Research Article

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Serum bilirubin and platelet count: A simple predictive model for survival in patients with refractory ascites treated by TIPS

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Background & Aims: Refractory ascites in patients with cirrhosis is associated with poor survival. TIPS is more effective than paracentesis for the prevention of recurrence of ascites but increases the risk of encephalopathy while survival remains unchanged. A more accurate selection of the patients might improve these results. The aim of the present study was to identify parameters of prognostic value for survival in patients with refractory ascites treated with TIPS.

Methods: One hundred and five consecutive French patients with cirrhosis and refractory ascites treated with TIPS were used to assess parameters associated with 1-year survival. The model was then tested in two different cohorts: a local and prospective one including 40 patients from Toulouse, France, and an external one including 48 patients from Barcelona, Spain.

Results: The actuarial rate of survival in the first 105 patients was 60% at 1 year. Using multivariate analysis, only lower bilirubin levels and higher platelet counts were independently associated with survival. The actuarial 1-year survival rate in patients with both a platelet count above 75×10^9/L and a bilirubin level lower than 50 μmol/L [3 mg/dl] was 73.1% as compared to 31.2%, in patients with a platelet count below 75×10^9/L or a bilirubin level higher than 50 μmol/L. These results were confirmed in the two different validation cohorts.

Conclusions: The combination of a bilirubin level below 50 μmol/L and a platelet count above 75×10^9/L is predictive of survival in patients with refractory ascites treated with TIPS. This simple score could be used at bedside to help choose the best therapeutic options.

Keywords: Cirrhosis; Portal hypertension; TIPS; Refractory ascites; Survival model.

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Introduction

Refractory ascites was defined by the International Ascites Club [1,2] as ascites which cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by low sodium diet and diuretics. It is a severe complication observed in approximately 10% of the patients admitted with cirrhosis and is associated with poor quality of life, high risk of spontaneous bacterial peritonitis and hepatorenal syndrome, and low survival. All these patients should be considered for liver transplantation since, in the absence of such a treatment, 5-year survival is below 30% [3]. Whenever transplantation is contra-indicated, as well as in patients on the waiting list, refractory ascites can be treated with large volume paracenteses or TIPS [3,4]. Five randomized controlled studies comparing these two treatments have been published [5–9]. As a whole, they found TIPS to be more effective than paracenteses in preventing the recurrence of ascites, while, when considering the average number of episodes per patient, the risk of encephalopathy was increased, and survival was unchanged or slightly improved. The results of TIPS were improved by the use of polytetrafluoroethylene (PTFE)-covered stents [10]. A better selection of the patients should also improve the outcome after TIPS, and avoid useless expensive procedures in patients with an expected poor survival. Nevertheless, it still lacks criteria to allow an accurate selection.

The aim of the present study was therefore to identify parameters of prognostic value for survival in patients with refractory ascites treated with TIPS.

Patients and methods

All consecutive patients with cirrhosis and refractory ascites treated with TIPS in our institution from January 1994 to September 2008 were considered for this study. Ascites was diagnosed as "refractory" whenever it could not be mobilized by sodium restriction and high doses of diuretics (up to 400 mg of spironolactone and 160 mg of furosemide per day) ("diuretic resistant ascites") or whenever it could not be treated because of the occurrence of complications which precluded the use of effective dosages of diuretics ("diuretic intractable ascites") [1]. Fourteen of the patients included had associated hydrothorax. TIPS was performed as previously reported [10] using bare stents in the first 55 patients and PTFE-covered prostheses in the following ones. Hepatocellular carcinoma, polycystosis,

portal vein thrombosis, sever liver failure as assessed by a Child-Pugh score above 12, history of chronic or recurrent encephalopathy and cardiac failure were considered contra-indication for TIPS, or exclusion criteria for the present study. All the patients underwent Doppler-ultrasonography of the liver and echocardiography prior to TIPS. They were followed for 1 year and censored when lost to follow-up, at the time of death or liver transplantation. The data of the first 105 patients (test cohort or TC) were retrospectively collected and used to assess parameters associated with 30-day, 3 month, and 1-year survival. The following 40 patients, treated from January 2006 to September 2008, were used as a local prospective validation cohort (VC). Furthermore, between 1996 and 2008, 48 patients with refractory ascites were treated by TIPS in Barcelona (Spain) and were used as an external validation cohort (EC).

Statistical analysis

Unpaired Student *t*-test or Fischer exact test were performed as appropriate to compare quantitative variables. Survival was assessed according to the Kaplan–Meier method and curves were compared using the log-rank test. Patients who underwent liver transplantation were censored on the date of transplant. Cox proportional hazards method was used to assess the prognostic value of the variables found significantly different in univariate analysis. AUROC for the prediction of 1-year survival were calculated for quantitative variables selected by multivariate analysis. For those variables, cut-off values according to ROC curves, were determined so as to get a sensitivity over 90%. A p value of <0.05 was considered the level of significance. All statistical analyses were performed using SPSS, the software SPSS Graduate version 18.0 (SPSS, Chicago, IL).

Results

Characteristics of the patients

The main characteristics of the two French cohorts at baseline are presented in Table 1. Most patients (75%) had alcoholic cirrhosis, of whom 19% were not abstinent when included in the study. Fourteen patients (10%) underwent liver transplantation within 1 year after TIPS. The two cohorts were very similar at baseline, except for serum albumin, ascitic fluid protein concentration, and urinary sodium excretion (Table 1). The characteristics of the Spanish cohort are also presented in Table 1. Six patients underwent liver transplantation within 1 year after TIPS (12%). The main differences in EC as compared to the French cohorts were the sex ratio (70% versus 54% of males), the cause of cirrhosis (viral hepatitis in respectively 17% versus 59% of the French and the EC), a higher albumin concentration and creatinin level, and a lower platelet count.

Survival analysis

Actuarial rates of survival in the 105 patients of the TC were 96%, 78%, and 60%, respectively, at 30 days, 3 months, and 1 year (Fig. 1). All parameters listed in Table 1 were compared between the patients who died and those who survived. Lower bilirubin level, lower Child-Pugh score, lower INR, higher prothrombin index, higher ascitic fluid protein concentration, higher platelet count, and the absence of history of hepatic encephalopathy were all associated with better 1-year survival (Table 2).

Using multivariate analysis, only lower bilirubin level and higher platelet count were independently associated with 1-year survival as well as with 3-month survival. In the 40 patients of the VC, actuarial survival rates were 92%, 78%, and 58%, respectively, 30 days, 3 months, and 1 year after TIPS. These figures were not significantly different from those observed in the TC (log-rank test: $p = 0.309$). As in the TC, serum bilirubin level and platelet count were significantly different between the patients who died and those who survived at 1 year (Supplementary Table 1). Prothrombin index and MELD score were also found to be significantly different between the two groups. Survival rates did not differ according to either the study period (before versus after 2000) or the type of prostheses used (uncovered versus covered stents).

In the 48 patients of the Spanish cohort, actuarial rates of survival were 85%, 77%, and 53%, respectively, at 30 days, three months, and 1 year (NS with the 2 other cohorts). Serum bilirubin level and platelet count were also significantly different between the patients who died and those who survived at 1 year (Supplementary Table 2). Prothrombin index, Child Pugh score, serum sodium, and MELD score were also found to be significantly different between the two groups.

Prediction of 1-year survival

The AUROC for platelet count and serum bilirubin level for predicting 1-year survival were 0.692 [0.587–0.759] ($p = 0.001$) and 0.644 [0.529–0.759] ($p = 0.01$), respectively. Sensitivity and specificity of these two parameters according to different thresholds are listed in Table 3.

Finally, we selected cut-off values of 75×10^9/L for platelet count (sensitivity = 92%, specificity = 33%, positive predictive value = 71%, negative predictive value = 71%) and 50 μmol/L [3 mg/dl] for serum bilirubin level (sensitivity = 92%, specificity = 29%, positive predictive value = 68%, negative predictive value = 69%). Having a platelet count below this value was of similar frequency whether the patients were abstinent from alcohol (16%) or not (20%). The actuarial 1-year survival rate in a patient with both a platelet count above 75×10^9/L and a bilirubin level lower than 50 μmol/L was 73.1% as compared to 31.2% only in patients with a platelet count below 75×10^9/L or a bilirubin level greater than 50 μmol/L (log rank-test: p <0.001) (Fig. 2).

Serum bilirubin level, with a threshold of 50 μmol/L, and platelet count, using 75×10^9/L as a cut-off, were found to have an independent prognostic value. Actually, as shown in Fig. 3A and B, in patients with a bilirubin level lower than 50 μmol/L, 1-year survival was 71% and 39% when the platelet count was higher or lower than 75×10^9/L, respectively (log rank = 0.02). In patients with a platelet count greater than 75×10^9/L, 1-year survival was 71% and 40% according to whether serum bilirubin was lower or higher than 50 μmol/L (log rank = 0.016).

Validation of the model

The model was thereafter tested in the 40 VC patients. AUROC for serum bilirubin level and platelet count were 0.668 [0.497–0.839] and 0.823 [0.695–0.951], respectively (NS versus TC). The 50 μmol/L bilirubin cut-off had a sensitivity of 95% and a specificity of 31%, a positive predictive value of 59% and a negative predictive value of 83%. Figures for platelet count were: sensitivity 95%, specificity 32%, positive predictive value of 61% and negative predictive value of 86%. The 1-year survival rate in patients with both a platelet count above 75×10^9/L and a bilirubin level lower than 50 μmol/L, was 65.2% as compared to 31.3% in patients with a platelet count below 75×10^9/L or a bilirubin level greater than 50 μmol/L ($p = 0.02$) (Fig. 4).

The model was finally tested in the 48 patients of the Spanish EC. AUROC for serum bilirubin level and platelet count were 0.803 [0.680–0.927] and 0.750 [0.607–0.893], respectively (NS

Table 1. Characteristics of patients before TIPS according to the three different cohorts.

	First cohort (n = 105)	Validation cohort (n = 40)	*p*	External cohort (n = 48)
Age (year)	57.9 ± 8.9 [38-78]	58.9 ± 8.6 [39-75]	NS	58.9 ± 10.2 [36-77]
Male	70 (67%)	31 (77%)	NS	26 (54%)*
Cause of cirrhosis				
Alcohol	79 (75%)	32 (80%)	NS	15 (31%)
Viral hepatitis	18 (17%)	7 (17%)	NS	28 (59%)*
Others	8 (8%)	1 (3%)	NS	5 (10%)
Child Pugh score	9.5 ± 1.4 [7-12]	9.1 ± 1.6 [7-12]	NS	9.1 ± 1.3 [8-12]
Child Pugh class B/C	57 (54%) / 48 (46%)	25 (62%) / 15 (38%)	NS	32 (67%) / 16 (33%)
Episode of prior encephalopathy	23%	29%	NS	ND
Meld score	14 ± 4 [8-27]	14 ± 4 [8-26]	NS	16 ± 7 [3-37]
MeldNa	20 ± 6 [8-35]	19 ± 4 [9-28]	NS	24 ± 7 [9-38]
Serum bilirubin (μmol/L)	36 ± 39 [2-340]	33 ± 26 [8-145]	NS	54 ± 81 [7-458]
Serum sodium (mmol/L)	130 ± 7 [111-141]	130 ± 4 [121-140]	NS	127 ± 7 [110-141]
Urinary sodium (mmol/L)	16 ± 19 [2-103]	27 ± 26 [6-107]	0.03	12 ± 9 [1-35]
Serum albumin g/L	28 ± 5 [14-4]	32 ± 4 [24-43]	0.01	31 ± 6 [18-48]*
Prothrombin index (%)	62 ± 15 [29-97]	62 ± 13 [39-95]	NS	60 ± 18 [30-97]
INR	1.4 ± 0.2 [1.1-2.2]	1.5 ± 0.3 [1.1-2.3]	NS	1.4 ± 0.3 [1.0-2.2]
Serum creatinine (μmol/L)	98 ± 34 [43-301]	98 ± 28 [50-171]	NS	159 ± 128 [53-724]*
Platelets count (x10^9/L)	143 ± 74	149 ± 82	NS	105 ± 58 [32-84]*
Serum glucose (mmol/L)	5.9 ± 2.5 [3.4-19]	5.7 ± 1.3 [4.0-11.1]	NS	ND
Ascitic protein concentration (g/L)	15.3 ± 9.6 [3-44]	19.9 ± [5-52]	0.04	ND
PPG before TIPS (mmHg)	18 ± 5 [7-36]	17 ± 5 [10-33]	NS	20 ± 5 [12-32]
PPG after TIPS (mmHg)	6 ± 3 [0-15]	6 ± 6 [3-15]	NS	10 ± 3 [4-18]

$*p$ <0.05 between the external cohort ant the first internal cohort.

versus the two other cohorts). The 50 μmol/L bilirubin cut-off had a sensitivity of 89% and a specificity of 46%, a positive predictive value of 66% and a negative predictive value of 77%. Figures for platelet count (cut-off 75 × 10^9/L) were: sensitivity 77%, specificity 68%, positive predictive value 74%, and negative predictive value 71%. The 1-year survival rate in patients with both a platelet count above 75 × 10^9/L and a bilirubin level lower than 50 μmol/L, was 80.0% as compared to 26.0% in patients with a platelet count below 75 × 10^9/L or a bilirubin level greater than 50 μmol/L (p <0.001) (Fig. 5).

Discussion

The present study showed that platelet count and serum bilirubin were predictive of survival in 105 cirrhotic patients with refractory ascites treated by TIPS. This result was successfully challenged in two different validation cohorts including 88 patients. TIPS has been shown to be more effective than large volume paracenteses in preventing recurrence of ascites. However, the results of published series are conflicting regarding survival. In Lebrec et al. [5], in which only 20 patients were included, a higher mortality in Child C patients was reported. Subsequently, in two studies [6,9], survival was found to be higher after TIPS, while two other studies failed to show any difference [7,8]. Five meta-analyses were performed [11–15]. Four of them [11–14] reported a more effective prevention of ascites recurrence using TIPS, while the risk of encephalopathy was increased and survival was similar in patients treated with large volume paracenteses. The Salerno et al. meta-analysis pooled 4 randomized controlled trials with a total of 305 patients whose individual data were analyzed [15]. The actuarial probability of transplant free survival was better in patients allocated to the TIPS arm than in the paracenteses group, being 63% and 52% at 1 year, 49% and 35% at 2 years, respectively. These figures are similar to those in our series. On the contrary, the survival rate was lower in the Moreau et al. study [16]. This is probably because of different selection criteria of the patients, severe liver failure as assessed by a Child-Pugh score over 12, portal vein thrombosis or hepatocellular carcinoma as compared with the exclusion criteria in our series. Age has been reported to be predictive of survival in the Salerno et al. meta-analysis [15]. This was not confirmed in our whole sample of patients, though 27% of them were older than 65, nor in the Spanish EC (35% were older than 65). A selection bias cannot be excluded since our patients were not randomized and older ones might have been highly selected. However, in the prospective validation cohort, 1-year survival of patients older than 65 was only 17% (2/12) versus 67% (19/28) in younger ones (p <0.005). Accordingly, treating more than 65 year-old patients with refractory ascites by TIPS should be considered with caution.

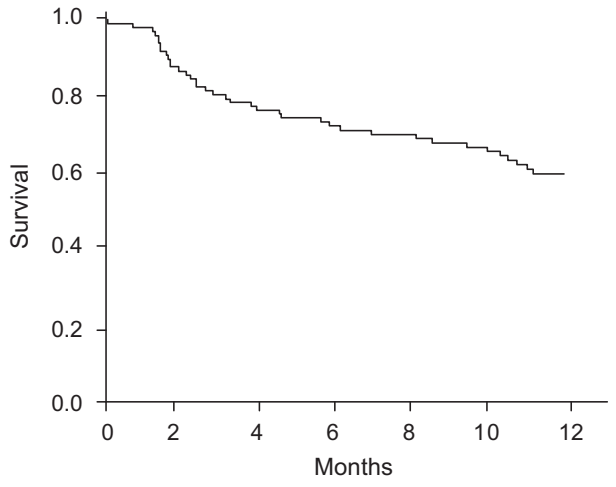

Fig. 1. Actuarial rates of survival observed in the whole population of patients with refractory ascites treated by TIPS (*n* = 105).

Table 3. Sensitivity and specificity of serum bilirubin and platelet count to predict 1-year survival, according to several cut-off values, observed in the first cohort.

	Sensitivity	Specificity
Platelet count		
<50.10^9/L	97%	5%
<75.10^9/L	92%	33%
<100.10^9/L	78%	49%
<125.10^9/L	59%	67%
<150.10^9/L	50%	74%
Serum bilirubin concentration		
15 µmol/L	27%	81%
25 µmol/L	50%	58%
35 µmol/L	78%	53%
50 µmol/L	92%	29%

Child-Pugh and MELD scores were not found to be useful for the prediction of survival in our patients. There was only a trend toward a difference for MELD score in the first cohort between patients who did or did not survive after 1 year. In the two validation cohorts, the MELD score was significantly different between patients who survived or not at 1 year (15.4 versus 12.5 in the French prospective validation cohort and 19.6 versus 13.8 in the EC). As a whole, no relevant threshold for clinical use was identified. This result is in accordance with those reported in other series of similar patients. This could be accounted for by the absence of renal failure in our patients from the first cohort. Sanyal et al. found that baseline MELD score was not associated with the outcome in patients with refractory ascites treated by TIPS or paracentesis [8]. As hypothesized by Sanyal et al., MELD score could be more predictive of outcome in patients with both renal and liver failure than in those with normal renal function. Our results are in accordance with this statement since the MELD score was found to be associated with outcome in the Spanish cohort. In the Spanish center, patients with renal failure were included. In the first cohort, the failure of the MELD score to correlate with post TIPS survival is probably related to the inclusion

Table 2. Characteristics of the 105 patients before TIPS according to whether or not they were alive or not 1 year after the TIPS procedure.

	Dead at one year (n = 39)	Alive at one year (n = 66)	*p*
Age (year)	59 ± 9	57 ± 9	NS
Male - Female	26 - 13	44 - 22	NS
Child Pugh score	9.9 ± 1.4	9.2 ± 1.3	0.015
Child Pugh class (B/C)	16/23	41/25	0.029
MELD score	14.6 ± 5.1	13.0 ± 3.5	0.08
MELDNa	21.5 ± 7.2	19.4 ± 5.0	0.115
Serum bilirubin (µmo/L)	49 ± 57	28 ± 20	0.032
Serum sodium (mmol/L)	129 ± 8	130 ± 6	0.299
Urinary sodium (mmol/L)	12 ± 13	18 ± 22	0.155
Serum albumin (g/L)	28 ± 6	28 ± 5	0.885
Prothrombin index (%)	57 ± 15	64 ± 15	0.031
INR	1.5 ± 0.3	1.3 ± 0.2	0.02
Serum creatinine (µmol/L)	92 ± 31	102 ± 35	0.123
Platelet count (x10^9/L)	115 ± 60	161 ± 77	0.001
Serum glucose (mmol/L)	6.1 ± 2.9	5.9 ± 2.4	0.699
Ascitic fluid concentration (g/L)	13 ± 9	17 ± 10	0.031
PPG before TIPS (mmHg)	19 ± 5	18 ± 5	0.332
PPG after TIPS (mmHg)	6 ± 3	5 ± 3	0.180

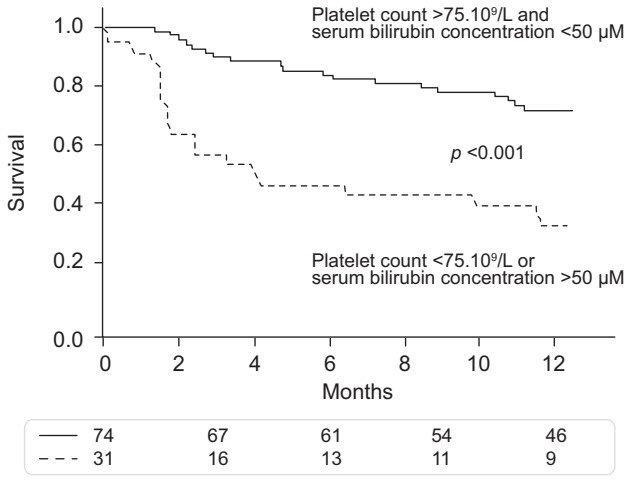

Fig. 2. Actuarial rates of survival in the 105 patients (TC) with cirrhosis and refractory ascites treated with TIPS according to serum bilirubin concentration and platelet count (number below the graph are patients at risk at each time point).

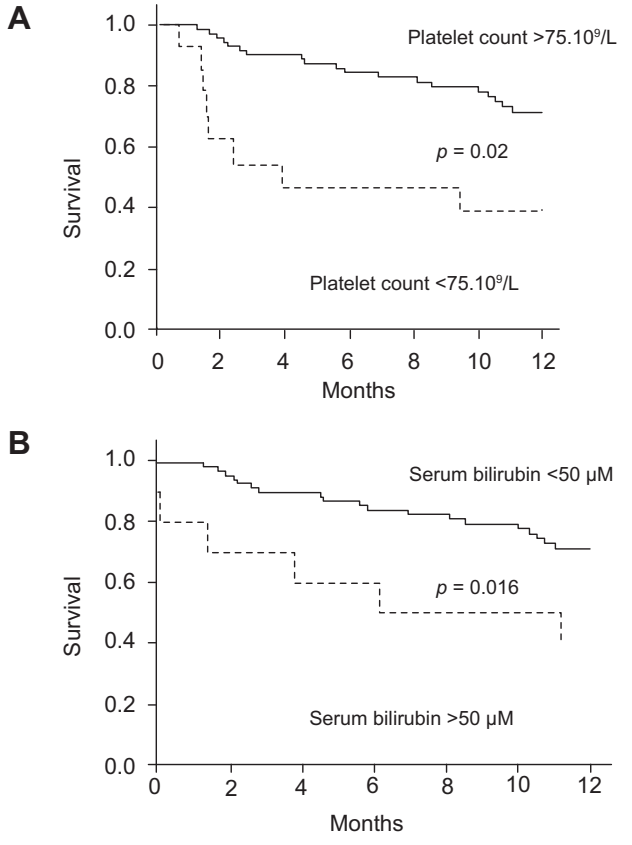

Fig. 3. Results of patients with a bilirubin level lower than 50 µmol/L. (A) Actuarial rates of survival of patients with serum bilirubin <50 µmol/L according to platelet count in the TC. (B) Actuarial rates of survival of patients with platelet counts >75 × 10^9/L according to serum bilirubin concentration.

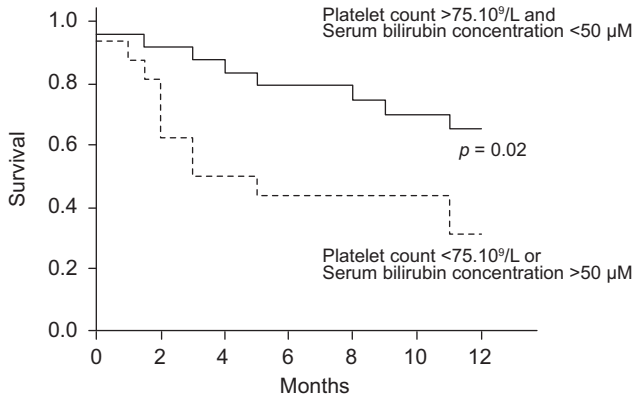

Fig. 4. Actuarial rates of survival of the 40 patients (VC) with cirrhosis and refractory ascites treated with TIPS according to serum bilirubin concentration and platelet count.

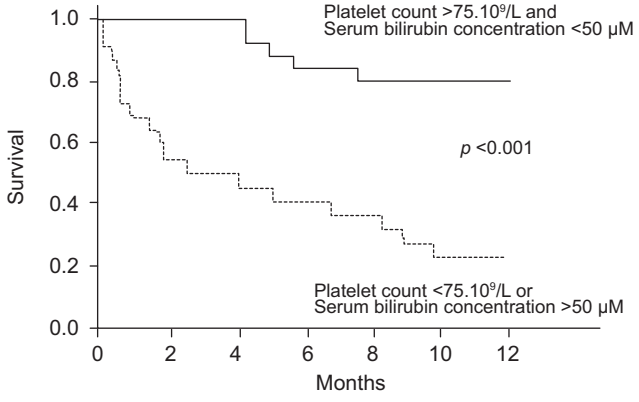

Fig. 5. Actuarial rates of survival of the 48 patients of Spanish external validation cohort (EC).

of subjects with preserved renal function. Finally, our results are also in accordance with those published in a very recent paper by Serste et al. [17] who showed in a cohort of 151 patients with refractory ascites that MELD score is not a predictive factor of mortality. MELDNa score, computed as previously described [18], was not found to improve that result. However, in patients with refractory ascites, natremia may vary tremendously according to diverse situations such as the use of diuretics, albumin infusions, renal function, and delay from paracentesis. Furthermore, most of these patients are hyponatremic which could weaken the discriminative value of natremia.

A high serum bilirubin level is a well established sign of liver failure in patients with cirrhosis and is consistently associated with poor survival. Actually, in the Salerno et al. study [15], higher serum bilirubin as well as older age, lower natremia and treatment allocation, had an independent prognostic value. Serum bilirubin level was also found to be predictive of survival in the present study and a cutoff value could have been determined. In patients with cirrhosis, low platelet count is usually considered a surrogate marker of portal hypertension (PHT), though patients with documented PHT may have a normal platelet count [19]. Actually, 40% of our patients had a normal platelet count, in spite of overtly decompensated PHT. It is difficult to know the prevalence of thrombopenia in this group of patients. Actually, platelet count was not reported in the five published

randomized studies and therefore was never assessed as a prognostic parameter. Several studies have shown that platelet count is not accurate enough for predicting significant portal hypertension [19,20]. Furthermore, 23% and 36% of the patients with significant PHT have a normal platelet count in the study by Qamar et al. [19] and Bashour et al. [21], respectively. Finally, in our study aiming to assess the parameters associated with significant PHT [22], 46% of the patients with significant PHT had a normal platelet count. Thrombocytopenia could also be, at least in part, accounted for by liver failure because of a decreased synthesis of thrombopoietin [23]. This could help explain that treatments aiming to reverse PHT have little effect on thrombocytopenia even when portal pressure is normalized [24]. Platelet count and serum bilirubin level had independent prognostic values in our study and their combination increased their accuracy in predicting survival. Both parameters are readily available and inexpensive. Their use could help select patients for TIPS or alternative treatments. The cut off values giving the best sensitivity were determined in a test cohort, and then successfully challenged in two different validation cohorts. The first one was a prospective cohort in the same center and most importantly, the second one was an external cohort from another European country with differences in the characteristics of the patients regarding sex, cause of cirrhosis, renal function, and platelet count. The performances of the two parameters tended to be better in the external validation set with reference to the calculated AUROC for the prediction of 1-year survival and to the observed 1-year survival. Hence, we are confident of the reproducibility of the score in similar patients. We are aware that these parameters could not be "TIPS specific" and also be associated with survival and useful in patients with refractory ascites who are not treated by TIPS. A similar observation can be made with most prognostic indexes such as MELD score for instance. Further studies are warranted to test this hypothesis. Poor outcome in a number of patients is likely related to the severity of the underlying disease and in the absence of a control group, we have no information regarding the survival of the same patients treated conservatively by paracentesis. No difference was observed according to the type of prosthesis used (covered versus non-covered). However, differences could appear in larger samples or with longer follow-up. In such series, the higher risk of dysfunction and related complications with the use of uncovered stents could influence survival. Finally, it is noteworthy that this model allows for selecting a good proportion of patients since in the French cohort, 70 patients were accurately classified and the TIPS's procedure could have been avoided in 38% of patients (55/145). In the Spanish cohort, using the same model, 77% of the patients were well classified and TIPS could have been avoided in 48% of patients (23/48).

In conclusion, a bilirubin level below 50 μmol/L [3 mg/dl] and a platelet count above 75×10^9/L are predictive of survival in patients with refractory ascites treated by TIPS. This simple score could be used at bedside to choose the best therapeutic options and avoid useless expensive procedures in patients with an expected poor survival.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2010.08.025.

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