Decision making for transjugular intrahepatic portosystemic stent shunt in refractory ascites and variceal bleeding: MELD, or not MELD, that is the question

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Purpose The model of end-stage liver disease (MELD) score has been shown to predict 3-month prognosis following transjugular intrahepatic portosystemic stent shunt (TIPS) in liver cirrhosis; however, that score was derived from a mixed cohort, including patients with refractory ascites and variceal bleeding. This study re-evaluates the role of the MELD score and focuses on differences between both groups of patients.

Methods A total of 301 patients (192 male and 109 female) received TIPS, 213 because of refractory ascites and 88 because of variceal bleeding. Univariate and multivariate Cox analyses were performed to identify predictors of mortality and area under the receiver operator characteristics (AUROC) were used to assess the prognostic capacity of the MELD score and of the results of predictors of the multivariate analyses.

Results In refractory ascites, age, bilirubin and albumin were independent predictors of mortality. In variceal bleeding, emergency TIPS during ongoing bleeding, concomitant grade III ascites, history of hepatic encephalopathy, spontaneous bacterial peritonitis, bilirubin and platelet count proved significant. AUROCs of the MELD score for 3-month survival yielded 0.543 and 0.836 for refractory ascites and variceal bleeding, respectively ($P<0.001$). For 1-year survival, the respective AUROCs yielded 0.533 and 0.767 ($P<0.001$). In contrast to MELD, the AUROCs based on the calculated risk scores of this study resulted in 0.660 and 0.876 for 3-month survival, and 0.665 and 0.835 for 1-year survival in patients with ascites and variceal bleeding, respectively.

Conclusion In refractory ascites, the prognostic capability of MELD is significantly inferior compared to variceal bleeding. The results of our multivariate analyses and AUROC calculations corroborate the impact of different prognostic variables in patients undergoing TIPS for ascites and variceal bleeding. Eur J Gastroenterol Hepatol 33: e214–e222

Introduction

Transjugular intrahepatic portosystemic stent shunt (TIPS) has gained widespread use in treatment of complications of end-stage liver cirrhosis [1]. By reducing the portosystemic pressure gradient (PSG), TIPS has been demonstrated to attenuate the formation of ascites and to reduce variceal bleeding [1–3]. Survival after TIPS depends on the clinical stage of liver cirrhosis; however, the underlying etiology of liver disease and personal co-factors might also impact the clinical results and interfere with outcome. The model of end-stage liver disease (MELD) is a widely-used risk score to graduate the functional stage of liver cirrhosis and to decide in favour or against the TIPS procedure in clinical practice [4,5]. Patients presenting with a MELD score >14 are usually deemed high-risk patients with possibly fatal clinical course after TIPS. In these patients, liver transplantation is the favoured treatment option but cannot be provided in many cases due to shortage of donor organs and comorbidities contraindicating liver transplantation. Accordingly, TIPS is a feasible treatment option for patients who are not candidates for liver transplantation but also for candidates on the waiting list and even in new-onset refractory ascites after liver transplantation [6].

The MELD score has initially been created to prospectively predict 3-month mortality after TIPS in a mixed cohort of patients with recurrent variceal bleeding and refractory ascites [4]. In our department, the majority of TIPS procedures are being performed because of refractory

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ascites. Clinical experience gave reason to the question whether MELD would provide an equally good and reliable prediction of survival in both indication groups, namely in patients undergoing TIPS for variceal bleeding and patients for refractory ascites, and if this is true not only for short-term prognosis but also for long-term survival.

Thus, the aim of this study was to analyse clinical predictors of survival in both groups and to evaluate the predictive value of the MELD score in patients undergoing TIPS due to refractors ascites or variceal bleeding.

Methods

Study population

Between July 2002 and August 2016, a total of 339 patients were treated with TIPS in our tertiary care center. Patients with Budd–Chiari syndrome, portomesenteric vein thrombosis or TIPS procedures following liver transplantation were excluded from further analysis. The remaining patients ($n = 301$) were split into the two basic indication groups for TIPS procedures: refractory ascites and variceal bleeding. Actually, indication for TIPS and allocation for both groups was based on clinical findings at time of decision making for TIPS, regardless of past episodes of bleeding in the ascites group or ascites in the bleeding group, respectively. That separation was made on clinical grounds – that is, according to the indication recorded in the protocol of the TIPS procedure regardless of history of bleeding in the ascites group and vice versa. In addition, International Classification of Diseases-9/10 codes and consistence with guideline definitions [7] were checked independently by two authors (M.B.P. and T.Z.). Patient baseline characteristics were obtained from our institutional databases. Follow-up included work-up of our clinical databases, outpatients' records and of records from referring physicians and external hospitals. Survival data were obtained from our databases and/or registration offices. The study was carried out according to the Helsinki Declaration and was approved by the local ethics committee.

Transjugular intrahepatic portosystemic stent shunt technique

The basic technique of the TIPS procedure has been initially described in 1994 [8] and has been refined during the following years. For TIPS creation, a 10F sheath was advanced into the inferior vena cava. The right hepatic vein was intubated with a selective catheter followed by the sheath placement. A dedicated flexible trocar stylet was advanced through the liver parenchyma until the tip entered the right portal vein (RUPS-100, Cook, Bloomington, Indiana, USA). In selected cases, an alternative access from the left hepatic or middle hepatic vein to the left portal vein was created. The artificial puncture tract was bridged using a dedicated ePTFE-covered stent graft (Viatorr, Gore, Flagstaff, Arizona, USA). Pressure measurements were performed in all patients before and after shunt creation. A graduated 5F pigtail catheter was advanced into the main portal vein, whereas the tip of the sheath remained in the right atrium near the cavoatrial junction. The PSG was calculated by simultaneous pressure measurements from the pigtail catheter and the tip of the sheath. In variceal bleeding, respective varices were embolized at the operator's discretion. After completion of TIPS creation, patients were transferred to the intermediate care unit and were set on heparin or low-molecular-weight heparin according to the underlying comorbidities and previous coagulation status.

Statistical methods

Statistical analysis included descriptive demographic data, comorbidities, laboratory findings, and technical and clinical outcome measured in both patient groups. Patients undergoing liver transplantation after TIPS were censored at the point of liver transplantation and were excluded from further analysis. Clinical risk factors for survival were investigated using univariate and multivariate Cox proportional hazard regression. Optimal cut-off values for continuous risk factors were determined by maximising the score test statistic. The corresponding hazard ratios between the resulting strata were calculated. Based on significant predictors of each multivariate Cox analysis, separate risk analyses were performed for short-term (3 month) and long-term survivals (1-, 3- and 5-year survivals) in both groups of patients. To this end, the sum of the products of the regression coefficients of predictors multiplied by the respective individual values was formed in analogy to the report of Malinchoc *et al.* [4]. Receiver operating characteristics (ROC) was used to evaluate the accuracy of risk prediction. Areas under the ROC (AUROC) curves were calculated for short-term survival at 3 months and long-term survival at 1, 3 and 5 years for both groups. To demonstrate the impact on survival, Kaplan–Meier survival curves were stratified by the quartiles of the results of the calculated score models and the MELD score. An optimal cut-off point was suggested for the refractory ascites score in order to identify patients with increased 3-month mortality. Positive predictive values (PPV) and negative predictive values (NPV) were calculated for the suggested cut-offs. Given the exploratory nature of the study, no adjustment for multiple testing was done. P values ≤ 0.05 were considered significant. Statistical calculations were performed using SPSS Statistics, IBM, version 26, Armonk, New York, USA.

Results

Patients' characteristics

Patient baseline characteristics and outcome data were obtained from our institutional databases as well as from medical reports and are summarized in Table 1. A total of 301 consecutive patients (192 male and 109 female) qualified for the analysis within this study, comprising 213 patients with TIPS for refractory grade III ascites according to the European Association for the Study of the Liver (EASL) [7] and 88 patients with TIPS for repetitive or acute variceal bleeding. During follow-up after TIPS, 22 of 213 patients with refractory ascites (10.3%) and 7 of 88 patients with variceal bleeding (8%) received liver transplantation at a median of 6 months (1/11 months, Q1/Q3) and 28 months (7/53 months, Q1/Q3), respectively, and were excluded from further analysis.

The refractory ascites group included 42 patients (19.7%) with a previous episode of variceal bleeding which had been effectively managed by means of endoscopy. In all of those patients, bleeding episodes dated back at least more than 3 months before TIPS creation to ensure

Table 1. Demographic data, clinical presentation at time of transjugular intrahepatic portosystemic stent shunt creation and technical outcome

	Refractory ascites		Variceal bleeding		
	n = 213	%	*n* = 88	%	*P* value
Male/female	129/84	60.6/39.4	63/25	71.1/28.4	0.09[a]
Age mean ± SD; median (range)	58.9 ± 10.5 (24–84)		54.2 ± 13.1 (19–86)		0.001[b]
Etiology of liver cirrhosis					0.059[a]
Alcohol	148	69.5	51	58.0	
Viral hepatits	37	17.3	16	18.2	
Others	28	13.1	21	23.9	
History of clinical course					
Hepatorenal syndrome	75	35.2	12	13.6	<0.001[c]
Spontaneous bacterial peritonitis	44	20.7	6	6.8	0.002[c]
Hepatic encephalopathy	37	17.4	20	22.7	0.332[b]
Endoscopic band ligation of varices	49	23.0	71	80.1	<0.001[c]
Clinical stage					<0.001[a]
Child-Pugh-A	2	0.9	14	15.9	
Child-Pugh-B	167	78.4	53	60.2	
Child-Pugh-C	44	20.7	21	23.9	
MELD score					
≤14	131	61.5	54	61.4	0.982[a]
>14	82	38.5	34	38.6	
Technical success					
Primary	207	97.2	87	98.9	
Secondary	5	2.3	1	1.1	0.675[a]
Mortality					
3d – periprocedural mortality	2	0.9	10	11.4	<0.001[c]
30d – mortality	18	8.5	21	23.9	<0.001[c]
Major complications					
Bleeding from accidental laceration of segmental arteries	4	1.9	1	1.1	
Hemobilia from accidental laceration of segmental arteries	2	0.9			
Cardiac events	4	1.9	2	2.2	
Pressure gradient					
PSG before before shunt creation	17.4 ± 5.5		18.7 ± 5.1		0.021[b]
PSG after shunt creation	5.4 ± 2.7		5.9 ± 2.8		0.069[b]
PSG reduction	12.1 ± 5.1		12.8 ± 4.8		0.112[b]

MELD, model of end-stage liver disease; PSG, portosystemic pressure gradient.
[a]Chi-square test.
[b]Mann–Whitney *U* test.
[c]Fisher test.

that the decision for TIPS was made due to refractory ascites only. The variceal bleeding group covered cases with repetitive variceal bleeding despite endoscopic band ligation ($n = 46$) and emergency TIPS ($n = 42$). Patients with repetitive bleeding presented with bleeding events dated back between 2 weeks and 8 months. Emergency cases were treated within 24 h after noneffective endoscopic treatment ($n = 26$) or immediately without any endoscopic attempts in the state of circulatory shock ($n = 16$). In the latter 16 patients, massive bleeding prevented effective endoscopic bleeding control (e.g. band ligation) and/or a rescue balloon compression had been performed (Sengstaken-Blakemore or Linton-Nachlas tube). Fifty-one of 88 patients with variceal bleeding presented with some concomitant ascites, 24 (27.3%) with grade II ascites and 27 (30.7%) with grade III according to EASL.

In several respects, patients' characteristics of those two groups were significantly different (Table 1). That applies, in particular, to clinical data such as history of hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP) and prophylaxis or treatment of variceal haemorrhage. Patients undergoing TIPS for ascites suffered more frequently from alcoholic cirrhosis as compared to those with the indication of variceal bleeding who comprised more frequently other forms of cirrhosis (primary biliary cirrhosis, hemochromatosis, cystic fibrosis, sarcoidosis, Alström Syndrome, porphyria and cryptogenic cirrhosis). The difference in etiology of cirrhosis was only marginally different, most probably because of the limited number. However, the stage of cirrhosis was significantly more advanced in patients with refractory ascites (Child-Pugh-B and Child-Pugh-C = 99.1 %) as compared to the bleeding group.

Survival and prognostic variables

The overall technical success rate for TIPS creation was 100%. In six patients, a second attempt for successful TIPS completion was required. Effective reduction of PSG was achieved in all cases after TIPS procedure reflecting hemodynamic success in all, respectively. The 3-day mortality was 0.9% in refractory ascites and 11.4% in variceal bleeding. Procedure-related major complications occurred in 4.7% (10 of 213) in refractory ascites versus 3.4% (3 of 88) in variceal bleeding, including seven procedure-related bleeding events in six patients and six peri-interventional cardiac events (Table 1).

The median follow-up was 398 (1–4747) days in the ascites group and 356 (1–4086) days in patients with TIPS for variceal bleeding. Median survival was 756 [95 % confidence interval (CI), 340–1172] for patients with ascites and 761 (95 % CI, 303–1219) for patients with variceal bleeding. The survival rates at 3 months, 1, 3 and 5 years after TIPS were, respectively, 81.2, 63.9, 46.2 and 33.7 % in the ascites group compared to 70, 58.8, 42.9 and 29.9 % in patients undergoing TIPS for bleeding ($P = 0.441$). The univariate Cox analysis of predictors of survival is summarized in Table 2.

Table 2. Risk factors for survival, univariate and multivariate Cox analysis.

	Refractory Ascites					Variceal Bleeding			
Univariate Cox analysis of risk factors for survival									
	HR	95.0% CI		*P* value		HR	95.0% CI		*P* value
Age	1.043	1.024	1.063	0.000		1.023	1.000	1.047	0.051
Gender male	1.253	0.862	1.821	0.237		1.217	0.677	2.187	0.511
Alcoholic cirrhosis versus other origin	1.346	0.912	1.989	0.558		2.155	1.183	3.926	0.010
Comorbidity	1.904	1.204	3.010	0.006		1.002	0.564	1.782	0.997
Cardiac	2.546	1.427	4.542	0.002		1.029	0.424	2.496	0.949
Others	1.773	1.108	2.837	0.017		0.996	0.549	1.808	0.990
Emergency TIPS	n.a.	n.a.	n.a.	n.a.		1.790	1.046	3.062	0.043
Endoscopic treatment of varices	0.997	0.660	1.507	0.990		0.891	0.459	1.731	0.734
Radiologic embolization of varices	0.871	0.215	3.528	0.846		1.408	0.724	2.741	0.313
Grade II ascites (EASL) [7]	n.a.	n.a.	n.a.	n.a.		0.979	0.474	2.020	0.953
Grade III ascites (EASL)[7]	all	all	all	all		3.171	1.681	5.981	0.000
HRS	1.065	0.730	1.555	0.742		3.990	1.990	8.003	0.000
SBP	0.966	0.620	1.503	0.877		9.128	3.383	24.626	0.000
Hepatic encephalopathy	1.304	0.834	2.039	0.245		1.998	1.110	3.596	0.021
INR	2.855	1.092	7.463	0.032		3.829	1.708	8.587	0.001
Bilirubin	1.223	1.093	1.369	0.000		1.095	1.058	1.132	0.000
Creatinine	1.121	0.920	1.367	0.257		1.932	1.487	2.511	0.000
Albumin	0.969	0.937	1.001	0.057		0.952	0.918	0.988	0.008
Platelets	0.998	0.996	1.000	0.068		0.999	0.997	1.002	0.634
Sodium	1.016	0.983	1.049	0.353		0.987	0.933	1.044	0.642
MELD	1.081	1.032	1.132	0.001		1.111	1.072	1.151	0.000
Child-Pugh score	1.285	1.090	1.516	0.003		1.371	1.190	1.581	0.000
PSG prior to TIPS creation	1.015	0.982	1.049	0.389		0.984	0.932	1.040	0.575
PSG after TIPS creation	0.958	0.895	1.025	0.214		0.981	0.897	1.072	0.666
PSG after TIPS <5 mmHg	1.802	1.231	2.638	0.002		0.762	0.418	1.387	0.373
PSG after TIPS >9 mmHg	1.737	0.950	3.175	0.073		0.530	0.205	1.368	0.373
Multivariate Cox analysis for 3-month survival									
Age (years)	1.035	1.002	1.068	0.036	Grade III ascites	2.249	0.913	5.541	0.078
Bilirubin >2.28 mg/dl	2.1	1.024	4.308	0.043	Emergency TIPS	4.095	1.434	11.691	0.008
					Hepatic encephalopathy	2.519	1.067	5.947	0.035
					Bilirubin	1.072	1.030	1.117	0.001
					Platelets	0.992	0.985	1.000	0.055
Multivariate Cox analysis for 1-, 3- and 5-year survival									
Age (years)	1.039	1.018	1.06	0.000	Age >65 years	3.461	1.821	6.578	0.000
Bilirubin (mg/dl)	1.195	1.05	1.36	0.007	Grade III ascites	1.821	0.911	3.642	0.090
Albumin (mg/dl)	0.969	0.934	1.005	0.091	Hepatic encephalopathy	1.943	1.044	3.614	0.036
					SBP	6.280	2.112	18.672	0.001
					Bilirubin>2.93 mg/dl	2.883	1.505	5.523	0.001

Emergency transjugular intrahepatic portosystemic stent shunt (TIPS): TIPS creation during acute ongoing variceal bleeding. Grade II or III acites: grading according to EASL [7].

EASL, the European Association for the Study of the Liver; HRS, hepatorenal syndrome; INR, International Normalized Ratio; MELD, model of end-stage liver disease; PSG, portosystemic pressure gradient; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic stent shunt.

In refractory ascites, age, comorbidities and impaired liver function (International Normalized Ratio (INR) and bilirubin) were significant risk factors. Moreover, PSG of less than 5 mmHg after TIPS creation was a significant predictor as well as need for early dialysis within 4 weeks after TIPS placement (hazard ratio, 3.796; 95% CI, 1.849–7.795; $P < 0.0001$). However, because both variables cannot be assessed before TIPS creation, these variables were not included in the multivariate Cox analysis. In variceal bleeding, alcoholic cirrhosis, emergency TIPS under ongoing acute bleeding during TIPS creation, bilirubin, creatinine, INR, albumin, grade III ascites according to EASL, history of SBP, HRS and/or hepatic encephalopathy proved significant in univariate analysis and were included in the multivariate Cox analysis. The PSG level before or after TIPS creation proved NS in this group. In both groups, the Child-Pugh and MELD scores were, of course, significant variables in the univariate analysis but were excluded from the multivariate analysis as both scores contain the aforementioned parameters which we aimed to separately evaluate in this study. In addition to that, MELD served as the established reference method in this study (Table 2).

Multivariate Cox models were separately calculated for short-term survival (3 months) and long-term survival (1, 3 and 5 years) in each patient group. In refractory ascites, multivariate Cox analysis resulted in age and bilirubin being significant risk factors for short-term survival and age, bilirubin and albumin for long-term survival, respectively (Table 2). In variceal bleeding, bilirubin, platelets, emergency TIPS, grade III ascites according to EASL and history of hepatic encephalopathy proved significant for short-term survival. For long-term survival, age, bilirubin, grade III ascites, and history of hepatic encephalopathy and SBP were significant (Table 2).

Risk calculation and area under the receiver operator characteristics

In order to assess the risk of short-term and long-term survivals, the identified factors of significant predictors from multivariate Cox analysis were multiplied by the respective individual values (Table 3).

Table 3. Area under the receiver operator characteristics analysis of model of end-stage liver disease score and of calculated models according to the results of multivariate Cox regression in 213 patients with refractory ascites and 88 patients undergoing transjugular intrahepatic portosystemic stent shunt for variceal bleeding.

	Calculated predictors – AUROC (95% CI)		MELD – AUROC (95% CI)		
	Refractory ascites	Variceal bleeding	Refractory ascites	Variceal bleeding	*P* value*
3 months	0.660 (0.558–0.761)	0.876 (0.802–0.950)	0.543 (0.445–0.641)	0.836 (0.730–0.941)	<0.001
1 year	0.665 (0.586–0.744)	0.835 (0.749–0.921)	0.533 (0.449–0.617)	0.767 (0.659–0.875)	<0.001
3 year	0.693 (0.623–0.764)	0.827 (0.739–0.915)	0.629 (0.541–0.717)	0.744 (0.627–0.860)	0.12
5 year	0.691 (0.622–0.761)	0.849 (0.767–0.932)	0.627 (0.520–0.734)	0.702 (0.567–0.838)	0.39

*Significance of the difference between area under the receiver operator characteristics of both patient groups undergoing transjugular intrahepatic portosystemic stent shunt for refractory ascites versus variceal bleeding.
AUROC, area under the receiver operator characteristics; MELD, model of end-stage liver disease.

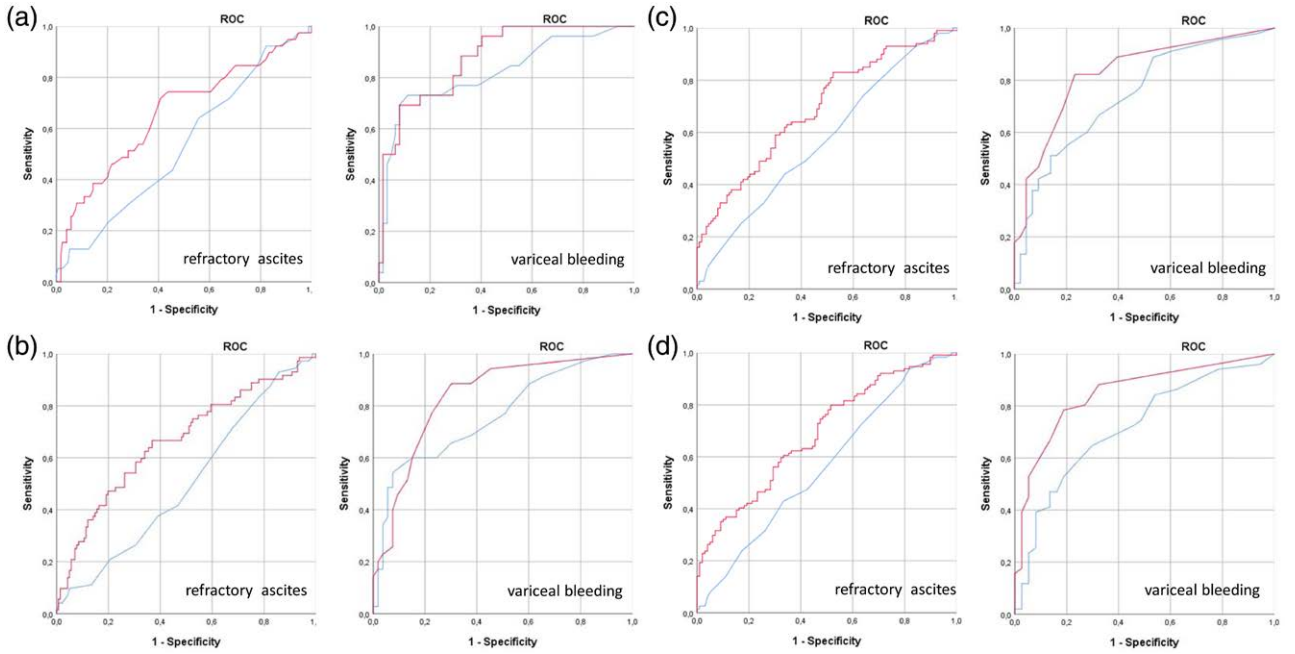

Fig. 1. Area under the receiver operator characteristics (AUROC) of calculated risk scores (red) and model of the end-stage liver disease (MELD) score (blue) for survival after transjugular intrahepatic portosystemic stent shunt in refractory ascites and variceal bleeding. (a) AUROC of the risk score A (red) for refractory ascites and risk score C (red) for variceal bleeding compared to MELD (blue) for 3-month survival. (b) AUROC of risk score B (red) for refractory ascites and risk score D (red) for variceal bleeding compared to MELD (blue) for 1-year survival. (c) AUROC of risk score B (red) for refractory ascites and risk score D (red) for variceal bleeding compared to MELD (blue) for 3-year survival. (d) AUROC of risk score B (red) for refractory ascites and risk score D (red) for variceal bleeding compared to MELD (blue) for 5-year survival.

In patients undergoing TIPS for ascites, the following formulas resulted from the multivariate Cox analysis:

(A) 3-month $_{\text{ascites}} = 0.034 \times \text{age} + 0.742 \times \text{bilirubin} > 2.28$
(age in *n* years; bilirubin >2.28 mg/dl yes = 1, no = 0).
(B) Overall $_{\text{ascites}} = 0.038 \times \text{age} + 0.178 \times \text{bilirubin} - 0.032 \times \text{albumin}$
(age in *n* years; bilirubin in mg/dl; albumin in mg/dl).

In patients undergoing TIPS for variceal bleeding, the respective formulas were:

(C) 3-month $_{\text{bleeding}} = 1.410 \times \text{bleeding} + 0.811 \times \text{ascites} + 0.924 \times \text{hepatic encephalopathy} + 0.070 \times \text{bilirubin} - 0.008 \times \text{platelets}$
(bleeding, acute or ongoing bleeding yes = 1, no = 0; ascites grade III yes = 1, no = 0; hepatic encephalopathy yes = 1, no = 0; bilirubin in mg/dl; platelets in *n* counts/nl).
(D) Overall $_{\text{bleeding}} = 1.242 \times \text{age} > 65 \text{ years} + 1.059 \times \text{bilirubin} > 2.92 \text{ mg/dl} + 0.600 \times \text{ascites} + 0.664 \times \text{hepatic encephalopathy} + 1.837 \times \text{SBP}$
(age >65 years yes = 1, no = 0; bilirubin >2.92 mg/dl yes = 1, no = 0; ascites grade III yes = 1, no = 0; hepatic encephalopathy yes = 1, no = 0; SBP yes = 1, no = 0).

The sums of those products were used for AUROC calculations and compared with AUROC calculations based on the MELD score. For short-term survival, the MELD score proved to be significantly superior in patients with variceal bleeding as compared to refractory ascites. Three-month and 1-year survivals in variceal bleeding were correctly predicted with an area under the curve (AUC) of 0.836 and 0.767, respectively. In refractory ascites, the respective ROC analysis of the MELD score resulted in a significantly inferior predictive AUC values 0.543 ($P = 0.0001$) and 0.533 ($P = 0.0008$), respectively (Table 3). Accordingly, the MELD score proved not clinically relevant for prediction of 3-month and 1-year survivals after TIPS in refractory ascites. Compared to MELD, the calculated score from our analysis resulted in a moderately superior prognostic capability for 3-month and 1-year survivals in refractory ascites (AUC = 0.66 and 0.665). In

variceal bleeding, the predictive capability of the calculated score was even slightly superior to that of the MELD score for 3-month survival. For long-term survival, the calculated score was again superior to MELD with fair AUC (0.827 and 0.849 for 3-year and 5-year survivals, respectively) (Fig. 1, Table 3).

In order to illustrate the prognostic capability of 3-month prognosis, survival curves were stratified according to the quartiles of the calculated score results of this study and of the MELD score. In variceal bleeding, the survival curves based upon the calculated scores of this study (Risk score C) appear to be basically comparable to the MELD score with excellent prognostic capability (Fig. 2c). In refractory ascites, however, the calculated score for 3-month survival (Risk score A) showed a significantly different outcome of this strata ($P = 0.002$) compared with the MELD score ($P = 0.814$ Fig. 2a).

Choosing a strict cut-off value of >2.66 for the 3-month score in refractory ascites (Risk score A) resulted in a sensitivity and specificity of 0.282 and 0.925, respectively, and

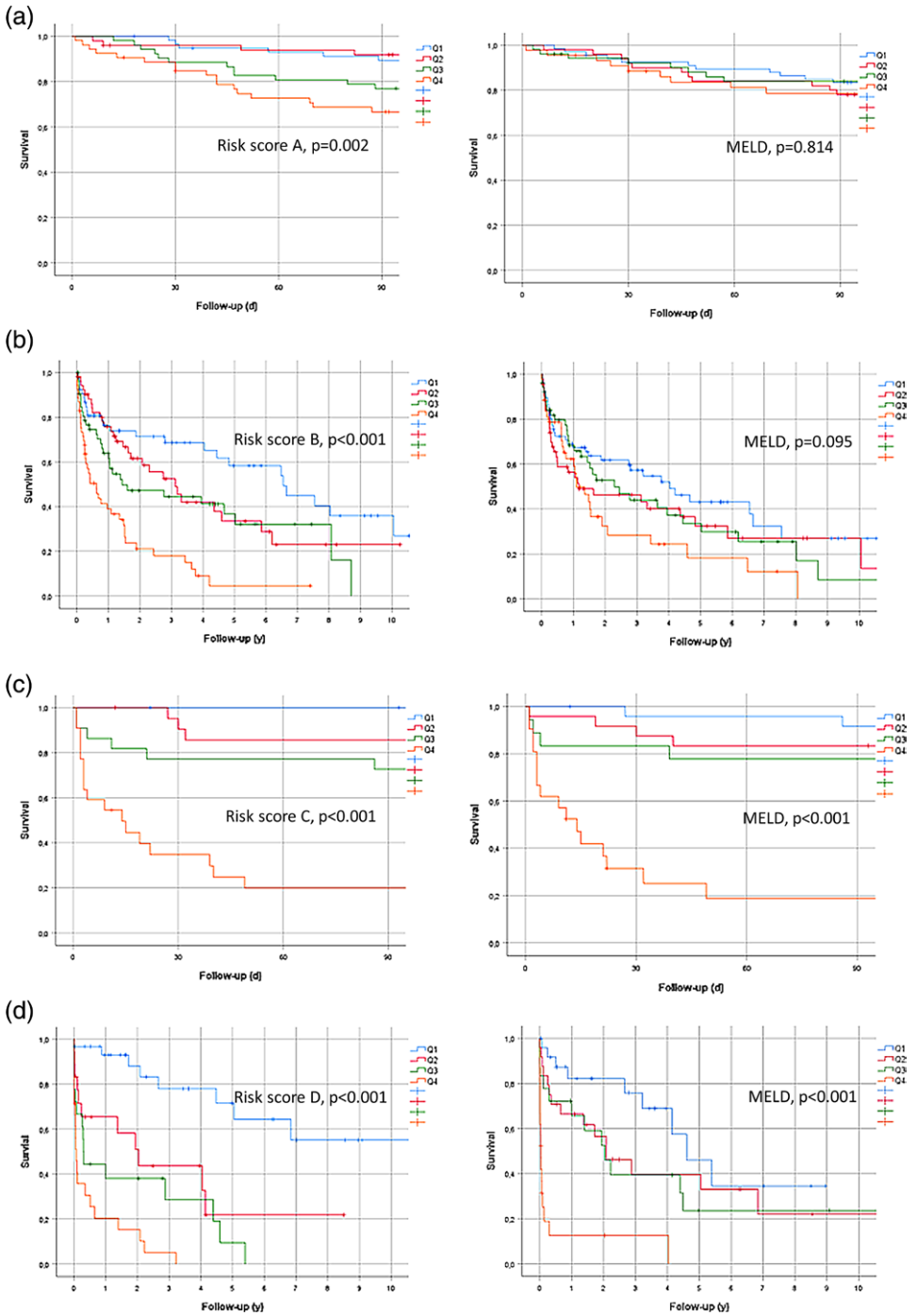

Fig. 2. Survival curves according to the calculated risk scores and model of the end-stage liver disease (MELD) score for refractory ascites and variceal bleeding, stratified according to the quartiles of the score points (Q1, Q2, Q3 and Q4). (a) Survival curves, risk score A and MELD score for 3-month survival in refractory ascites stratified according to the quartiles of the respective score results. (b) Survival curves, risk score B and MELD score for overall survival in refractory ascites. (c) Survival curves, risk score C and MELD score for 3 month survival in variceal bleeding. (d) Survival curves, risk score D and MELD score for overall survival in variceal bleeding.

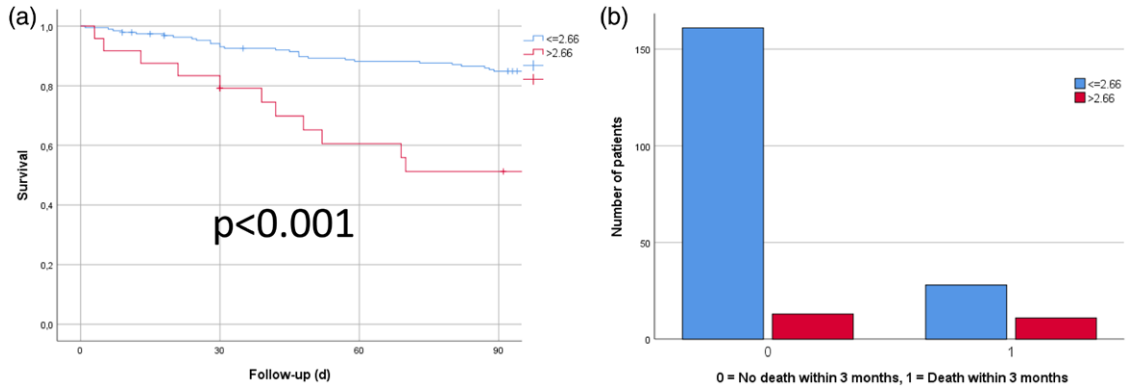

Fig. 3. Survival curve using risk score A for 3-month survival in refractory ascites, stratified according to the optimized cut-off of >2.66 (red) and ≤2.66 (blue) score points (a). Numbers of survivors and deaths within 3-month follow-up using a cut-off of >2.66 score points of risk score A. Death within 3 months (0 = no, 1 = yes, b).

a PPV and NPV of 0.458 and 0.852 (Fig. 3). The excellent specificity and NPV of this cut-off would identify high-risk patients and help for decision making (Fig. 3). On the contrary, using a more moderate cut-off of >2.16 had resulted in an increased sensitivity of 0.718, but a reduced specificity of 0.586, PPV of 0.280 and NPV of 0.903.

Discussion

MELD has been created in 2000 in order to prospectively predict 3-month survival after TIPS depending on preinterventional laboratory findings [4,5]. The score was created in a mixed patient cohort, including 75% of patients with variceal bleeding and only 25% of patients for treatment of refractory ascites. The vast majority of variceal bleeding in this initial cohort should be emphasized for understanding that MELD may be dominated and overlaid with results from variceal bleeding and may, therefore, be questioned in patients treated for refractory ascites.

Numerous studies confirmed the specific prognostic value of the MELD score in acute variceal bleeding after early TIPS and underscored its suitability for clinical decisions. According to Casabadan *et al.*, MELD yielded an excellent predictive capability with AUROC values of 0.842 for 3-month mortality in patients undergoing emergency TIPS for variceal bleeding [9]. In a small group of patients with the low MELD score, Hermie *et al.* reported excellent survival results of early-TIPS treatment for acute variceal bleeding but contested the benefit of TIPS in patients with MELD score >19 and, particularly, in patients with active bleeding [10]. In contrast to this, the survival benefit in 1425 patients undergoing TIPS in 12 Chinese university hospitals correlated with increasing MELD and Child-Pugh scores. That result was confirmed in a randomized study [11,12]. Hence, TIPS for variceal bleeding may also be advocated in patients with advanced cirrhosis.

According to the literature, the predictive capacity of the MELD score appears to be only moderate for refractory ascites and alternative scores have been used in this context. Ronald *et al.* compared the albumin–bilirubin grade (ALBI grade) and the MELD score but ALBI grade proved inferior to MELD in predicting 30-day and overall survivals after TIPS [13]. Khabbaz *et al.* investigated the Platelet–ALBI grade (PALBI grade) as well as ALBI grade and concluded that both were inferior to MELD for prediction of post-TIPS survival [14]. Because acute-on-chronic liver failure (ACLF) might be a major concern after TIPS in patients with advanced liver cirrhosis, the chronic liver failure (CLIF) Consortium ACLF score (CLIF-C ACLFs) was used in patients with ACLF and reported to be superior compared to MELD in predicting mortality [15]. Likewise, Allegretti *et al.* compared the CLIF-C ACLF score with MELD and others with respect to their prognostic capability in patients after TIPS. The data confirmed superior AUROC values of 0.707 for the CLIF-C ACLF score compared to MELD in refractory ascites. The prognostic capability of MELD was increased by introducing patients' age in a particular prognostic model [16].

Our study was performed to compare the prognostic capability of the MELD score and identify predictors of survival in the two principal indication groups of the TIPS procedure. As stated in the Methods section, the separation of both groups was made according to the actual indication for TIPS according to the current clinical symptoms in the clinical records regardless of history of former bleeding in the ascites group and vice versa. The comparison of clinical data and patients' characteristics yielded profound differences between both groups. Patients undergoing TIPS for refractory ascites presented significantly more clinical complications of impaired liver function such as SBP and HRS compared to the variceal bleeding group (Table 1). Even with a common underlying disease of cirrhosis, the course of the disease and the prognosis in both groups, therefore, depended not only on the stage of cirrhosis but on different complications that might account for mortality.

In patients with variceal bleeding, the prognostic capability of the MELD score was confirmed in this study. AUC for short-term survival of 3 months based upon the MELD score was highly predictive, and for 1-, 3- and 5-year survivals it was, with slightly decreasing values, fairly predictive. It needs to be noted that, in contrast to the original articles of Malinchoc and Kamath [4,5], our study included patients with emergency TIPS, that is, with acute ongoing variceal bleeding after endoscopic treatment failure. The inclusion of those patients may be the reason why the prognostic predictors resulting from our multivariate analysis were different from the original constituents of the MELD score. However, the AUROC calculations combining emergency TIPS with (acute) bleeding,

grade III-ascites, history of hepatic encephalopathy, bilirubin and platelets to assess 3-month survival and age, bilirubin, grade III-ascites, hepatic encephalopathy and SBP to predict long-term follow-up are only slightly superior to the MELD score, which underscores the excellent predictive capability of this score.

In contrast to variceal bleeding, the MELD score failed to reflect the outcome in patients undergoing TIPS for refractory ascites (AUC for short-term prognosis 0.543). Out of the three parameters underlying that score, only bilirubin remained highly significant in the multivariate analyses. Even in the univariate analysis, the influence of INR on survival was only moderate ($P = 0.032$) and that of creatinine was NS ($P = 0.257$). As a frequently encountered issue, the creatinine level may have been impacted by coexisting problems such as SBP, hepatorenal syndrome and high volume paracentesis. In patients treated for ascites, renal dysfunction and MELD recover in many instances after effective TIPS creation once diuretics can be reduced and large volume paracenteses are ceased. Preinterventional MELD might, therefore, overestimate the extent of renal damage in refractory ascites in contrast to patients with acute or subacute variceal bleeding, for whom such extensive diuretic treatment is usually not performed [17].

As age turned out to be an independent predictor of survival in patients with TIPS for ascites, TIPS creation should be of particular concern in elderly patients with pre-existing cardiac diseases. Potentially impaired ventricular contractility may become an issue after TIPS procedures as that treatment reduces portal venous pressure but increases portosystemic blood volume and preload. In a mixed cohort including 70.5% patients with refractory ascites and only 27.5% with variceal hemorrhage, Saad *et al*. reported reduced post-TIPS survival for patients with age ≥70 years [18]. Jansen *et al*. investigated the relation between left cardiac contractility, mortality and acute liver failure after TIPS creation. The authors identified left ventricular global longitudinal strain as an independent precipitating factor for acute-on-chronic liver failure and mortality after TIPS [19]. The diversity of complications of liver cirrhosis combined with age in patients undergoing TIPS for ascites appears to result in a multitude of variables which makes powerful prognostic predictions difficult. Accordingly, our analysis using age and bilirubin for short-term risk assessment and, in addition to those, albumin for long-term risk assessment resulted in moderately improved AUROCs compared to MELD (Table 3). It should be emphasized that survival of patients in the fourth quartile of our score model is significantly worse than that of patients in the first three quartiles. In contrast to our model, a similar stratification of outcome was not possible with the MELD score. However, definition of cut-off values remains basically a clinical decision and depends on the intention either to result in high sensitivity or high specificity. We suggest a score value of > 2.66 for the 3 month ascites score (A) in order to define patients at risk for early death after TIPS in refractory ascites. However, the increased risk with advanced liver disease or greater age should be balanced against the potentially therapeutic option in individual cases. Any exclusion of patients from treatment, however, would require respective randomized studies on TIPS versus non-TIPS in the respective strata which might be unethical and, therefore, not feasible. Liver transplantation may be a therapeutic alternative in both indication groups for TIPS. However, typical factors contraindicating liver transplantation might be older age of patients >70 years, compliance of patients and the limited number of donor organs.

Some drawbacks of this study should be mentioned. First, all patients were recruited from a single institution and, therefore, the respective prognostic models might be intrinsically overfitted to some extent to our specific patient cohorts. The respective data should, therefore, be confirmed in independent cohorts of patients. Second, the number of included patients – particularly in the group with variceal bleeding – is limited. The impact of significant differences between both groups regarding age, etiology of cirrhosis and clinical complications on outcome as shown in this study should, therefore, be confirmed in greater cohorts of patients, strictly separated for the clinical TIPS indication in refractory ascites or variceal bleeding. Respective data would be needed in order for a precise future decision making for patients undergoing TIPS for different clinical entities.

In conclusion, the MELD score failed to reliably estimate post-TIPS survival in patients with refractory ascites. In patients with variceal bleeding, the excellent prognostic capability of the MELD score was confirmed not only for 3-month survival but also for long-term outcome up to 5 years after TIPS. Moreover, our data confirmed the prognostic capability of MELD in emergency TIPS. Differences in clinical course of patients with refractory ascites and variceal bleeding entail, obviously, different independent prognostic variables. This statement should be verified in independent and greater cohorts of patients.

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Conflicts of interest

There are no conflicts of interest.

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