, Austria. The study protocol was approved by the institutional review board of the Medical University of Graz (30-169 ex 17/18) and the study was registered at clinicaltrials.gov (NCT03459378). Data was collected between 03/2018 and 11/2018 via the local medical information system. All patients received PTFE-covered stent grafts, which is the current standard of care. TIPS revisions were not counted as independent cases but were recorded and assigned to the corresponding case. Patients were excluded in case of a complete lack of pre-TIPS medical history and laboratory data or non-existent follow-up data.

2.1.1 | Survival analysis

In the first step, univariate Cox proportional hazards regression was performed to identify factors predictive for 90-day mortality in the total cohort as well as in the subgroup of patients with renal insufficiency, defined by a baseline glomerular filtration rate of less than 60 ml/min/1.73. In the second step, laboratory parameters that significantly predicted 90-day mortality in univariate analysis were included in a multivariate Cox regression model with stepwise backwards selection. Kaplan–Meier estimates were created and compared using log-rank test and chi-square. Patients were censored at the day of the last follow-up, if they were lost to follow-up and at the day of transplantation if they received liver transplantation.

2.1.2 | Score development

Laboratory parameters that significantly predicted 90-day mortality in the multivariate stepwise backwards survival analysis were included in the scoring model. As (active) bleeding as well as administered blood products have an impact on many routine laboratory parameters such as haemoglobin, platelet count, international normalized ratio (INR), urea and other renal functional parameters, we decided to define the cut-off values of our score parameters by means of the group of patients receiving TIPS for ascites indications. First, receiver operating characteristic (ROC) curves of the parameters predicting 90-day mortality in multivariate analysis were charted and ROC coordinates were listed. Youden's index (J; J = sensitivity + specificity − 1) was determined for all coordinates. For each parameter, the best three cut-off values with the highest Youden's indices were selected and three scores were developed: Score 1 integrated the cut-off with the highest Youden Index for each parameter, score 2 integrated the cut-offs with the second-highest index and score 3 integrated the cut-offs with the third-highest index. In order to further simplify the model, one point was allocated for each parameter with a value exceeding the cut-off threshold. The predictive performance of all three models was then compared using area under receiver operating characteristic (AUROC) statistics and the score with the highest AUROC predicting 90-day mortality was selected as our final scoring model. AUROC statistics were also utilized to assess the prognostic capability of our newly created MOTS as well as for model comparison. The capability was expressed as AUROC value (=*c*-value) and corresponding 95% confidence interval. Pairwise comparison of AUROCs was performed using the method described by DeLong et al.[25]

2.2 | Model validation

To evaluate the performance of our MOTS in an external validation cohort, we collaborated with the Department of Internal Medicine I at the University Hospital of Innsbruck, Austria. The study protocol was approved by the institutional review board of the University Hospital of Innsbruck with an amendment to the study protocol AN2017-0016 369/4.21. Patients who received PTFE-covered TIPS between 2000 and 2019 were included. As in our training cohort, exclusion criteria were a complete lack of pre-TIPS medical history and laboratory data as well as non-existent follow-up data. Additionally, we excluded patients who received TIPS for an indication that could not be assigned to one of the three indication categories of our training cohort: "bleeding", "ascites" and "hepatic pleural effusion".

2.3 | Statistical analysis

Statistical calculations were performed using IBM SPSS 26.0 (IBM Corp). Continuous variables were expressed as median (interquartile range, IQR [25th percentile–75th percentile]) and categorical variables as absolute number (percentage). For the comparison of categorical data, Fisher's exact test was utilized, whereas for the comparison of continuous variables, Mann–Whitney *U* test was used. Additionally, for comparison of baseline variables between cohorts, standardized difference was calculated for both, continuous and categorical baseline variables. For all statistical tests, *p* values <.05 were considered significant.

3 | RESULTS

3.1 | Patient characteristics of the training cohort

A total of 158 patients received TIPS between January 2004 and December 2017 at the Medical University Hospital of Graz, Austria. Fourteen were excluded as a result of missing data (Figure 1). Table 1 summarizes the baseline characteristics of the 144 patients of the training cohort. Most patients were male (n = 113, 78%) with a median age of 56 (IQR: 48–63) years and evidence of cirrhosis (n = 137, 95%). Indications for TIPS placement were diuretic-refractory or recurrent ascites (n = 82, 57%), portal hypertensive bleeding (n = 51, 35%) and refractory pleural effusion (n = 11, 8%). Of the 51 patients who underwent the intervention for bleeding indications, 26 (51%) received early TIPS, defined as TIPS placement within 72 h after a bleeding event. During a median time of post-TIPS follow-up of 17.6 (IQR: 2.9–48.1) months, 31 (22%) patients received liver transplantation and 71 (49%) died.

3.2 | 90-day follow-up

90-day mortality rate was 19% (n = 27), and 6% of patients (n = 8) were transplanted within this time period. Eight patients (6%) were lost to follow-up, hence, the transplantation-free 90-day survival rate

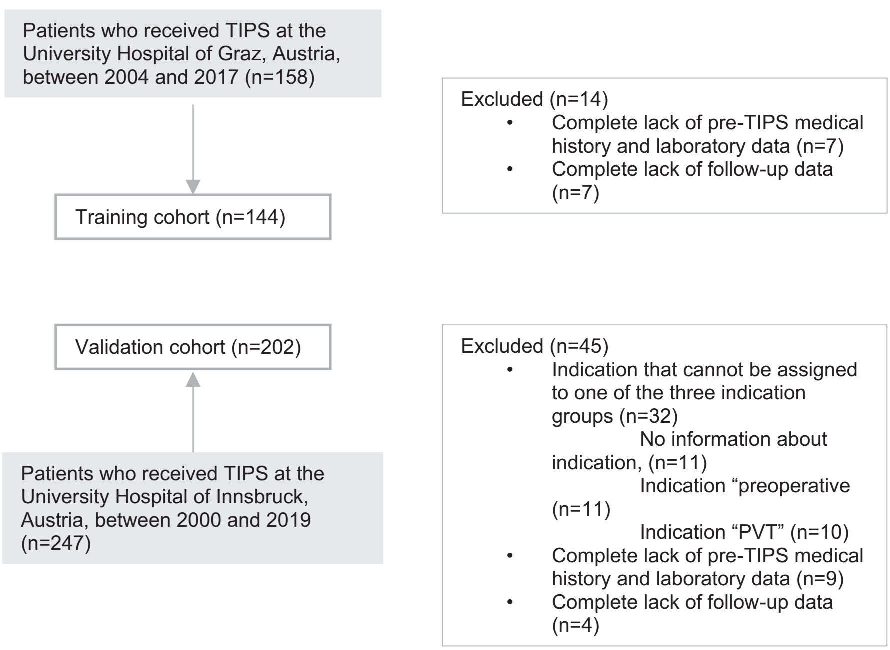


FIGURE 1 Flowchart of patients in the study. Three indication groups: diuretic-refractory or recurrent ascites, portal hypertensive bleeding and refractory pleural effusion. PVT, portal venous thrombosis; TIPS, transjugular intrahepatic portosystemic shunt

TABLE 1 Baseline characteristics of patients in the training cohort (n = 144)

Parameters		Values existing
Age (years)	56 (48–63)	144
Female	31 (22%)	144
Aetiology of portal hypertension		144
Alcohol-related liver disease	107 (74%)	
Chronic viral hepatitis	13 (9%)	
Budd-Chiari syndrome	5 (4%)	
Non-alcoholic fatty liver disease	4 (3%)	
Other aetiology	15 (10%)	
Evidence of cirrhosis		144
Yes	137 (95%)	
No	7 (5%)	
Budd-Chiari syndrome	5 (4%)	
Idiopathic portal hypertension	1 (1%)	
Chronic GvHD	1 (1%)	
Portal vein thrombosis at the time of TIPS		144
Partial	12 (8%)	
Total	2 (1%)	
TIPS main indication		144
Refractory/recurrent ascites	82 (57%)	
Portal hypertensive bleeding	51 (35%)	
Pre-emptive (early) TIPS	26 (51%)	
Refractory pleural effusion	11 (8%)	
Pre-TIPS medical history		144
Large volume paracentesis (≥1 time)	102 (71%)	
Gastrointestinal bleeding (≥1 episode)	63 (44%)	
Spontaneous bacterial peritonitis (≥1 episode)	16 (11%)	
Hepatic encephalopathy (≥1 episode)	21 (15%)	
Diagnosis of HCC[a]	4 (3%)	
Diabetes	36 (25%)	
Pre-TIPS HVPG (mmHg)	17 (13–20)	107
Post-TIPS HVPG (mmHg)	7 (5–10)	125
MELD	13 (10–17)	113
MELD-Na	16 (13–21)	113
Child-Pugh	8 (7–9)	92
A	11 (12%)	
B	64 (70%)	
C	17 (19%)	
CLIF-C AD	50 (45–58)	132
FIPS	−0.21 (−1.0–0.42)	95
BILI-PLT		120
Platelet count >75 G/L *and* bilirubin <3 mg/dl	76 (63%)	
Platelet count <75 G/L *or* bilirubin >3 mg/dl	30 (25%)	
Platelet count <75 G/L *and* bilirubin >3 mg/dl	14 (12%)	
Sodium (mmol/L)	136 (133–139)	142
Potassium (mmol/L)	4.1 (3.6–4.5)	141
eGFR (ml/min/1.73)	79 (57–103)	124
Creatinine (mg/dl)	0.98 (0.74–1.29)	139
Urea (mg/dl)	41 (27–78)	136
Bilirubin (mg/dl)	1.49 (0.90–2.62)	120
Albumin (g/L)	3.3 (2.9–3.6)	98
INR	1.36 (1.21–1.54)	135
AST (U/L)	40 (33–58)	132
ALT (U/L)	22 (16–35)	133
GGT (U/L)	94 (53–170)	128
CRP (mg/L)	11.1 (6.0–24.3)	131
Haemoglobin (g/dl)	10.1 (8.9–11.5)	142
Platelets (G/L)	110 (69–164)	142
Leucocytes (G/L)	6.6 (4.4–8.7)	142
Fibrinogen (mg/dl)	225 (174–333)	77

Note: Continuous variables are expressed as median (interquartile range, IQR). Categorical variables are expressed as absolute number (percentage).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI-PLT, model combining bilirubin (BILI); CLIF-C AD, CLIF-C Acute Decompensation model; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FIPS, Freiburg index of post-TIPS survival; GGT, gamma-glutamyltransferase; GvHD, graft-versus-host disease; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, model for end-stage liver disease; MELD-Na, Sodium-MELD; PLT, platelet count; TIPS, transjugular intrahepatic portosystemic shunt.

[a]All four patients had Barcelona-Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma at time of TIPS.

was 74% (101/136). Acute-on-chronic liver failure was the most common cause of death within 90 days (n = 5; 19% of deaths). Notably, the second leading cause of early mortality was the primary bleeding event that could not be solved by early or rescue TIPS (n = 4; 15%). Three patients (11%) died of a severe episode of HE with aspiration pneumonia within 90 days (Table S1).

3.3 | Factors predicting 90-day mortality

Among baseline laboratory parameters, higher bilirubin, urea, creatinine, INR, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and leucocytes as well as lower haemoglobin, platelets, gamma-glutamyltransferase and fibrinogen were significantly associated with poor survival (Table 2). Other factors that significantly predicted 90-day mortality in univariate analysis were history of HE, previously diagnosed hepatocellular carcinoma, an aetiology of portal hypertension classified among "other aetiologies" (see Table S2) as well as high MELD and Child-Pugh score. When laboratory parameters with univariate significance were entered in a multivariate stepwise backward Cox regression model, high urea and INR remained independently associated with 90-day mortality. We additionally studied prognostic laboratory features in the subgroup of patients with renal insufficiency, defined by a glomerular filtration rate below 60 ml/min/1.73 m^2 (n = 37; 26%). In these patients, high urea, bilirubin and leucocytes significantly predicted 90-day mortality in univariate analysis and bilirubin and leucocytes remained significant predictors in the multivariate model (Table 2).

3.4 | Selection of score parameters

The next step was to select the parameters of our future risk score. In the total cohort, high urea and INR were independent predictors of mortality. Given our intention to create a predictive model based on MELD, we decided to integrate bilirubin as a third variable being a significant mortality predictor in univariate analysis of the total cohort as well as in uni- and multivariate analysis of patients with renal insufficiency. Thus, a score integrating urea, INR and bilirubin was developed as described in the methods section.

3.5 | Modified TIPS score

The MOTS ranges from zero to three points: urea exceeding 71 mg/dl, an INR higher than 1.6 and bilirubin higher than 2.2 mg/dl account for one point each. We next calculated MOTS in all patients in whom the three parameters were available (110 patients, 76%).

3.6 | Score performance

Calculating MOTS in individual patients results in a score between zero and three points. In our training cohort, in patients with a MOTS of zero (n = 50) 90-day mortality rate was 4%, in patients with a MOTS of one (n = 40) 13%, with a MOTS of two (n = 12) 50% and with a MOTS score of three points (n = 8) 75% (p < .001) (Figure 2). To assess the capability of our new MOTS, AUROC-statistic was performed and AUROC-values (c-values) were calculated for MELD, MELD-Na, Child-Pugh score, BILI-PLT score (a model combining bilirubin and platelet count[8]), CLIF-C AD score and the Freiburg index of post-TIPS survival (FIPS). All scores were available in 82 patients. MOTS predicted 90-day mortality with an AUROC-value of 0.845, p < .001, compared to MELD (c = 0.830, p < .001), MELD-Na (c = 0.779, p < .001), CLIF-C AD (c = 0.764, p = .001), FIPS (c = 0.751, p = .001), BILI-PLT (c = 0.736, p = .002) and Child-Pugh score (c = 0.693, p = .01) (Table 3; Figure 3). Pairwise comparison of AUROCs showed significant superiority of MOTS, MELD and MELD-Na over Child-Pugh (MOTS vs. Child-Pugh, p = .01; MELD vs. Child-Pugh, p = .01; MELD-Na vs. Child-Pugh p = .049). The numerical AUROC-differences between MOTS and MELD, MELD-Na, BILI-PLT-score, CLIF-C AD and FIPS were not statistically significant (Table S3).

To see, whether MOTS can provide sufficient prognostic stratification in patients with renal insufficiency as well as in patients with ascites/bleeding indication, subgroup AUROC analysis was performed for the different indications as well as in patients with a baseline estimated glomerular filtration rate (eGFR) <60. All scores were available in only 19 of 37 patients with eGFR <60. With an AUROC-value of 0.830, p = .02, MOTS showed good predictive accuracy in this patient subgroup, as well as FIPS, MELD and BILI-PLT. MELD-Na, Child-Pugh and CLIF-C AD scores did not significantly predict mortality in patients with renal insufficiency (Table S4). In patients with bleeding indications, all models could be calculated in 30 patients. MOTS significantly predicted mortality with an AUROC of 0.784, p = .02, in line with CLIF-C AD and MELD-Na. By contrast, FIPS, MELD, Child-Pugh and BILI-PLT were not significantly predictive in patients receiving TIPS for bleeding indications (Table S4). In the ascites-subgroup (n = 45), MOTS predicted the outcome with an excellent AUROC of 0.949, p < .001, in line with all six other models (Table S4). In pairwise AUROC-comparison none of these differences within the smaller subgroups were statistically significant (Table S3). In summary, MOTS predicted the outcome with high accuracy and was the only model that significantly predicted 90-day mortality in all examined subgroups. Statistic superiority of MOTS was only reached over Child-Pugh score in the total training cohort.

3.7 | Score validation

In order to validate our newly created post-TIPS mortality-predicting model, we analysed data of 202 patients from an external validation cohort. MOTS and MELD scores were available in 187 patients (93%). Table 4 shows a comparison of baseline- and follow-up data between the validation cohort (Vc) and the training cohort (Tc) from which our model was derived. In the validation cohort, significantly more patients received TIPS for ascites and less for bleeding than in the training cohort. No significant differences were seen in baseline MELD and MOTS. Notably, 90-day mortality rate was significantly lower in the validation cohort (Vc: 6% vs. Tc: 17%; d = .35, p = .01) and a higher percentage of patients was lost to follow-up in the validation cohort (Vc: 13% vs. Tc: 4%; d = −.33, p = .01). 90-day mortality rate was 1%, 6%, 23% and 25% with MOTS of 0 (n = 92), 1 (n = 70), 2 (n = 22) and 3 (n = 4) (p < .001) (Figure 4). MOTS predicted 90-day mortality with an AUROC-value of 0.803, p = .001. The performance of MELD was comparable (c = 0.777, p = .002) (Table 3). In patients with renal insufficiency (n = 61), MOTS showed good predictive

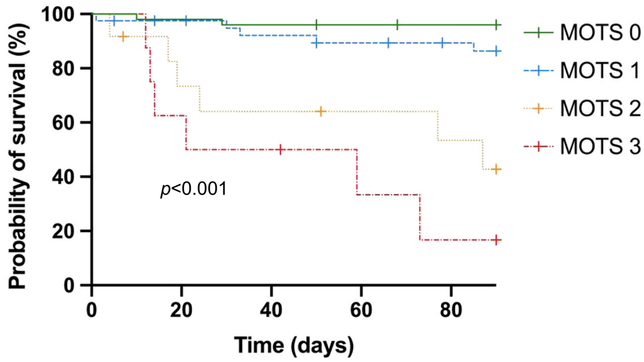
TABLE 2 Factors predicting 90-day mortality within the total training group as well as in patients with renal insufficiency

Univariate analysis	Total training cohort		Patients with renal insufficiency	
Parameter	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Female sex	1.07 (0.43–2.64)	.89	1.43 (0.36–5.53)	.61
Aetiology of PH				
Alcohol	1.00		1.00	
Viral	1.70 (0.49–5.85)	.40	–	–
BCS	1.29 (0.17–9.74)	.81	1.91 (0.22–16.48)	.56
Others	3.10 (1.28–7.56)	**.01**	2.76 (0.74–10.32	.13
TIPS-indication				
Ascites	1.00		1.00	
Bleeding	1.20 (0.53–2.73)	.67	1.47 (0.41–5.20)	.56
Pleural effusion	2.71 (0.88–8.32)	.08	–	–
Diabetes	0.82 (0.50–1.34)	.43	0.91 (0.40–2.07)	.83
Pre-TIPS bleeding	0.81 (0.37–1.74)	.58	1.28 (0.36–4.54)	.70
Pre-TIPS SBP	1.33 (0.46–3.84)	.60	1.31 (0.34–5.06)	.70
Pre-TIPS HE	2.48 (1.09–5.67)	.03	0.61 (0.08–4.85)	.64
Pre-TIPS ascites	1.35 (0.57–3.20)	.49	1.40 (0.30–6.60)	.67
Pre-TIPS PVT				
None	1.00		1.0	
Partial	1.40 (0.42–4.65)	.59	1.43 (0.30–6.74)	.065
Total	2.26 (0.31–16.72)	.43	–	–
Pre-TIPS HCC	4.81 (1.14–20.38)	.03	–	–
Age	1.02 (0.99–1.06)	.20	0.97 (0.92–1.02)	.28
Pre-TIPS HVPG	0.97 (0.90–1.04)	.35	1.01 (0.90–1.13)	.88
Post-TIPS HVPG	0.88 (0.76–1.0)	.06	0.93 (0.74–1.17)	.52
HVPG difference	1.01 (0.94–1.08)	.83	1.04 (0.92–1.18)	.51
Sodium (mmol/L)	0.97 (0.91–1.05)	.45	1.01 (0.92–1.12)	.84
Potassium (mmol/L)	1.56 (0.94–2.61)	.09	1.50 (0.69–3.27)	.30
Creatinine (mg/dl)	1.27 (1.02–1.58)	.03	1.12 (0.82–1.52)	.48
eGFR (ml/min/1.73)	1.00 (0.99–1.01)	.61	0.97 (0.93–1.01)	.13
Urea (mg/dl)	1.02 (1.01–1.03)	<.001	1.02 (1.01–1.04)	.001
Bilirubin (mg/dl)	1.09 (1.05–1.13)	<.001	1.10 (1.02–1.18)	.02
Albumin (g/L)	0.70 (0.35–1.40)	.31	0.41 (0.14–1.19)	.10
INR	6.68 (3.03–14.73)	<.001	2.58 (0.85–7.85)	.09
AST (U/L)	1.001 (1.0–1.002)	.002	1.001 (1.0–1.002)	.06
ALT (U/L)	1.001 (1.0–1.002)	.03	1.001 (1.0–1.002)	.20
GGT (U/L)	0.99 (0.99–1.0)	.03	1.00 (0.99–1.01)	.91
CRP (mg/L)	1.01 (0.99–1.02)	.08	1.01 (0.99–1.03)	.14
Haemoglobin (g/dl)	0.76 (0.61–0.94)	.02	0.76 (0.51–1.14)	.19
Platelets (G/L)	0.99 (0.98–1.00)	.009	0.99 (0.98–1.00)	.14
Leukocytes (G/L)	1.07 (1.01–1.14)	.02	1.11 (1.02–1.22)	.02
Fibrinogen (mg/dl)	0.99 (0.99–1.00)	.03	1.00 (0.99–1.00)	.60
Multivariate analysis				
Urea (mg/dl)	1.01 (1.0–1.02)	.003		[a]
INR	6.67 (2.05–21.76)	.002		[a]
Bilirubin (mg/dl)		[a]	1.10 (1.02–1.19)	.02
Leucocytes (G/L)		[a]	1.16 (1.03–1.31)	.01

Note: Univariate and multivariate Cox proportional hazard models to identify factors associated with 90-day mortality. Laboratory parameters that were significantly predictive in univariate analysis were included in a multivariate Cox-Regression with stepwise backwards selection. Of the multivariate analysis, only significant parameters are shown in the table. –, no HR calculated because of low number of patients.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCS, Budd-Chiari syndrome; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HR, hazard ratio; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; PVT, portal venous thrombosis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

[a]Not represented in the result of the multivariate model.



Patients at risk

MOTS 0	50 (0)	49 (0)	48 (0)	47 (1)	46 (2)
MOTS 1	40 (0)	37 (2)	34 (3)	32 (4)	29 (6)
MOTS 2	12 (0)	8 (1)	7 (1)	6 (2)	4 (2)
MOTS 3	8 (0)	5 (0)	4 (0)	2 (1)	1 (1)

FIGURE 2 Kaplan–Meier curves illustrating the probability of 90-day survival of MOTS groups in the training cohort. $p < .001$; number of patients at risk (number of patients censored) at day 0, 20, 40, 60, 90. MOTS, modified transjugular intrahepatic portosystemic shunt-score

TABLE 3 AUROC statistics of models predicting 90-day mortality

	Model	AUROC	*p*-value
Training cohort (*n* = 82)	MOTS	0.845 (0.73–0.96)	<.001
	MELD	0.830 (0.72–0.94)	<.001
	MELD-Na	0.779 (0.65–0.91)	<.001
	Child-Pugh	0.693 (0.55–0.84)	.01
	BILI-PLT	0.736 (0.60–0.88)	.002
	CLIF-C AD	0.764 (0.63–0.90)	.001
	FIPS	0.751 (0.60–0.90)	.001
Validation cohort (*n* = 187)	MOTS	0.803 (0.67–0.94)	.001
	MELD	0.777 (0.62–0.93)	.002

Note: Training cohort: all scores available in *n* = 82; Validation cohort: MELD and MOTS available in *n* = 187; Values indicate AUROC (95% confidence interval).

Abbreviations: AUROC, area under the receiver operating characteristic Curve; BILI-PLT, model combining bilirubin and platelet count; CLIF-C AD (Acute Decompensation); FIPS, Freiburg index of post-TIPS survival; MELD, model for end-stage liver disease; MOTS, modified TIPS score; TIPS, transjugular intrahepatic portosystemic shunt.

value ($c = 0.814$, $p = .02$), whereas MELD did not significantly predict mortality. MOTS and MELD predicted mortality in the ascites subgroup ($n = 124$; MOTS: $c = 0.760$, $p = .01$; MELD: $c = 0.725$, $p = .02$). There was only one observed death within 90 days in the subgroup of patients with bleeding indication ($n = 37$), which was correctly predicted by both scores (Table S4). The differences were not statistically significant in pairwise AUROC-comparison (Table S3).

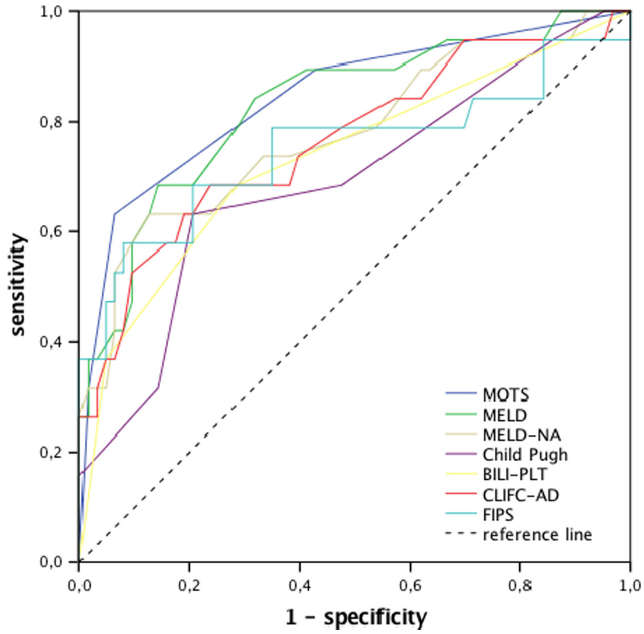


FIGURE 3 ROC curves illustrating the predictive capability of models in the total training cohort. All scores available in $n = 82$; BILIPLT, model combining bilirubin and platelet count; CLIF-C AD, CLIF-C Acute Decompensation score; FIPS, Freiburg index of post-TIPS survival; MELD, model for end stage liver disease; MELD-Na, MELD sodium score; MOTS, modified TIPS score; ROC, receiver operating characteristic curve; TIPS, transjugular intrahepatic portosystemic shunt; all models were significantly predictive. For reference see Table 3 showing the related area under receiver operating characteristic, confidence intervals and *p*-values

3.8 | Six-month follow-up of renal parameters

To investigate the effect of TIPS on parameters reflecting renal function (i.e. eGFR, creatinine, urea), postprocedural laboratory values at a time interval of about 6 months were obtained. Median time between TIPS and follow-up blood sampling was 6.2 (IQR: 5.1–6.9) months. Significant improvement of creatinine and eGFR was observed in patients with renal insufficiency at baseline (patients with baseline eGFR <60 ($n = 12$): median baseline eGFR 43 [IQR 23–57], vs. 62 [41–85] at 6-month follow-up, $p = .01$; baseline creatinine 1.68 [1.23–2.93], vs. 1.02 [0.90–1.77] at 6-month follow-up, $p = .03$), whereas urea levels decreased independent of the presence of renal insufficiency at baseline (total cohort ($n = 38$) baseline urea 43 [30–68] vs. 32 [20–48] at 6-month follow-up, $p = .01$) (Table S5).

4 | DISCUSSION

In clinical practice, decision-making on invasive procedures in patients with severe chronic liver disease is challenging. Particularly in the context of TIPS, not only liver disease-related risk factors such as impaired coagulation and immune dysfunction but also severe shunting-related complications (e.g. development or worsening of

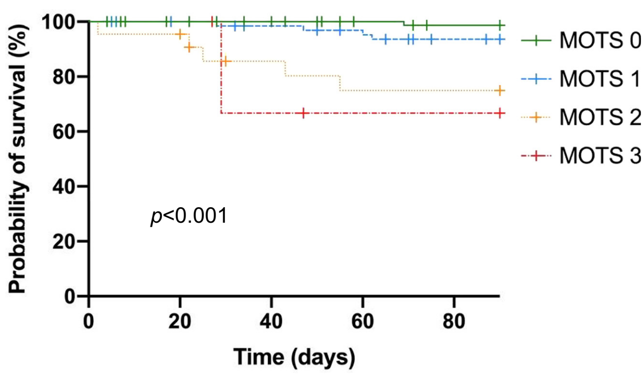
TABLE 4 Comparison of baseline- and follow-up data between patients of the validation cohort and the training cohort with available MOTS and MELD

Parameter	Training cohort (n = 110)	Validation cohort (n = 187)	Standardized difference[a]	p-value
Female sex	25 (23%)	60 (32%)	−0.20	.11
Age, median (IQR)	57 (50–63)	58 (51–65)	−0.09	.36
TIPS indication			1.69	.002
Ascites	62 (56%)	142 (76%)		.001
Bleeding	39 (36%)	37 (20%)		.004
Pleural effusion	9 (8%)	8 (4%)		.2
MELD, median (IQR)	13 (10–17)	13 (10–16)	0.15	.59
MOTS			0.10	.38
0	50 (46%)	91 (49%)		.63
1	40 (36%)	70 (37%)		.90
2	12 (11%)	22 (12%)		1.00
3	8 (7%)	4 (2%)		.06
90-day mortality	19 (17%)	11 (6%)	0.35	.01
90-day loss to follow-up	4 (4%)	25 (13%)	−0.33	.01
90-day LTX	7 (6%)	9 (5%)	0.04	.60

Note: Continuous variables are expressed as median (interquartile range, IQR). Categorical variables are expressed as absolute number (percentage). Data were compared using Fisher's exact test for categorical data and non-parametrical tests for continuous variables.

Abbreviations: LTX, liver transplantation; MELD, model for end-stage liver disease; MOTS, modified TIPS score; TIPS, transjugular intrahepatic portosystemic shunt.

[a]Standardized difference, d = difference in means or proportions divided by the standard error; imbalance between groups defined as an absolute value >0.20 (small effect size).[26]



Patients at risk

MOTS 0	92 (0)	88 (4)	84 (8)	79 (13)	76 (15)
MOTS 1	70 (0)	65 (5)	62 (7)	58 (9)	52 (14)
MOTS 2	22 (0)	20 (1)	16 (3)	14 (3)	14 (3)
MOTS 3	4 (0)	4 (0)	2 (1)	1 (2)	1 (2)

FIGURE 4 Kaplan–Meier curves illustrating the probability of 90-day survival of MOTS groups in the validation cohort. $p < .001$; number of patients at risk (number of patients censored) at day 0, 20, 40, 60, 90

HE, acute on chronic liver failure) demand very careful risk–benefit analysis. Previous studies emphasized the importance of individual risk assessment and careful patient selection for TIPS procedure.[27,28] Originally developed to predict 3-month survival after TIPS, MELD has remained the best validated prognostic tool for patients undergoing TIPS.[10,14,29] However, despite its sustainable prognostic value, MELD may have limited validity in some TIPS candidates, such as those with impaired renal function.[19]

International guidelines have found different ways to define patients who may not benefit from TIPS because of their severity of liver disease.[30,31] In the current clinical practice guidelines of the European Association for the Study of the Liver (EASL), this group of patients is defined by a BILI-PLT, even though predictive advantage over MELD has never been confirmed in a validation cohort.[8,31] Furthermore, although previous studies have shown predictive inferiority to MELD,[10,14,32] Child-Pugh score is still broadly used for the selection of patients to receive TIPS. In a recent study, Sturm et al. found the CLIF-C AD score to be a suitable prognostic tool.[33] One thousand and eighty-eight cases of TIPS placement were analysed, patients who met the criteria of acute-on-chronic liver failure (19%) were excluded. CLIF-C AD predicted 3-month transplant-free survival significantly better than Child-Pugh score and with numerically (but not significantly) higher c-value than MELD and ALBI but slightly lower c-value than MELD-Na. The authors concluded that CLIF-C AD score is superior to MELD and Child-Pugh but not to MELD-Na. Notably, 31% of patients received uncovered TIPS stents and with a c-value of 0.688 (0.64–0.74) for CLIF-C AD predicting 3-month transplant-free survival, the number of incorrect classifications was high. More recently, a novel post-TIPS mortality-predicting model was published by Bettinger et al. Utilizing retrospective data of 1496 patients who had received elective TIPS for ascites or bleeding, the

Freiburg index of post-TIPS survival (FIPS), calculated from age, bilirubin, albumin and creatinine, was developed. FIPS showed better prognostic discrimination than Child-Pugh, MELD, MELD-Na score and the bilirubin-platelet model. The results were reproducible in a validation cohort from the same patient pool but validation failed in the second group of external patients receiving early-TIPS[22] However, in two external cohorts from Denmark and China, FIPS showed markedly lower discriminatory performance than in the original publication.[23,24] In clinical practice, in the absence of the possibility of liver transplantation, TIPS is often performed as an effective option to manage severe portal hypertensive complications in elderly patients with comorbidities. The implementation of FIPS could lead to an exclusion of those patients with scarcely treatment alternatives. For example, a 71-year-old patient with refractory, symptomatic ascites, a creatinine of 2 mg/dl, bilirubin of 1.7 mg/dl and normal albumin levels (40 g/L) would be allocated to the high-risk group, therefore not receive elective TIPS. Furthermore, besides the below-described limitations of creatinine, albumin is a relatively unstable parameter because of frequent supplementation in the setting of decompensated cirrhosis.

With the MOTS, we developed a point-based tool to predict post-TIPS mortality, that can be calculated at the bedside from a minimal laboratory dataset. MOTS achieved significant prognostic discrimination reflected by 90-day mortality of only 8% in patients with MOTS 0–1 but as high as 60% in patients with MOTS 2–3 ($p < .001$). Our model predicted 90-day mortality with high accuracy and showed statistic superiority over Child-Pugh score. Moreover, of all examined models, MOTS was the only score, that significantly predicted mortality in all subgroups, whereas FIPS, MELD, Child-Pugh and BILI-PLT did not predict mortality in patients with bleeding indications and MELD-Na, Child-Pugh and CLIF-C AD were insufficient in patients with renal insufficiency. The good predictive capability of MOTS was confirmed in an external validation group.

Sharing the two components INR and bilirubin with MELD, MOTS contains urea instead of creatinine as a third parameter. Several aspects support the assumption that creatinine may not be an ideal prognostic indicator for patients undergoing TIPS. First, the majority of TIPS candidates are patients with decompensated cirrhosis. In these patients, creatinine and creatinine based equations have proved inaccurate to assess renal function inter alia because of the high prevalence of malnutrition and sarcopenia leading to an overestimation of renal function as less creatinine is produced.[34–36] Second, several studies have shown that especially in patients with renal insufficiency at baseline, renal function improves significantly after TIPS.[20,21] Concordantly, in our training cohort, a 44% increase of GFR as well as a 39% decline of serum creatinine was observed approximately 6 months after TIPS in patients with a baseline GFR lower than 60 ml/min/1.73 whereas no significant change appeared in patients with higher GFR (Table S5). An increase in central blood volume and inotropic function contribute to this improvement of renal function in patients with renal insufficiency undergoing TIPS.[18] Furthermore, a previous study emphasized that MELD may overestimate mortality in patients with reduced renal function undergoing TIPS.[19] Hence, it appears likely that MELD could limit the chance to receive TIPS for patients with high creatinine, even if exactly these patients may particularly benefit from the intervention.

In uni- and multivariate survival analyses, urea clearly outperformed creatinine as a mortality predictor in our total cohort as well as in patients with eGFR<60 ml/min/1.73. Furthermore, urea levels significantly decreased after TIPS, in patients with and without renal insufficiency before TIPS-placement (Table S5). These findings suggest that besides renal dysfunction, urea might reflect other factors associated with mortality in patients undergoing TIPS. Several studies have shown an association between urea levels and the severity of upper gastrointestinal bleedings.[37–40] Pathophysiologically, this link can be referred to as a gastrointestinal breakdown of blood components that leads to reabsorption of amino acids which in turn causes a rise of urea, the end product of amino acid metabolism.[40] Furthermore, high urea is a marker for renal hypoperfusion and consequentially an indicator of hypovolemia.[41] In our study, urea was an independent predictor of mortality in patients receiving TIPS for bleeding indications as well as in patients with ascites indications. Furthermore, with 36% and 35%, the proportion of patients with bleeding indications was similar in patients with MOTS 0–1 and MOTS 2–3 respectively. Hence, the reabsorption of blood components cannot be the sole association between high urea/MOTS and mortality.

Another possible link between high urea levels and post-TIPS mortality might be HE. As a major complication of the intervention, post-TIPS HE affects between 20% to 45% of patients. In our cohort, 23% of patients developed symptoms of HE after TIPS intervention and three (11%) of the 27 patients who died within 90 days after TIPS, died in the course of aspiration pneumonia during a severe episode of HE (West-Haven grade III–IV). Despite intensive research, the pathophysiology of HE is not yet fully understood.[42,43] One presumed mechanism of post-TIPS HE is an increased direct shunting of ammonia, a toxic waste product of amino acid depletion, from the portal drained viscera via the portosystemic short circuit.[44] In addition, portosystemic shunting has been shown to stimulate the activity of intestinal glutaminase in rat models, which directly leads to an increase in intestinal ammonia production.[45] However, the measurement of blood ammonia levels has proved inappropriate to diagnose or rule out HE in patients with chronic liver disease,[46,47] inter alia as various factors, such as the use of a tourniquet for blood sampling and in-vitro deamination after sample taking, impair the validity of ammonia as a biomarker.[48–50] Thus, we presume that urea might also play a role as a more stable indirect maker of in vivo ammonia levels and possibly predict post-TIPS HE. However, as consistent assessment of clinically diagnosed syndromes, such as HE, can only be performed in prospective trials, we were not able to accurately investigate the ability of MOTS to predict post-TIPS HE.

We aimed to develop a point-based score, even though these models have been subject to criticism because of potentially higher accuracy of hazard models to directly estimate the incidence of the outcome for any risk factor.[51] However, in clinical practice, point-based risk scores such as Child-Pugh score,[52] SOFA-score,[53] Wells score[54] or CHA2DS2-VASc[55] often seem to prevail, whereas more complex models frequently fall into oblivion. In order to see whether it outperformed the point-based MOTS, a model using the same variables but with a continuous scale (named LogMOTS) was created. Additionally, we created a scoring model that allocated points according to the hazard ratio of each parameter (HR-MOTS) (Table S6). As these two adapted models did not show superior prognostic value compared to MOTS, we chose the point-based score that allocates one point for each parameter exceeding the cut-off for practicability.

Our study has some certain limitations and there are issues to be discussed. First and foremost, except for Child-Pugh score, we did not obtain statistical superiority of MOTS over other established models, even though MOTS was the only model that significantly predicted mortality in all examined subgroups. In the training cohort, within patients with ascites indications, FIPS and MELD predicted mortality with an even slightly higher *c*-value than MOTS, whereas, in the validation cohort, MOTS showed a higher *c*-value than MELD. This can at least partly be explained by the relatively small sample size, as a direct comparison of prognostic capability was only possible in 82 patients of our training cohort in which all parameters were available and subgroup analysis was carried out in even smaller groups. Furthermore, as a result of the small number of patients, we were not able to investigate the predictive features of MOTS in patients with (early) pre-emptive TIPS. The number of patients who were lost to follow-up was relatively high, especially in the validation cohort, and increased over time. Thus, we were not able to obtain long term follow up data. Another issue to be discussed is the relatively heterogenous cohort from which our model was derived. Unlike in some previous studies, we deliberately did not exclude patients with active or recent bleeding, acute on chronic liver failure or early to intermediate stages of hepatocellular carcinoma, as we aimed to develop a prognostic tool that is widely applicable to "real-life" TIPS candidates and not only for a specific group of patients.

To conclude, we developed a bedside tool to predict early post-TIPS mortality with high accuracy in all subgroups. Our results were reproducible in an external validation cohort. Bedside calculation of MOTS (INR >1.6, urea >71 mg/dl and bilirubin >2.2 mg/dl imply plus one point each) enables us to subdivide the individual risk into four different risk groups. We are confident that this tool will significantly simplify decision making and may contribute to the reduction of early post-TIPS mortality. Its clinical applicability should be further investigated and steadily improved.

CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

ETHICS STATEMENT

The study protocol was approved by the institutional review board of the Medical University of Graz (30–169 *ex* 17/18) and was registered at clinicaltrials.gov (NCT03459378). For the validation cohort, the study protocol was approved by the institutional review board of the University Hospital of Innsbruck with an amendment to the study protocol AN2017-0016 369/4.21.

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SUPPORTING INFORMATION

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