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FACTORS PREDICTING MORTALITY AFTER TIPS FOR REFRACTORY ASCITES: A SINGLE CENTER EXPERIENCE

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1. Abstract

Introduction: Transjugular intrahepatic porto-systemic shunt (TIPS) is an accepted indication for treating refractory ascites. Different models have been proposed for the prediction of survival after TIPS; aim of present study was to evaluate the factors associated with mortality after TIPS for refractory ascites.

Methods: Seventy-three consecutive patients undergoing a TIPS for refractory ascites in our centre between 2003 and 2008, were prospectively recorded in a database ad were the subject of the study. Mean follow-up was 17±2 months. Forty patients were awaiting liver transplantation (LT) and 12 (16.4%) underwent LT during follow-up.

Results: Mean MELD at the moment of TIPS was 15.7±5.3. Overall mortality was 23.3% (n=17) with a mean survival after TIPS of 17±14 months. MELD score (B=0.161, p=0.042), AST (B= 0.020, p=0.090) and pre-TIPS HVPG (B=0.016, p=0.093) were independent predictors of overall mortality. On multivariate analysis MELD (B=0.419, p=0.018) and pre-TIPS HVPG (B=0.223, p=0.060) independently predicted 1 year survival. Patients were stratified into categories of death risk, using ROC curves for the variables MELD and HVPG. Patients with MELD<10 had a low probability of death after TIPS (n=6, 16% mortality); patients with HVPG <16 mmHg (n=6) had no mortality. Maximum risk of death was found in patients with MELD score ≥19 (n=16, 31% mortality) and in those with HVPG ≥25 mmHg (n=27, 26% mortality).

Conclusions: TIPS increases overall survival in patients with refractory ascites. Liver function (assessed by MELD), necroinflammation (AST) and portal hypertension (HVPG) are independent predictors of survival; patients with MELD>19 and HVPG>25 mmHg are at highest risk of death after TIPS.

2. Introduction

Refractory ascites is a severe complication of cirrhosis with a 1 year survival of about 50% (1). Transjugular intrahepatic porto-systemic shunt (TIPS) is an accepted indication for the treatment of refractory ascites and a valid alternative to large volume paracentesis (LVP) (2, 3). Survival after TIPS placement for refractory ascites has been suggested to be worse than for variceal bleeding (4, 5). Although this finding has not been confirmed by larger studies, survival after TIPS has been related to the degree of hepatic dysfunction expressed mainly by bilirubin, aminotransferases and creatinine levels, and also to age and urgent indication to the procedure (2, 4-7).

Different models have been proposed for the prediction of survival after TIPS; these included the Mayo score, later modified into the MELD score (Model for End stage Liver Disease), and others (4, 8-13). These scoring systems, however, are based on populations of patients with various indications to TIPS, mainly variceal bleeding, and have not been validated in a cohort of patient with refractory ascites alone.

Aim of this study was to evaluate the factors associated with mortality after TIPS positioning for refractory ascites in our centre.

3.0 Materials and Methods

All consecutive patients undergoing a TIPS procedure in our centre were prospectively recorded in a database; patients who underwent TIPS for refractory ascites, defined as lack of response to a low sodium diet and adequate doses of diuretics (14) requiring repeated LVP in S. Orsola-Malpighi Hospital, between February 2003 and January 2008, were identified from the database and were the subject of the present study. Mean follow-up was 17±2 months.

For all patients, the following data were collected in a database: age, sex, etiology of liver disease, HVPG before TIPS, presence and grade of encephalopathy before and after the procedure, standard blood test (including INR, creatinine, electrolytes, transaminases), early and late complications of the procedure, number of revisions performed, survival, presence in the waiting list for liver transplantation (LT) and LT. For all patients the Mayo score (12) and MELD score were calculated. All hematological tests were measured using conventional test at the Central Laboratory of S. Orsola-Malpighi Hospital. Budd-Chiari syndrome was an exclusion criterion for the inclusion in the database regarding the present paper. All patients gave their written informed consent to the TIPS procedure. This study followed the Declaration of Helsinki principles.

3.1 Statistical analysis

Kaplan-Meier curves were used to analyze long term survival. Cox proportional-hazards regression model was performed to assess risk factors for mortality, and factors significant at univariate analysis were entered in a multivariate model to identify independent predictors of mortality. ROC curves were used to define the best cut-off of continuous variables for mortality prediction. Patients who underwent orthotopic liver transplantation were censored at the moment of OLT. P values < 0.05 were considered statistically significant. All data analyses were performed using Statistical Package for Social Science (SPSS), version 15.

3.2 HVPG measurement and TIPS positioning

The TIPS procedure was performed in the angiographic suite with the patients deeply sedated. The right jugular vein was punctured under sonographic guidance and a first catheter was advanced to reach the right atrium and then the hepatic veins: free and wedged hepatic venous pressures were then measured by a balloon catheter (7F balloon-tipped catheter, OB-Medi-Tech, Boston Scientific Cork Ltd., Cork, Ireland), and hepatic venous pressure gradient (HVPG) was calculated as the difference between wedge and free pressures. A standard RUPS-100 Rosch-Uchida transjugular liver access set (Cook®) was used for TIPS creation (i.e. the shunt between right portal branch and the hepatic vein). In most patients, the sagittal hepatic vein and the right portal vein were used to create the track, under fluoroscopic and/or ultrasound (US) guidance. After puncture of the portal branch, a portal venogram was obtained to assess the track length and in order to exclude the presence of portal vein thrombosis or enlarged gastric veins. Then a measurement of portal vein pressure was obtained.

In all cases self-expandable metallic uncovered stent (Wallstent 12 mm in diameter and 6 to 9 mm in length) were positioned and subsequently dilated through high-pressure angioplasty balloon catheters of equivalent size to the nominal diameters of the stent. At the end of the procedure a portography was performed to verify the shunt patency, the direction of the portal flow and to exclude the persistent filling of varices. In patients with variceal persistent perfusion, a selective coil embolization of left gastric or short gastric veins varices was performed. Portal pressure and right atrial pressure after TIPS positioning were measured, and porto-atrial gradient was calculated. After the procedure, all patients underwent clinical follow-up and stent patency was monitored by ECD-US before discharge and by MDCT one month later.

4.0 Results

Seventy-three patients (67% males) were included in the study. Table 1 summarizes the main characteristics of patients at inclusion. Median age at the time of TIPS creation was 59 years (range, 34-76 y). Mean MELD score at the moment of TIPS positioning was 15.7±5.3. Forty patients were in the waiting list for LT and 12 (16.4%) underwent LT during follow-up. Thirty-three patients were not awaiting LT; 2 of them were performing the work-up for inclusion in the waiting list, the remaining were excluded from LT for the following reasons: 18 for age over 67 years, 2 for hepatocellular carcinoma (HCC) exceeding Milan criteria, and 11 for low MELD score (according to the statements of our transplant centre establishing that the minimum score needed for inclusion in the waiting list is 13).

4.1 Overall survival

Overall mortality rate was 23.3% (n=17) with a mean survival after TIPS of 17±14 months. At univariate analysis (Table 2), increasing values of MELD score, Mayo Risk Score, AST and ALT, bilirubin, INR and pre-TIPS HVPG significantly increased the risk of death on follow-up. In our population age, gender, etiology of liver disease, creatinine and sodium were not associated to mortality (Table 2).

Given the limited number of events (n=17), and given the wide use of MELD score in clinical practice, which includes creatinine, INR and bilirubin, we chose to consider in the multivariate analysis the following variables: MELD score, AST, diastolic arterial blood pressure and HVPG. The model identified as independent predictors of overall mortality the following variables: MELD score (B=0.161, p=0.042), AST (B= 0.020, p=0.090) and pre-TIPS HVPG (B=0.016, p=0.093).

By using the previously identified risk threshold for TIPS, namely a MELD score below or higher than 18 (13), in the present series, patients with a high (>18) MELD score had a poorer OLT-free survival after TIPS placement than low risk patients (MELD ≤18; p=0.002).

4.2 Three months survival

Six patients died during the first three months after TIPS, and 7 patients were transplanted in the same period.

Patients with poor short-term prognosis differed from survivors at 3 months for the following variables: bilirubin, AST, ALT and MELD score. On multivariate analysis high AST (B=0.065, p=0.136) and bilirubin (B=0.606, p=0.046) values independently predicted a <3-months survival.

4.3 One year survival

Thirteen patients died during the first year after TIPS and 12 underwent OLT.

Survivors at 1 year had lower values of MELD score, Mayo Risk Score, bilirubin, INR and HVPG at the time of TIPS placement as compared with patients who died on follow-up. On multivariate analysis MELD score (B=0.419, p=0.018) and pre-TIPS HVPG (B=0.223, p=0.060) independently predicted 1 year survival.

However, the added value of considering pre-TIPS HVPG in adjunct to MELD score alone was minimal since no significant difference in the discriminative ability of the model was observed (Table 3).

In order to easily stratify patients into categories of death risk after TIPS, we calculated the ROC curves for the two variables selected by the model for 1 year survival. We then

selected from the ROC curves the best cut-offs to identify the highest and lowest risk of death in our population (Figure 1 and 2).

The AUROC were as follows: MELD score: 0.754, p=0.001; HVPG: 0.664, p=0.027.

Therefore, based on these results, patients could be classified into three groups of risk according to MELD and HVPG: low risk (MELD <10, HVPG <16 mmHg), intermediate risk (MELD 10-19, HVPG 16-25 mmHg) and high risk (MELD >19, HVPG 25 mmHg).

According to this classification patients with MELD score <10 had a low probability of death after TIPS (n=6, 16% mortality); patients with HVPG <16 mmHg (n=6) had no mortality in this study. Maximum risk of death was found in patients with MELD score ≥19 (n=16, 31% mortality) and in those with HVPG ≥25 mmHg (n=27, 26% mortality).

4.4 Ascites and need for TIPS revision

Within 1 year from TIPS placement, 40 (54%) patients had a resolution of ascites or a significant improvement of ascites control with no need of paracentesis. In the remaining 46%, no significant improvement was obtained.

Forty patients (52.3%) underwent minor TIPS revision during the follow-up due to TIPS dysfunction, clinically detected for the relapse of ascites or for the ultrasonografic (US) finding of hepatofugal flow in the portal vein during the periodical US follow-up.

Additionally, 2 patients required TIPS reduction for the onset of severe early encephalopathy and a severe liver dysfunction.

5. Discussion

In our population of patients with refractory ascites, TIPS placement led to a long survival in the majority of patients. Survival rates obtained in our study are similar to the previously reported results in a similar setting of patients being 65% after 1 year (2, 15).

Liver function (assessed by MELD score), necroinflammation (assessed by AST) and portal hypertension (assessed by HVPG) are independent predictors of mortality after TIPS. However, necroinflammation holds a predictive value in the short-term period, while liver function and portal hypertension help stratifying patients in the middle-long term period. In the univariate analysis decreasing values of diastolic blood pressure and mean arterial pressure showed a trend towards increasing risk of death: these parameters are the expression of the hyperdynamic syndrome due to portal hypertension. Interestingly, HVPG is one of the independent factors associated to mortality after TIPS in this study, thus confirming the impact of the severity of portal hypertension on the prognosis of cirrhotic patients undergoing TIPS.

However, the strongest independent predictor of mortality in our series was MELD score. This was not unexpected, since MELD was originally designed to predict mortality after TIPS (13). Contrarily to other studies, in our population sodium level and creatinine were not associated to mortality (2, 16, 17). This may depend from the clinical protocols applied in our Hospital, which include the routine infusion of human albumin in cirrhotic patients with refractory ascites (18) with a beneficial effect on renal function.

The main original result of the present study is the finding of the independent prognostic value of HVPG on survival after TIPS. However, HVPG was inferior to MELD in the prediction of mortality, as shown by the area under the ROC curve; moreover the addition of HVPG to MELD did not significantly increase the precision of the risk model

only based on the MELD score. The combination of the two parameters, from a practical point of view, allowed us to stratify patients into three risk categories. Patients at higher risk of death after TIPS were those with high MELD (>19) and high HVPG (>25 mmHg). The ideal patients were the ones with relatively preserved liver function (MELD<10) and HVPG<16 mmHg.

Considering that TIPS allows a good survival and that death after TIPS is related to MELD and HVPG, our results suggest that, in order to obtain the best outcome, referral to TIPS for refractory ascites should be done as early as possible, when the liver function is not too impaired and the portal pressure is still not extremely high. For patients with advanced liver disease (MELD >19) and high HVPG (>25 mmHg), the risk-benefit evaluation might suggest to perform TIPS only in patients awaiting LT, as mortality is > 25% after 1 year.

A limitation of the present study is its retrospective design. Nonetheless, we included and analyzed all the consecutive patients who underwent TIPS for cirrhosis and refractory ascites in our Center. The present series includes only patient treated with bare stents for the TIPS creation and none treated with PTFE-covered stents positioning. Although it has been suggested that PTFE-covered stent may improve the outcome of patients treated with TIPS, due to a reduction of stent dysfunctions and to improved long term primary stent patency (19-22), the survival rate of patients in the present study only employing bare stents is comparable to that of previous series using covered stents [19-22] as well as the TIPS patency rates, with cumulative primary and secondary patency rates respectively 79% and 99% at a mean of 30 months, similarly to those reported by other authors (23)

In conclusion, our study confirms that TIPS increases overall survival in patients with refractory ascites. Liver function (assessed by MELD), necroinflammation (assessed by AST) and portal hypertension (assessed by HVPG) are independent predictors of survival; the highest mortality after TIPS is observed in those patients presenting with MELD>19 and HVPG>25 mmHg, therefore suggesting that the referral for TIPS in presence of refractory ascites should be limited to the patients in the waiting list for liver transplantation.

Table 1:

Demographic, biochemical and hemodynamic features in patients undergoing elective transjugular intrahepatic portosystemic shunt for refractory ascites included in the present study (n=73).

	n	%	Mean (SD)
Demographic			
Age (y)			57 (10)
Gender (males)	52	71.2	
Cause of cirrhosis			
Virus related	39	53.5	
Alcoholic	24	32.8	
Cryptogenic	6	8.3	
Cholestatic	2	2.7	
Other	2	2.7	
Biochemical			
Serum bilirubin (mg/dl)			2.5 (2.4)
Serum creatinine (mg/dl)			1.22 (0.52)
INR			1.45 (0.26)
AST (U/ml)			44 (22)
ALT (U/ml)			27 (15)
Serum Na (mEq/L)			134 (5)
MELD Score			15.7 (5.3)
Mayo risk score			1.2 (0.6)
Hemodynamic			
SBP (mmHg)			109 (12)
DBP (mmHg)			67 (8)
MAP (mmHg)			81 (9)
FHVP (mmHg)			9.7 (5.2)
WHVP (mmHg)			32.6 (7.6)
HVPG (mmHg)			23.1 (6.2)

Table 2:

Univariate analysis of risk factors for death (overall survival) among included patients undergoing TIPS for refractory ascites (Cox proportional hazards regression model).

Parameter	Regression coefficient	Standard error	p
Sex (male)	0.111	0.443	0.801
Age	–0.016	0.021	0.441
Cause of cirrhosis	–0.015	0.105	0.885
Aetiology (HCV)	–0.119	0.393	0.761
Bilirubin	0.243	0.068	**<0.0001**
Creatinine	–0.030	0.473	0.950
INR	2.403	0.875	**0.006**
AST	0.028	0.010	**0.004**
ALT	0.038	0.014	**0.009**
Na	–0.059	0.046	0.204
MELD score	0.198	0.042	**<0.0001**
Mayo risk score	1.288	0.455	**0.005**
SBP	–0.022	0.021	0.302
DBP	–0.065	0.036	*0.070*
MAP	–0.056	0.032	*0.079*
FHVP	–0.026	0.045	0.565
WHVP	0.047	0.024	*0.055*
HVPG	0.078	0.031	**0.012**

Table 3:

Overall C-Statistic for Cox's Predictive Model in the prediction of 1-year survival after TIPS in the studied population.

Variables in the Model	**Overall C-Statistic**	**95% CI**
MELD	0.73	0.59–0.87
MELD + HVPG	0.74	0.58–0.84

Figure 1

ROC curve for the prediction of OLT-free survival based on pre-TIPS MELD score and HVPG

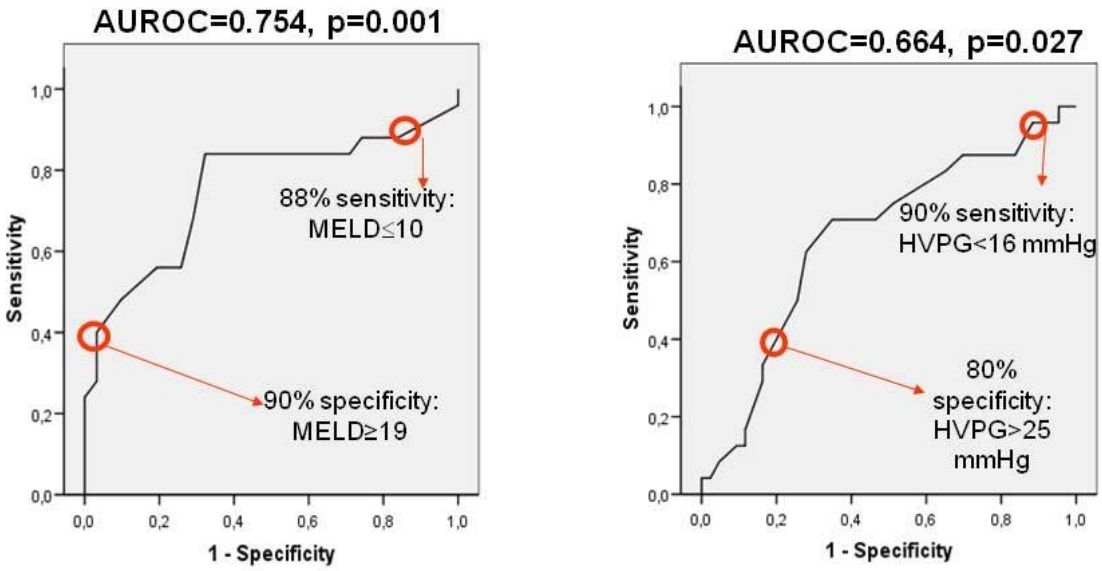
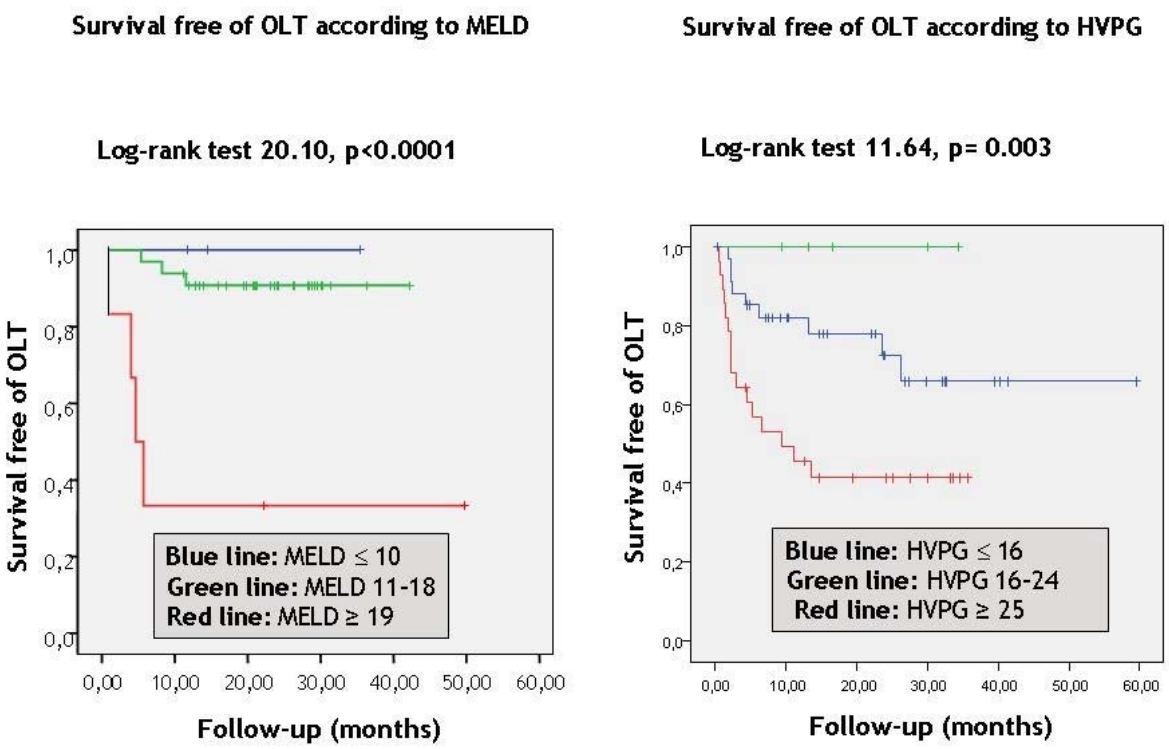


Figure 2


Survival free of OLT according to MELD
Log-rank test 20.10, p<0.0001
Survival free of OLT
1,0
0,8
0,6
0,4
0,2
0,0
0,00
10,00
20,00
30,00
40,00
50,00
60,00
Follow-up (months)
Blue line: MELD ≤ 10
Green line: MELD 11-18
Red line: MELD ≥ 19
Survival free of OLT according to HVPG
Log-rank test 11.64, p= 0.003
Survival free of OLT
Follow-up (months)
Blue line: HVPG ≤ 16
Green line: HVPG 16-24
Red line: HVPG ≥ 25

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