Predictors of re-bleeding and mortality among patients with refractory variceal bleeding undergoing salvage TIPS

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Abbreviations: TIPS, transjugular intrahepatic porto-systemic shunt; PTFE, polytetrafluoroethylene; MELD, model for end stage liver disease; PHB, portal hypertensive bleeding; INR international normalized ratio; AST, aspartate aminotransferase; ALT. alanine aminotransferase; CPS, Child-Pugh score; HVPG, hepatic venous pressure gradient; RBCs, number of blood units transfused; ITUs, length of intensive care unit stay; MV, mechanical ventilation; HE, hepatic encephalopathy; CP1 Child-Pugh score 5 to 9; CP2, Child-Pugh score 10 to 15; OR, Odds Ratio; 95%CI, 95% Confidence Interval; NAFLD, non-alcoholic fatty liver disease.

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Ethics: This was a single-centre retrospective audit including consecutive patients with cirrhosis and variceal bleeding admitted at the Royal Free Hospital who underwent TIPS placement. As such, ethical approval and consent was not required.

Abstract

Background & Aims: Transjugular intrahepatic portosystemic shunt (TIPS) has proven clinical efficacy as salvage therapy for cirrhotic patients with acute portal hypertensive bleeding who fail endoscopic treatment. We evaluated predictive factors of 6-week and one year mortality in such patients undergoing emergency TIPS.

Methods: Retrospective evaluation of 144 consecutive patients. Three logistic regression multivariate models were estimated to individualize prognostic factors for 6-week and 12-month mortality. Log-rank test was used to evaluate survival according to Child-Pugh classes, Bureau's criteria, time to TIPS and type of stent used.

Results: Mean age 51±10 years, 66% male, mean MELD xx, Child Pugh A/B/C x%/y%/z%. Emergency TIPS controlled bleeding in 84% of cases. TIPS failure, defined as re-bleeding within 6 weeks, occurred in 23 (16%) patients and was associated with pre-TIPS hepatic venous pressure gradient and pre-TIPS intensive care unit stay. Six-week and 12-month mortality was 36% and 42%, respectively. Pre-TIPS intensive care unit stay, re-bleeding and MELD score were independently associated with mortality at 6 weeks. Predictors of mortality at 12 months were pre-TIPS intensive care unit stay and Child-Pugh score.

Conclusions: In this large cohort of patients undergoing salvage TIPS, MELD and Child-Pugh scores were predictive of short and long-term mortality, respectively. Pre-TIPS intensive care unit stay was independently associated with TIPS failure and mortality at 6 weeks and 12 months. Emergency TIPS is futile in patients with Child-Pugh score of 14-15.

Key words: Acute portal hypertensive bleeding, Emergency TIPS, Child-Pugh score, MELD score.

Key Points

- MELD score is a good predictor of 6-week survival after emergency TIPS for acute bleeding from oesophageal varices in patients with liver cirrhosis.

- Pre-TIPS hepatic venous pressure gradient allows a good risk stratification of patients at high risk of treatment failure.

- Need of intensive-care support significantly influences short-term and long-term outcome of cirrhotic patients undergoing emergency TIPS.

- Long-term mortality following emergency TIPS mainly depends on liver disease stage, as can be expressed by Child-Pugh score. The procedure is futile in patients with Child-Pugh score of 14-15.

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is a radiological procedure widely used to treat complications of portal hypertension.[1] This procedure was introduced 35 years ago as a substitute for surgical shunts to avoid operative mortality and possibly reduce encephalopathy rates.[2] Only three indications for TIPS have been evaluated in randomized clinical trials: secondary prophylaxis of variceal bleeding, treatment of acute variceal bleeding and refractory/resistant ascites.[3-5] Other indications for TIPS include hepatic hydrothorax, Budd–Chiari syndrome, veno-occlusive disease, portal vein thrombosis, hepato-pulmonary and hepatorenal syndrome.[6] The procedure can be complicated by thrombosis/occlusion, and stent migration, but the use of polytetrafluoroethylene (PTFE) covered stents has reduced the incidence of such technical and mechanical complications.[7-9]

There are several prognostic models for patients undergoing TIPS for variceal bleeding but there are only few robust predictors of mortality, such as high bilirubin levels and higher Child-Pugh (class C).[10,11] Recently, the Mayo Clinic mathematical model for end stage liver disease (MELD) was developed to predict early mortality after elective TIPS[12] but only a retrospective study has evaluated the model in emergency TIPS.[13] In patients with refractory ascites treated with TIPS, the combination of a bilirubin level below 50 μmol/L (3 mg/dl) and a platelet count above 75×10^9/L is predictive of survival.[14]

TIPS has proven clinical efficacy as salvage therapy for cirrhotic patients with acute portal hypertensive bleeding (PHB) that fail endoscopic and/or pharmacological therapy. Early mortality in this high-risk group is about 50%.[15] A recent trial in patients with cirrhosis and acute variceal bleeding at high risk for treatment failure demonstrated that the early use of TIPS was associated with a significant improvement in survival.[3]

Our first aim was to evaluate prognostic variables in relation to mortality in consecutive patients who had salvage TIPS for refractory bleeding and to assess if MELD score, which has been derived from cohorts undergoing elective TIPS, maintains the same accuracy in the stratification of risk for patients undergoing emergency TIPS. Secondly, we evaluated the variables associated with TIPS failure (defined as re-bleeding within 6 weeks from the procedure)[16] and 6-week and 12-month survival.

Patients and Methods

We evaluated 144 consecutive patients with cirrhosis who underwent salvage TIPS for acute portal hypertensive bleeding refractory to standard endoscopic treatment at the Royal Free Sheila Sherlock Liver Unit from June 1992 to May 2008. Data were collected prospectively in a database, which was then analysed retrospectively. Epidemiological and laboratory factors (gender, age, bilirubin, albumin, sodium, international normalized ratio (INR), creatinine, white blood cells, aspartate aminotransferase (AST), alanine aminotransferase (ALT), haemoglobin, platelets), Child-Pugh score (CPS), MELD score, MELD-Na, as well as hepatic venous pressure gradient (HVPG) before and after TIPS, number of blood units transfused (RBCs), length of intensive care unit stay (ITUs) before TIPS, need of mechanical ventilation (MV), presence of ascites or hepatic encephalopathy (HE), type of stent inserted (uncovered vs. PTFE-coated) and time from admission to TIPS procedure (<24, 24-72 hours, >72 hours) and Bureau's criteria (a combination of platelet count above $75x10^9$/L and a bilirubin level lower than 50 μmol/L (3 mg/dl)[14] were recorded.

Criteria for TIPS use were based on failure to control bleeding with endoscopic therapy and vasoactive drugs. These conformed in essence to the Baveno IV criteria.[16]

TIPS was preferably performed within 72 hours after endoscopy, and vasoactive drugs were administered until TIPS placement. Child-Pugh class stratification was performed as follow: score 5 to 9 (CP1), score 10 to 15 (CP2).

Before the TIPS procedure, patients underwent a routine electrocardiography, computed tomography of the abdomen and/or Doppler ultrasound of the liver portal venous system and routine laboratory tests.

TIPS procedure

The TIPS procedure was performed in the interventional radiology suite after obtaining a signed informed consent by the patients or their relatives. TIPS procedure was executed as previous described.[17] Variceal embolization was also performed to occlude the filling of large collaterals feeding gastro-oesophageal varices and maximise the flow to the liver [18]. PTFE-coated stents were used since 2002.[19]

The target value of portal pressure gradient was 12 mmHg or, alternatively, a reduction of at least 20% from the baseline.[20] However, all efforts were made to maintain the shunt diameter as small as possible in order to avoid the risk of severe encephalopathy, particularly in patients who had already experienced this complication. Thus, the final diameter of the shunt and the reduction of the portal pressure were left to a decision of operator, either a hepatologist or a liver radiologist who worked in combination.

Statistical Analysis

Data are presented as mean±standard deviation or median and range values for numerical variables with parametric and non-parametric distributions respectively and as percentage for categorical variables. Statistical analysis was performed using t-test, ANOVA, Mann-Whitney test or Kruskal-Wallis test for comparisons of continuous variables between or among groups, corrected chi-squared method or two-tailed Fisher's exact test for comparisons of qualitative data and Spearman's coefficient for correlations of quantitative data, when appropriate. Multivariate analysis was performed using logistic regression models. Data were censored at the time of the last contact with the patient, liver transplantation or death. Predictive variables for re-bleeding rate at 6 weeks, as well as 6-week and 12-month mortality were assessed by binary logistic regression (providing Odds Ratio (OR), relative 95% Confidence Interval (95%CI) and p-value). In order to individualize the main prognostic factors for short-term (6 weeks) and long-term (12 months) mortality, we performed different logistic regression models. The multivariate model included the variables significant at the univariate approach (significance level $p<0.05$) and also the time from bleeding to TIPS procedure and the type of stent used (covered vs. uncovered). Twelve months mortality was described by the Kaplan-Meier curve, stratifying the patients according to Child-Pugh class. Log-rank test was applied to evaluate significant differences in the survival function in the above-mentioned classes (CP1 and CP2, respectively). All significance tests were two-sided, and p values <0.05 were considered statistically significant. Data processing and analyses were performed by SPSS for Windows (version 22.0, IBM, New York, NY, USA).

Results

Study patients

Baseline patients' characteristics are summarized in **Table 1**. Mean age was 51±10.7 years, with male predominance (n=95, 66%). The aetiology of liver disease was alcohol, viral, non-alcoholic fatty liver disease (NAFLD) and autoimmune/cryptogenic in 83 (57.6%), 20 (13.9%), 14 (9.7%) and 27 (18.8%) of cases, respectively. TIPS procedure was performed within 72 hours from PHB in 70% of cases and was technically successful in all but 7 patients (5%). Eighty patients (55.6%) had uncovered TIPS insertion, while a PTFE covered stent was placed in sixty-four (44.4%).

Median follow-up was 116.5 days (range 0 - 4.164 days). Six-week and 12-month mortality was 36% and 42%, respectively. Follow-up at 12 months was available for 39 patients (51.3%) of patients who didn't reach an endpoint.

HVPG decreased from a median of 21 mmHg (range 7-48 mmHg) before the shunt to a median of 11 mmHg (1-33 mmHg) post procedure ($p<0.001$). Post-TIPS encephalopathy occurred in 22/144 (15%) patients, and was moderate in the majority of cases. All patients with encephalopathy responded to medical treatment and no stent revision was required.

Rebleeding

Recurrent bleeding occurred in 42 patients (29%), thirty-four of whom re-bled from oesophageal varices, 5 from portal hypertensive gastropathy and 3 from other causes (splenic artery rupture, ectopic varices). Twenty-three of these patients (23/42, 54.8%) re-bled within six weeks from TIPS placement. In 3/23 (13%) patients, re-bleeding at 6 weeks was due to failure in achieving an HVPG reduction less than 20% and in 3/23 (13%) to concurrent bacterial infection. In 10/23 (43.5%) subjects, re-bleeding at 6 weeks was caused by stent occlusion/stenosis. In the remaining 7/23 (30.5%) of cases the causes of re-bleeding was undetermined. Stent occlusion/stenosis occurred in 18 (12.5%) patients overall, at a median of 146 days after TIPS placement. Re-bleeding related to stent dysfunction was associated to uncovered TIPS in the majority of cases (14/18 patients, 78%). We included in the study 63 patients with CPS 10-13 and 10 patients with CPS 14-15. Re-bleeding rate was similar in the two groups, occurring in 20 patients (32%) in the CPS 10-13 group and in 3 (30%) of the subjects with a CPS 14-15. Univariate logistic regression analysis showed that re-bleeding rate at six weeks was related to pre-TIPS HVPG, pre-TIPS ITUs and uncovered vs. PTFE stent. Pre-TIPS HVPG (OR: 1.267, 95%CI: 1.032-1.555, p=0.024) and pre-TIPS ITUs (OR: 2.765, 95%CI: 1.237-4.398, p=0.012) were independently associated with re-bleeding at multivariate logistic regression analysis.

Mortality

Models for six-week mortality.

The variables significantly associated with 6 weeks mortality at the univariate analysis ($p<0.05$) were bilirubin, creatinine, INR, platelet count, HE, presence of ascites, CPS, MELD score, pre-TIPS ITUs, MV, re-bleeding within 6 weeks and Bureau's criteria (**Table 2**).

In order to individualize the main prognostic factors related to mortality at 6 weeks and, in particular, to evaluate the significance of CPS and MELD score or their single components, we estimated different logistic regression models. Although not statistically significant at the univariate analysis, uncovered vs. PTFE stent and time to TIPS procedure were included in the models.

In the first model (MODEL 1), we included both CPS and MELD score (but not the single components of both scores). Factors related to six weeks mortality in the multivariate analysis were: MELD score (OR 1.068, 95%CI 1.001-1.140, p=0.046), pre-TIPS ITUs (OR: 3.138, 95%CI 1.082-9.098, p=0.035) and re-bleeding within 6 weeks (OR: 2.344, 95%CI 1.013-5.427, p=0.047).

In the second model (MODEL 2) CPS was replaced by the CPS individual components (bilirubin, albumin, INR, ascites, HE). Pre-TIPS ITUs (OR: 3.298, 95%CI 1.082-10.050, p=0.036) and MELD score (OR: 1.085, 95%CI 1.026-1.147, p=0.004) remained the only statistically significant predictors of mortality at 6 weeks post-emergency TIPS.

The third model (MODEL 3) evaluated MELD individual components: independent predictors of mortality at 6-weeks were CPS (OR 1.259, 95%CI 1.031-1.539, p=0.024), pre-TIPS ITUs (OR: 3.594, 95%CI 1.196-10.801, p=0.023), re-bleeding within 6 weeks (OR: 2.415, 95%CI 1.037-5.623, p=0.041) and creatinine (OR 2.156, 95%CI 1,068-4.350, p=0.032) (**Table 3**).

Models for 12 months mortality.

Significant variables at the univariate analysis (p<0.05) for 12 months mortality were bilirubin, creatinine, INR, platelet count, HE, presence of ascites, CPS, MELD score, pre-TIPS ITUs, MV and Bureau's criteria (**Table 2**).

The variables statistically significant at the univariate approach were then entered in the multivariate logistic model (**Table 4**). Although not significant at the univariate, analysis, time to TIPS procedure (<24, 24-72 hours, >72 hours) and uncovered vs. PTFE stent were included in the multivariate.

Applying the same approach used for the 6 weeks mortality, we estimated three different logistic regression models in order to individualize the main prognostic factors of mortality at 12 months.

In the first model (MODEL 1), we included both CPS and MELD scores. In this model, only CPS (OR 1.381, 95%CI 1.096-1.740, p=0.006) and pre-TIPS ITUs (OR 4.927, 95%CI 1.125-21.584, p=0.034) were independently associated with mortality. (**Table 4**).

The second model (MODEL 2) was aimed to evaluate the significance of CPS single factors or CPS; independent predictors of mortality at 12 months were pre-TIPS ITUs (OR 5.630, 95%CI 1.245-25.462, p=0.025), MELD score (OR 1.058, 95%CI 1.000-1.119, p=0.049), the presence of HE (OR 2.613, 95%CI 1.026-6.658, p=0.044) and ascites (OR 3.537, 95%CI 1.436-8.712, p=0.006) (**Table 4**).

The third model (MODEL 3) evaluated MELD components in relation to 12 months mortality; pre-TIPS ITUs (OR 5.116, 95%CI 1.179-22.207, p=0.029) and CPS (OR 1.410, 95%CI 1.155-1.721, p=0.001) were independently associated with mortality (**Table 4**).

Log-rank test was applied to compare survival between patients in Child-Pugh class 5-9 (CP1) and patients in Child-Pugh class 10-15 (CP2). Overall survival was significantly longer in CP1 compared to CP2 (median 334 vs. 48 days, respectively, p=0.002). A similar significance was found, at the Kaplan Mayer analysis, for survival at 6 weeks (p=0.008) and 12 months (p=0.001) (**Figure 1**). Mortality rate in the 63 patients with CPS 10-13 was of 29.4% at 6 weeks and 65% at 12 months; all 10 patients in CPS 14-15 died within 6 weeks.

Finally, we performed a survival analysis stratifying patients according to Bureau’s criteria and time to TIPS placement. At 12 months, patients who met Bureau’s criteria had significantly longer survival than those who did not meet them (p=0.008) (**Figure 2A**). When we evaluated only patients in CP1, this difference was maintained (p=0.050) (**Figure 2B**), while Bureau’s criteria did not influence survival in patients in CP2 (p=0.891) (**Figure 2C**). No statistically significant difference in survival was found when patients were stratified according to time to TIPS insertion (data not shown).

Discussion

In this retrospective study of salvage TIPS placement for acute PHB refractory to standard endoscopic treatment, we showed that the absence of re-bleeding, a lower MELD score and no ITU stay prior to TIPS are all associated with improved 6-week survival. No ITU stay was also an important predictor of survival at 12 months, together with a lower Child-Pugh score. Importantly, the use of TIPS was futile for patients with Child-Pugh scores 14-15.

In cirrhotic patients with PHB, the standard treatment algorithm based on early vasoactive medications, prophylactic antibiotics and therapeutic endoscopic procedures has still a 10-20% of treatment failure and mortality.[15,21,22] Patients with advanced liver disease (Child-Pugh class C class B with active bleeding at endoscopy) are at higher risk of treatment failure and increased mortality. [23] In such patients, emergency TIPS performed within 72 hours of the PHB leads to a significant reduction of treatment failure, re-bleeding and mortality rate.[3,20,24] The improved outcomes due to the use of emergency TIPS in high-risk patients have been confirmed by three recently published studies.[3,24,25] Herein, we observed a cumulative one-year mortality of 42%, which is significantly higher than that reported in the two randomised trials by Monescillo et al. and Garcia Pagan et al.[3,20] This was expected, as all patients in our cohort had salvage TIPS due to refractory bleeding and not an emergency TIPS after a successful endoscopic procedure in order to reduce the risk of re-bleeding.

Several prognostic models have been evaluated for patients undergoing emergency TIPS for PHB, with the subsequent development of various scoring systems.[26-28] Although they have never been validated in urgent/emergency TIPS, MELD and Child-Pugh (class and score) have been widely and ubiquitously applied in this setting either to stratify patients or to predict risk of treatment failure, re-bleeding and mortality.[3]

High serum bilirubin level is a well established index of liver dysfunction in patients with cirrhosis and is consistently associated with a poor survival in patients undergoing TIPS placement.[29] In cirrhosis, low platelet count is usually considered a surrogate marker of portal hypertension, although patients with documented PH may have a normal platelet count.[30] In a study aimed at identifying parameters of prognostic value for survival in patients with refractory ascites treated with TIPS, Bureau and colleagues found that a combination of a bilirubin level below 50 µmol/L (3 mg/dl) and a platelet count above $75x10^9$/L is a predictor of mortality within one year from the procedure.[14] Herein, we investigated, for the first time, the predictive role of these criteria, in a cohort of patients treated by emergency TIPS following an episode of gastrointestinal bleeding. In our setting, these cut-offs were not predictive for 6 weeks and 12 months mortality. However, when we stratified patients according to Bureau's criteria, patients who had a platelet count $<75x10^9$/L and a total bilirubin >3 mg/dl had a statistically significant higher mortality rate up to a Child-Pugh score of 9. These criteria lost their utility for stratifying risk in patients who had more advanced disease (CPS 10-15).

Child-Pugh (class or score) was originally developed as a model to predict success in porto-caval shunt[31] and is nowadays widely utilized. On the contrary, MELD score has been developed to predict short-term survival in patients undergoing elective TIPS.[12] MELD score is widely accepted as the best predictor of early mortality after TIPS. In accordance to our results, a recent retrospective study concluded that MELD score has the same accuracy in predicting the three months mortality in patient undergoing emergency TIPS for portal hypertensive haemorrhage as in elective TIPS placement.[13] In a large cohort of patients admitted to a specialist liver ITU for acute variceal haemorrhage, MELD score was reported to be even comparable to physiological and organ failure scores in predicting hospital mortality.[32]

In order to investigate the predictive value of CPS and MELD score in emergency TIPS, we constructed three models of multivariate analysis, considering the single components of CPS and MELD scores and comparing the two scores (CPS vs. MELD). In agreement with what reported in a recent meta-analysis, in our population MELD score was an independent predictor of 6 weeks mortality. Mortality at 12 months, instead, was better predicted by the CPS. The reason for this is probably related to the fact that, despite MELD score - as a result of a mathematical calculation based on biochemical parameters- is a more objective tool, it might underestimate the risk of death, since it does not take in consideration factors such as HE and ascites, which reflect a more advanced liver disease and are known to have a strong impact on patients survival.[33,34]

Since CPS 14-15 was one of the exclusion criteria for the early-TIPS trial,[3] we wanted to evaluate re-bleeding and mortality rate in this subgroup of patients. In our cohort, none of the patients in CPS 14-15 survived at 30 days, confirming the futility of a treatment with TIPS in patients with severely decompensated disease.

Hemodynamic parameters expressed by HVPG measurements allow a good risk stratification of patients at high risk of treatment failure.[20] HVPG is considered the only predictive factor of short and long-term mortality as well as of re-bleeding in patients who do not reach a target portal pressure reduction of $\geq$ 20% from baseline or a value of HVPG $\leq$ 12 mmHg after TIPS placement.[20,35] However, HVPG is not widely available and may be difficult to be performed early (i.e. within 24 hours) in bleeding patients. In our series, re-bleeding within 6 weeks (TIPS failure) was related to pre-TIPS HVPG in both CPS classes.

Pre-TIPS intensive care unit stay was the second factor related to TIPS failure in our cohort. Furthermore, ITU stay before the procedure was a strong independent predictor of both short and long-term mortality. Need of ITU support before the TIPS procedure was in fact associated with a 3 and 5-folds increased risk of death at 6 weeks and 12 months, respectively. Cirrhotic patients often develop complications such as grade III-IV HE, septic shock and variceal bleeding which require intensive care support for invasive monitoring and airway protection. Short-term prognosis in cirrhotic patients who develop multiple organ dysfunction, including refractory circulatory failure, remains poor despite ITU support, with most deaths occurring during the first week from admission.[36,37]

The use of PTFE-coated stents has reduced the occurrence of complications related to shunt dysfunction such as bleeding episodes consequent to occlusion. Although the rate of occlusion was statistically lower for the PTFE-covered stents than for the bare ones, the use of coated stent did not result in survival advantage at both 6 weeks and 12 months, in keeping with the results of a recent randomized controlled trial.[38]

In conclusion, according to our findings, MELD score seems to be a reliable predictor of short-term mortality in patients with PHB undergoing emergency TIPS, whose long-term follow-up is greatly influenced by the stage of liver disease and its complications and therefore by CPS. Bureau’s criteria have a potentially good prognostic value for one-year survival in patients with Child Pugh A and B. Severity of clinical condition at the time of TIPS placement and the need of intensive care support, greatly influence patients’ outcome. The combined use of prognostic scores applied in critically ill patients and MELD score should be considered in the attempt to stratify this high-risk population and to identify which ones may benefit from an emergency TIPS. Furthermore, according to previously reported data[3], our results show that emergency TIPS placement for acute PHB should be avoided in patients with severely decompensated liver disease (CPS 14-15), in view of the universal short-term mortality of this group despite intensive care management and early TIPS placement.

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Table 1. Baseline demographic, clinical and biochemical characteristics of the study population.

Age (years)*	51±10.7
Male sex, n (%)	95 (66)
Aetiology (Viral/Alcohol/NAFLD/AIH-crypto), %	13.9/57.6/9.7/18.8
TIPS indication (oesophageal bleeding/others), n (%)	128/16 (88.8/11.2)
Encephalopathy (absent/mild/moderate/severe), %	54.3/27.6/17.2/0.9
Ascites (absent/moderate/tense), %	23.6/30.7/45.7
Child-Pugh class (A/B/C) n (%)	11 (8)/55 (38)/78 (54)
CPS*	10±2.4
MELD score*	18.5±8.3
Pre-TIPS-HVPG (mmHg)**	21 (7-48)
Post-TIPS-HVPG (mmHg)**	11 (1-33)
ITUs before TIPS (yes/no), %	53.1/46.9
MV (yes/no)	46/54
RBCs before TIPS (units)*	3.5 (0-15)
Time from admission to TIPS (days)**	2 (0-77)
Uncovered/PTFE TIPS, n (%)	80 (55.6)/64 (44.4)
Re-bleeding n (%)	42 (29)
OLT, n (%)	17 (11.8)
Bilirubin (mg/dl)**	2.8 (0.3-32.7)
Creatinine (mg/dl)*	1.1±0.7
INR*	1.9±0.7
Albumin (g/dl)*	3.1±0.8
Na (mmol/L)*	138.5±5.8
PLTs (n/mmc)*	102.7±6

Hb (g/dl)*	9.2±2.1
WBC (n/mmc)**	7.5 (1.3-26.8)
Bureau's criteria§ (yes/no), %	54/90 (37.5/62.5)

** Values expressed as mean ± standard deviation; **values expressed as median (minimun-maximum)*

§ *Platelet count above 75x10^9/L and bilirubin level lower than 3 mg/dl.*

NAFLD, non-alcoholic fatty liver disease; AIH, autoimmune hepatitis; TIPS, transjugular intrahepatic porto-systemic shunt; CPS, Child-Pugh score; MELD, model for end stage liver disease; HVPG, hepatic venous pressure gradient; ITUs, length of intensive care unit stay; MV, mechanical ventilation; RBCs, number of blood units transfused; OLT, orthotopic liver transplant; INR international normalized ratio; Na, sodium; PLTs, platelets; Hb, haemoglobin; WBCs, white blood cells.

Table 2. Univariate analysis for predictors of mortality at 6 weeks and 12 months.

Variable	**6 weeks**		**12 months**	
	OR (95%CI)	**p**	**OR (95%CI)**	**p**
Gender (male)		ns		ns

Age		ns		ns
Albumin		ns		ns
Bilirubin	**1.090(1.030-1.154)**	**0.003**	**1.106 (1.039-1.177)**	**0.002**
Creatinine	**2.187 (1.149-4.164)**	**0.017**	**1.814 (1.100-1.300)**	**0.049**
Na		ns		ns
INR	**2.566 (1.460-4.508)**	**0.001**	**2,168 (1.257-3.738)**	**0.005**
Hb		ns		ns
PLTs	**0.992 (0.986-0.999)**	**0.029**	**0.994 (0.988-0.999)**	**0.048**
WBCs		ns		ns
Ascites	**3.066 (1.480-6.350)**	**0.003**	**3.926 (1.922-8.018)**	**0.0001**
HE	**2.280 (1.385-3.754)**	**0.001**	**4.375 (1.947-9.829)**	**0.0001**
CPS	**1.424 (1.208-1.679)**	**0.0001**	**1.498 (1.266-1.773)**	**0.0001**
MELD	**1.101 (1.048-1.155)**	**0.0001**	**1.096 (1.044-1.150)**	**0.006**
MELD-Na		ns		ns
Pre-TIPS HVPG		ns		ns
Post-TIPS HVPG		ns		ns
MV	**2.861 (1.417-5.776)**	**0.003**	**3.427 (1.715-6.846)**	**0.0001**
RBCs		ns		ns
Pre-TIPS ITUs	**3.841 (1.871-7.885)**	**0.0001**	**4.125 (2.011-8.417)**	**0.0001**
Uncovered vs. PTFE stent		ns		ns
Time to TIPS-procedure >72h		ns		ns
Re-bleeding	**2.333 (1.125-4.839)**	**0.023**		ns
Bureau's criteria	**0.415 (0.196-0.878)**	**0.021**	**0.368 (0.178-0.759)**	**0.007**

Na, sodium; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, haemoglobin; PLTs, platelets; WBCs white blood cells; HE, hepatic hencephalopathy; CPS, Child-Pugh score; MELD, model for end stage liver disease; TIPS, transjugular intrahepatic porto-systemic shunt; HVPG, hepatic venous pressure gradient; MV, mechanical ventilation; RBCs, number of blood units transfused; ITUs, length of intensive care unit stay before TIPS; PTFE, polytetrafluoroethylene.

Table 3. Multivariate logistic regression models to individualize predictive factors for mortality at 6 weeks.

Variable	OR (95%CI)	p
MODEL 1		
MELD	**1.068 (1.001-1.140)**	**0.046**

Uncovered vs. PTFE stent	0.688 (0.304-1.556)	ns
Re-bleeding	**2.344 (1,013-5.427)**	**0.047**
Pre-TIPS ITUs	**3.138 (1.082-9.098)**	**0.035**
Time to TIPS procedure >72h	1.034 (0.462-2.315)	ns
MV	1.066 (0.364-3.117)	ns
CPS	1.164 (0.923-1.468)	ns
Bureau's criteria	1.082 (0.407-2.872)	ns
MODEL 2		
MELD	**1.085 (1.026-1.147)**	**0.004**
Uncovered vs. PTFE stent	0.942 (0.394-2.254)	ns
Re-bleeding	2.124 (0.863-5.227)	ns
Pre-TIPS ITUs	**3.298 (1.082-10.050)**	**0.036**
Time to TIPS procedure >72h	1.038 (0.441-2.447)	ns
MV	1.176 (0.382-3.618)	ns
HE	0.466 (0.182-1.193)	ns
Ascites	0.437 (0.174-1.095)	ns
Bureau's criteria	0.891 (0.328-2.421)	ns
MODEL 3		
CPS	**1.259 (1.031-1.539)**	**0.024**
Uncovered vs. PTFE stent	0.698 (0.306-1.593)	ns
Re-bleeding	**2.415 (1.037-5.623)**	**0.041**
Pre-TIPS ITUs	**3.594 (1.196-10.801)**	**0.023**
Time to TIPS procedure >72h	0.968 (0.433-2.166)	ns

MV	1.150 (0.386-3.429)	ns
Creatinine	**2.156 (1,068-4.350)**	**0.032**
Bureau's criteria	1.381 (0.524-3.643)	ns

OR= Odds ratio; 95%CI= 95% Confidence Interval;

Multivariate analysis included only variables significant at a level<0.05 at univariate analysis.

TIPS, transjugular intrahepatic porto-systemic shunt; PTFE, polytetrafluoroethylene; HVPG, hepatic venous pressure gradient; ITUs, length of intensive care unit stay before TIPS; MV, mechanical ventilation; CPS, Child-Pugh score; HE, hepatic hencephalopathy; MELD, model for end stage liver disease.

Table 4. Multivariate logistic regression models to individualize predictive factors for mortality at 12 months.

Variable	OR (95%CI)	p
MODEL 1		

MELD	1.022 (0.958-1.089)	ns
Uncovered vs. PTFE stent	0.858 (0.396-1.861)	ns
Pre-TIPS ITUs	**4.927 (1.125-21.584)**	**0.034**
Time to TIPS procedure >72h	1.228 (0.561-2.690)	ns
MV	0.644 (0.149-2.790)	ns
CPS	**1.381 (1.096-1.740)**	**0.006**
Bureau’s criteria	0.908 (0.367-2.246)	ns
MODEL 2		
MELD	**1.058 (1.000-1.119)**	**0.049**
Uncovered vs. PTFE stent	1.270 (0.551-2.928)	ns
Pre-TIPS ITUs	**5.630 (1.245-25.462)**	**0.025**
Time to TIPS procedure >72h	1.145 (0.501-2.619)	ns
MV	0.581 (0.133-2.540)	ns
HE	**2.613 (1.026-6.658)**	**0.044**
Ascites	**3.537 (1.436-8.712)**	**0.006**
Bureau’s criteria	0.869 (0.340-2.223)	ns
MODEL 3		
CPS	**1.410 (1.155-1.721)**	**0.001**
Uncovered vs. PTFE stent	0.859 (0.395-1.867)	ns
Pre-TIPS ITUs	**5.116 (1.179-22.207)**	**0.029**
Time to TIPS procedure >72h	1.244 (0.570-2.716)	ns
MV	0.634 (0.148-2.708)	ns
Creatinine	1.355 (0.687-2.672)	ns

Bureau's criteria	0.839 (0.345-2.042)	ns

OR= Odds ratio; 95%CI= 95% Confidence Interval;

Multivariate analysis included only variables significant at a level<0.05 at univariate analysis.

TIPS, transjugular intrahepatic porto-systemic shunt; HVPG, hepatic venous pressure gradient; MV, mechanical ventilation; ITUs, length of intensive care unit stay before TIPS; PTFE, polytetrafluoroethylene; CPS, Child-Pugh score; HE, hepatic hencephalopathy; MELD, model for end stage liver disease.

Figure 1. Kaplan-Meier curve: mortality according to CPS (CP1 vs. CP2).

Footnotes: CP1, Child-Pugh score 5-9; CP2 Child-Pugh score 10-15.

Figure 2A. Kaplan Meyer curve: 12 months mortality according to Bureau's criteria.

Figure 2B. Kaplan Meyer curve: 12 months mortality according to Bureau's criteria stratified for CP1.

Figure 2C. Kaplan Meyer curve: 12 months mortality according to Bureau's criteria stratified for CP2.