# The outcome after Transjugular Intrahepatic Portosystemic Shunt (TIPS) for hepatic hydrothorax is closely related to liver dysfunction : a long-term study in 28 patients

Jean-Yves Wilputte[1], Pierre Goffette[2], Francis Zech[3], Armando Godoy-Gepert[1], André Geubel[1]

Departments of (1) Gastroenterology, (2) Radiology and (3) Internal Medicine, Saint-Luc university Hospital, Université Catholique de Louvain, Brussels, Belgium.

## Abstract

***Objectives :*** **Hepatic hydrothorax is a rare but challenging complication of cirrhosis. The Transjugular Intrahepatic Portosystemic Shunt (TIPS) appears as one of the most successful approach of therapy.**

***Methods :*** **To assess long-term efficacy and safety, we reviewed 28 patients (Child B/C : 43/57%) who underwent TIPS placement for refractory hepatic hydrothorax in our institution between 1992 and 2001.**

***Results :*** **The 30-days mortality was 14%, reaching 25% at 90 days. The one-year survival without liver transplantation was 41.2%. Reduction in the volume of pleural effusion and improvement in clinical symptoms was observed in 68% while a complete radiological and echographic disappearance of hydrothorax was documented in 57%. Statistical analysis showed that poor liver function was predictive of mortality and non-response. Of the different liver function parameters and in this small series, the Child-Pugh score was more discriminating than the recently described Mayo risk score.**

***Conclusion :*** **This study shows that TIPS is effective in the treatment of hepatic hydrothorax for selected patients. Poor liver function is a strong predictive of bad outcome.** (Acta gastroenterol. belg., **2007**, 70, **6-10**).

**Key words** : cirrhosis, hepatic hydrothorax, Transjugular Intrahepatic Portosystemic Shunt, Child-Pugh score, liver function.

## Introduction

Hepatic hydrothorax is defined as the accumulation of ascitic fluid in the pleural space without cardiac or pulmonary disease. In cirrhosis, its prevalence is about 5% (0.4% to 12%) (1-3). Pleural effusion is usually right sided (85%) and accompanied with ascites (95%). Its pathophysiology remains unclear, the most widely accepted mechanism being the migration of ascitic fluid from the peritoneal cavity into the pleural space, through diaphragmatic defects (4,5). The negative pressure in the pleural space works as a ''one-way'' valve, explaining in some cases the absence of ascites (6,7).

Medical therapy (diuretics and sodium restriction) is ineffective in the majority of cases. Other therapeutic approaches proposed for refractory hepatic hydrothorax include pleurodesis, surgical repair of the diaphragmatic leak by videothoracoscopy and peritoneovenous shunts. Nevertheless, they have never been largely used due to the fact that they are not aiming at reducing ascites formation and that they are associated with various infectious, thrombotic and/or mechanical complications (8,9).

The Transjugular Intrahepatic Portosystemic Shunt (TIPS) has been advocated as the treatment of choice for patients with refractory hepatic hydrothorax, this therapy allowing a reduction in sinusoidal pressure, the main cause of fluid accumulation in cirrhosis (6,10-12). Published data from small series indicate a relatively high rate of early mortality due to liver failure (about 25%) as well as of non-response (26 to 42%) (13-18). Older age (more than 60 or 65 years) has been suspected as predictor of non-response or early mortality (14,16).

To assess the long term results of TIPS in the treatment of hepatic hydrothorax and to further evaluate predictors of early mortality and/or non response, we reviewed our experience in 28 cases treated between 1992 and 2001 and followed during a mean period of 358 days.

## Patients and methods

Between 1992 and 2001, twenty-eight consecutive patients presenting with hepatic hydrothorax refractory to medical therapy underwent TIPS placement in our institution. Their medical records (clinical, laboratory and radiological) were reviewed. Baseline characteristics of these patients are shown in table 1. All patients had pleural effusion not responding to medical management which included sodium and fluid restriction together with maximum tolerated doses of spironolactone and furosemide.

Out of 22 patients, nineteen (68%) underwent TIPS placement for an intractable hepatic hydrothorax as the primary indication, 3 being excluded on the basis of the presence of encephalopathy grade III (following the EEG Child scoring system) . In the 9 remaining patients, refractory ascites (8 cases) or occult gastrointestinal bleeding due to portal hypertension (one case) was the primary indication for TIPS placement. No patient had

Corresponding author : André Geubel, Department of Gastroenterology, Saint-Luc university Hospital, Université Catholique de Louvain, av. Hippocrate, 10, B-1200 Brussels, Belgium. E-mail : geubel@gaen.ucl.ac.be.

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Table 1. — **Baseline characteristics of the patients**

| | |
|---|---|
| Age | 53.6 years (range 38-77) |
| Gender | 15 males, 13 females |
| Causes of cirrhosis | |
| Alcohol | 15 (53.6%) |
| Viral (HBV and HCV) | 8 (28.6%) |
| Mixed (alcohol and viral) | 3 (10.7%) |
| Cryptogenic | 2 (7.1%) |
| Child-Pugh | |
| Class B | 12 (43%) |
| Class C | 16 (57%) |
| Score | 9.7 (+/- 0.3) |
| Number of patient having previous | |
| Chest tube | 8 |
| Pleurodesis | 3 |
| Location of pleural effusion | |
| Right | 26 (93%) |
| Left | 2 |
| Gastro-oesophageal varices | 23 (82%) |
| Aminopyrine breath-test (N ≥ 2.8%) | 0.56% (+/- 0.13) |
| Mayo Risk score | 1.15 (+/- 0.11) |
| S. creatinine (N : 0.6 – 1.4 mg/dl) | 1.27 mg/dl (+/- 0.16) |
| INR (N : 0.9 – 1.3) | 1.50 (+/-0.07) |
| S. total bilirubin (N : 0.3 – 1.2 mg/dl) | 3.39 mg/dl (+/- 0.66) |
| S. albumin (N : 3.5 – 5.2 mg/dl) | 2.84 g/dl (+/- 0.11) |

hepatocellular carcinoma, acute alcoholic hepatitis or significant cardio-pulmonary disease. Infectious cause of hydrothorax was ruled out by fluid analysis in all instances. Child-Pugh scoring was performed using the routine clinical method, 3 points being invariably given for ascitis. Only one patient had end-stage kidney failure due to hepato-renal syndrome and required haemodialysis.

TIPS placement was performed as described previously mainly using the PALMAZ balloon-expandable prosthesis (P 308E or PS 784, CORDIS, Johnson& Johnson company, Miami, Florida USA). For the more recent procedures, a GORE VIATORR TIPS endoprosthesis (W.L. GORE & ASSOCIATES, INC, Flagstaff, Arizona USA) or an OPTIMED nitinol SINUS-STENT TIPS (40° curved, Optimed Medizinische Instrumente GmbH, Ettlingen, Germany) were used (19). The procedure was done under sedation or general anaesthesia with short term (3 days) prophylactic selective digestive decontamination. The sinusoidal pressure gradient was measured before and after the procedure. It falls from 17.38 mm Hg (+/- 0.67) to 7.08 mm Hg (+/- 0.53). TIPS patency was assessed by Doppler ultrasound after 24 hours, 1, 2, 3, 6, 9, 12 months, and every 6 months thereafter, whenever possible. Indications for stent revision included stenosis, obstruction or relapsing hydrothorax.

The average duration of follow-up was 358 (+/- 121) days (median : 121 days, range : 12 hours to 104 months).

## Data evaluation and Statistics

Results are expressed as mean +/- SEM or with a 95% confidence interval. We used the Mann Whitney's rank test for the comparisons of variables between groups. Confidence interval for the percentage and comparisons of the percentage were exacts. The odds ratio percentages were expressed with a confidence interval according to Cornfield approximation. Survival was expressed according to Kaplan-Meier, confidence interval calculated according to Kalbfleish and Prentice. Patients who underwent liver transplantation were censored at the date of surgery since their survival was no longer dependent of TIPS placement. For comparison of mortality between groups we assumed a proportional-hazards model, and used a logrank test, calculating the odds ratios according to the conditional likelihood method. All the tests were two-sided and differences were considered significant for $P < 0.05$.

We assessed multiple clinical and biochemical variables ; the choice of these variables being based on the consistency of results across previous prognostic series, including the recent liver function parameter named "Mayo score" described by Malinchoc *et al.* (20). We preferred using this primarily described score instead of the more commonly used MELD (21) score (which is the Mayo score multiplied by 10 and rounded to the nearest integer) because the Mayo score was "historically" developed on a TIPS survival model.

## Results

*Survival - Mortality*

Overall survival is showed in fig. 1. During follow-up, 17 patients died after a mean period of 173 days (median 101 days), related to complications of liver disease. The early mortality occurring in 4 patients within 30 days after the procedure – leading to a rate of 14.3% (95% confidence interval : 5.6-33.7%) – was due to gastric ulcer intractable bleeding, hepatic bleeding, sepsis or acute renal failure and pulmonary oedema. Two months later, 3 others patients died of sepsis (1 case) or liver failure (2 cases), leading to a 90-days mortality rate of 25% (12.8-45.4%). The 150 days mortality rate reached 53% (35,5%-72,7%). Six patients underwent orthotopic liver transplantation after a mean period of 222 days (median 234 days). Of the remainders, 4 patients were still alive after a mean period of 47 months and one was lost to follow-up after 70 days.

Age was not predictor of mortality but a Child score higher than 10 was a strong predictor of mortality : odds ratio at 7,62 (confidence interval : 2,34-24,83 ; $p < 0,001$). A graph showing the difference in survival between patients having a Child score higher or lower than 10 is showed in fig. 2. A Mayo score higher than 1.5 was also associated with a significant increase in mortality : odds ratio at 3,53 (1,25-9,98 ; $p < 0,02$). These odds ratio were independent during time.

Another liver function parameter, the aminopyrine breath-test available for 18 patients did not shown any significant predictive value. Other biomedical variables, including age, gender, serum creatinine, natremia, total

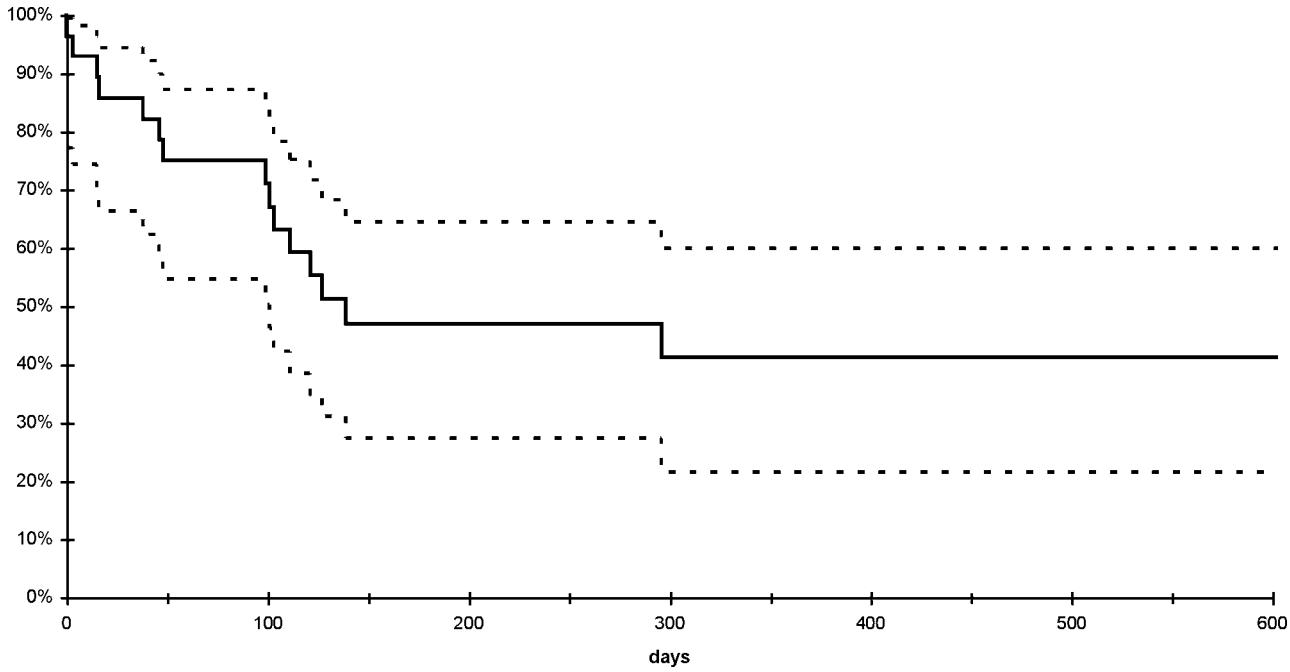


Fig. 1. — Kaplan-Meier survival
With 95% confidence interval

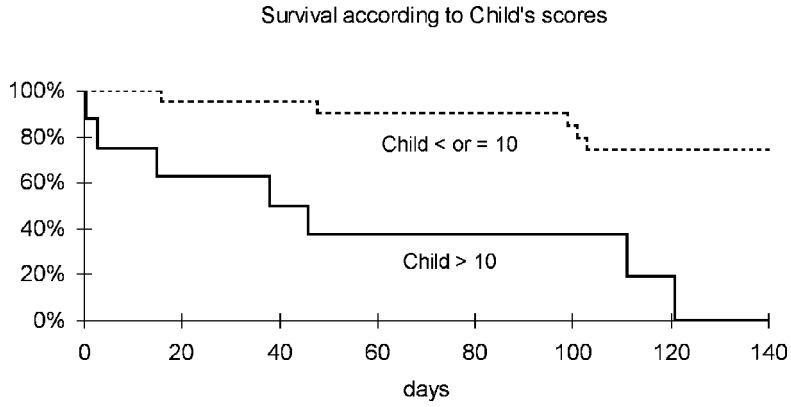


Fig. 2. — Survival for patients with Child score higher or lower than 10

serum bilirubin, INR, amino-transferase, serum albumin, aetiology of cirrhosis, pre-TIPS portal pressure, post-TIPS portal pressure, pre-TIPS encephalopathy, type of stent placed, previous peritoneal or pleural infection, previous pleurodesis or chest tube were not predictive of mortality.

*Efficacy - Response*

A complete efficacy of TIPS defined by the absence of pleural and peritoneal effusion confirmed at chest X-ray and abdominal ultrasound, was observed in 57% (16 patients out of 28 ; confidence interval : 37,2-75,5%), after a mean period of 4 (+/- 0.4) months (median 3 months). Three other patients had a partial response (reduction of the volume of pleural effusion and clinical improvement), leading to a clinical response rate of 68%. All the patients surviving longer than 7 months had a successful procedure. The TIPS placement was effective in 15 out 20 patients who had a Child score lower than 10 and in 1 out 8 patients who had a Child score higher than 10 (Odds ratio at 21,0 ; confidence interval 2,5-158,5 ; $p < 0,01$). The procedure was effective in 14 out 19 patients with a Mayo score lower than 1.5 and in 2 out 9 patients with a Mayo score higher than 1.5 (Odds ratio at 9,8 ; confidence interval : 1,6-56,2 ; $p < 0,05$).

*Reduction – Dilatation*

On the overall and during the follow-up period, 6 patients of the "clinical efficacy group" needed one or more revision of the TIPS within a mean period of 5.3 (+/- 1.8) months after its placement (range : 1 day to 16 months), indicating the occurrence of TIPS dysfunction in 33% of patients. There was no predictive factor for TIPS dysfunction. Early (30 days) TIPS dysfunction was correlated to a primary non-response. Delayed (2.5 to 16 months) stenosis was associated with the relapse of pleural effusion which resolved within 3 months after TIPS revision. Two patients underwent a TIPS reduction due to intractable hepatic encephalopathy. They both died of liver failure in the following months after the procedure.

## Discussion

Hepatic hydrothorax is an infrequent complication of liver cirrhosis which is refractory to well conducted medical therapy in the majority of cases (3-5). TIPS placement has been proposed for this refractory hydrothorax and published data under the form of case–reports or small series favour its use (6,10-18). Our data show that an overall 68% success rate can be achieved in such a setting. We have also showed that in our group of patients, the early (30 days) mortality was 14%, reaching 59% after 1 year, this being mainly due to complications of cirrhosis. Analysis of efficacy showed that TIPS revision was needed in 6 instances, leading to TIPS patency of 67%.

In our study, we found that the best predictive parameter for mortality and non-response was liver dysfunction, as evaluated under the form of computed scores. The Child-Pugh score seemed the best predictive parameter, all patients dying within 3 months being Child C.

Of the four other series which analysed results of TIPS placement for refractory hydrothorax (13-16), only one had a longer follow-up (16 months) and included more patients (40 patients) than ours (16). The other studies had shorter follow-up (173 to 223 days) and included less patients (12 to 24 patients). Comparing our data with those of these studies, we found a good correlation between TIPS efficacy and longer survival (15,16). Nevertheless, our data disagree with those showing that early mortality and non-response were associated with older age (more than 60 or 65 years) but not with the degree of pre-TIPS liver dysfunction, as assessed by Child score (14,16). As expected from our own results, series in which more patients in Child B class than Child C were included showed better survival as in the larger trial in which 40% patients were in Child C and in which the 3-months mortality was only 15% (16). On the contrary, in another series in which 79% patients were Child C, the early (45 days) mortality was 21% (13). Furthermore, in two studies in which 50% and 67% patients were in Child C, the 30-days mortality reached 25% and 29%, respectively (14,15).

The response rate observed in our series (overall efficacy of 57% and clinical response of 68%) was similar to that of the other studies (complete response of about 58%) (13-17). Nevertheless, we must keep in mind that our criteria of overall efficacy included a complete radiological (chest X-ray and abdominal ultrasound) resolution of both pleural and peritoneal effusion. This likely explains why the delay for complete response (mean 4 months, median 3 months) was longer than in other studies in which criteria of response only included the relief of respiratory symptoms with a reduction in pleural fluid (13), no more requirement for therapeutic thoracentesis (14) or clinical response (15). When a complete radiological response was considered, only 30% of patients reached this goal in one series (15), better liver function being associated with a better complete (71%) response rate (16).

Comparing published predictive parameters obtained in studies in which TIPS was indicated mainly for refractory ascites (22,23) or relapsing variceal bleeding (20,24-29) to our data, we observed that different parameters reflecting liver function (such as Child score, Mayo score or total serum bilirubin) were reliable predictive factors for survival or efficacy.

In conclusion, TIPS is an effective therapeutic approach for the treatment of refractory hepatic hydrothorax. Outcome is closely related to the degree of liver dysfunction and using this therapy in patients with severely impaired liver function, i.e. a Child score higher than 10, is associated with a high early mortality rate and should be considered as a contraindication to the procedure.

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