Covered stents are better than uncovered stents for transjugular intrahepatic portosystemic shunts in cirrhotic patients with refractory ascites : a retrospective cohort study

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Abstract

***Background and study aims* : Transjugular intrahepatic portosystemic shunt (TIPS) is an accepted interventional technique to treat refractory ascites in cirrhotic patients with severe portal hypertension. The expanded-polytetrafluoroethylene (e-PTFE) covered stent-graft (cs-TIPS) gives a better shunt patency rate than uncovered stents (ncs-TIPS). Our aim was to retrospectively evaluate whether cs-TIPS indeed improves refractory ascites and overall survival in a more effective way than ncs-TIPS in patients with cirrhosis.**

***Patients and methods* : From 1992 to 2006, 222 cirrhotic patients with refractory ascites underwent a TIPS-procedure. In 126 patients a ncs-TIPS was inserted, in the remaining 96 patients a csTIPS was inserted. Liver transplantation and/or death were the end points of the follow-up.**

***Results* : The baseline characteristics of both groups were similar : age (55 ± 11 years, ncs-TIPS/56 ± 10 years, cs-TIPS), alcoholic cirrhosis (73% ncs-TIPS/80% cs-TIPS), Child-Pugh (9 ± 2.0 ncs-TIPS/9.2 ± 1.3 cs-TIPS) and MELD (15 ± 6 ncs-TIPS/15 ± 4.9 cs-TIPS), except that the bilirubin level was higher in the cs-TIPS group (2.5 ± 2.7 mg/dL in cs-TIPS vs. 1.5 ± 3.6 mg/dL in ncs-TIPS). One year shunt dysfunction occurred in 49% (n=63) of the ncs-TIPS vs. 19% (n = 18) of the cs-TIPS (P < 0.0001) and post TIPS encephalopathy in 56% (n = 70) of the ncs-TIPS vs. 22% (n = 22) in the cs-TIPS group. Ascites control and overall survival were better in the cs-TIPS (P = 0.0071). The gain in survival in the cs-TIPS patients occurred especially in patients with a baseline MELD score <16 (P < 0.0001). Post TIPS encephalopathy and ncs-TIPS were independently related with poor survival (P < 0.0001, P = 0.0150 ; respectively).**

***Conclusions* : In cirrhotic patients with refractory ascites cs-TIPS offers better symptomatic control of the ascites at one year follow-up and a better overall survival, especially in patients with a MELD score of <16 at baseline.** (Acta gastroenterol. belg., **2010,** 73, **336-341).**

Key words : refractory ascites, TIPS, covered stent, hepatic encephalopathy

Introduction

Portal hypertension is the main complication of cirrhosis and its most common clinical presentation is ascites. Five to 10% of the patients with ascites will finally develop refractory ascites. Refractory ascites is defined by the International Ascites Club as ascites that cannot be mobilized by medical therapy or that recurs early after initial mobilization despite continued treatment (1,2). Several studies have demonstrated that transjugular intrahepatic portosystemic shunt (TIPS) can resolve this condition with an even better outcome than conservative treatment based on regular paracenteses associated with albumin infusion therapy (3,4). However, TIPS can lead to deterioration of liver function and/or hepatic encephalopathy (1,2,5-9). In 2000, Mayo TIPS statistical model was designed in order to identify those patients with early liver-related mortality post-TIPS ; patients with a MELD (model for end-stage liver disease) score >18 had only a median survival of 3 months (6).

The first generation of TIPS stents were non-covered vascular stents (ncs-TIPS). The main drawback of these stents were a major dysfunction rate at one year in up to 50% of cases (6). Long-term shunt patency is only obtained with strict and regular monitoring and there is a need for a regular re-intervention (5,6,10,11), consisting mainly in repeat angioplasty and restenting of the shunt.

Although several randomized controlled trials could not clearly demonstrate better survival in patients treated with ncs-TIPS versus patients treated with regular paracentesis and albumin infusion (6,7,12), Salerno *et al.* (13) could demonstrate, in a meta-analysis, a better clinical outcome after TIPS compared to conservative treatment, based on paracentesis and albumin infusion. Finally, in all these randomized controlled trials, only bare metal stents were used to reline the shunt tract.

Currently, a better long-term patency rate of TIPS can be obtained with the use of expanded-polytetrafluoroethylene (e-PTFE) covered stent-grafts (cs-TIPS) (6,13). However, cs-TIPS might increase hepatic encephalopathy and the need of TIPS reduction. Recently, it has been reported that cs-TIPS decreases the number of clinical relapses without increasing the risk of encephalopathy. This study consisted predominantly of cirrhotic patients with variceal bleeding (10,14). There are today no convincing evidences that cs-TIPS might

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improve survival in cirrhotic patients with refractory ascites (6,7,12,13,15) as the main symptom of portal hypertension.

In this retrospective study we assessed in a well defined group of cirrhotic patients with refractory ascites the one-year clinical outcome with special attention to ascites control and overall survival after TIPS placement in the ncs-TIPS patient subgroup versus the cs-TIPS patient subgroup.

Materials and methods

Patients

Patients with cirrhosis and refractory ascites who received TIPS were included in the study. Two types of TIPS stents were used : from October 1992 until July 2000 a non-covered vascular stent (ncs-TIPS) was inserted in 126 patients and an e-PTFE covered stent (cs-TIPS) was inserted in 96 patients from July 2000 until June 2006. Refractory ascites was defined as ascites that could not be mobilized by medical treatment or that recurred early after initial mobilization despite continued treatment mainly consisting in regular paracentesis and administration of diuretics. Overall, the medical management of cirrhotic patients with refractory ascites did not change significantly over the study period (1992-2006), including administration of 100-200 mg spironolactone/day or a combination of spironolactone 100-200 mg/day with furosemide 40-80 mg every two days No beta-blockers were associated in patients with portal hypertension-related refractory ascites.

In all patients, the pre-TIPS MELD score (16) was calculated and patients were categorized in 2 subgroups : MELD score < 16 and MELD score > 16. A cut-off of 16 points was assessed based on an analysis by Montgomery *et al*. (17) demonstrating that a mean MELD score before TIPS was 14.0 (± 4.2) in the survivor group and 19.4 (± 5.9) in the group with early death after TIPS.

Patients with portal vein trombosis, hepatocellular carcinoma, grade 3 or 4 of encephalopathy and/or a Child-Pugh $\geq$ 12 were excluded from TIPS placement. In patients who were candidates for a liver transplantation, TIPS placement was considered as a bridge to transplantation.

Methodology and follow-up of TIPS placement

General anesthesia was usually performed. After puncturing the right internal jugular vein, a 10 French, 41-cm long sheath was placed in the suprahepatic portion of the inferior caval vein.

After catheterisation of the right hepatic vein, a wedged hepatic venogram, using iodine or CO_2 as a contrast agent, was then performed to guide the portal puncture (Rösch-Uchida Transjugular Liver Access Set, William Cook Europe, Bjaeverskov, Denmark). With the use of a hydrophilic guidewire, the portal vein was catheterized. The portosystemic pressure gradient was measured and the intrahepatic parenchymal tract dilated over an 0.035 inch Amplatz® superstiff guidewire (Cook Medical, Bjaeverskov, Denmark). A calibrated 5-French pigtail catheter was used to measure accurately the length of the parenchymal tract up to the inferior caval vein. Finally, a non-covered or covered stent (Viatorrr, W.L. Gore and Associates, Flagstaff, AZ, USA) (18,19) is placed to keep open the shunt tract.

Radiological follow-up consisted of duplex ultrasound 3 days, and 1, 3, 6, 12, 24 and 36 months after TIPS. Doppler criteria for TIPS dysfunction are : 1) shunt velocity measurements of less than 60 cm/s along the whole length of the stent-graft ; 2) change in peak velocity measurements in the shunt of more than 50 cm/s in comparison with the baseline values ; 3) change in flow velocity over a small segment in the shunt ; 4) no more flow detected. Invasive venography and pressure measurements were performed only when the ultrasound was inconclusive or abnormal.

Follow-up and outcome

The date of the TIPS procedure was the starting point, liver transplantation and death were considered as the endpoint of the follow-up. Additionally, rate of shunt dysfunction (angiographic and/or associated with clinical relapse) within one year, occurrence of post TIPS encephalopathy grade 3 or 4 within one year and overall survival were analyzed. Shunt dysfunction was defined as a >50% reduction of the lumen of the shunt at angiography and/or a portosystemic pressure gradient >12 mmHg. TIPS and/or insertion of a new stent were performed in this situation.

Hepatic encephalopathy was defined as a new onset or worsening of pre-existing neuropsychiatric symptoms after TIPS-creation. These neuropsychiatric symptoms are graded according to the West Haven criteria (20). Only grade 3 and 4-symptoms are considered as debilitating symptoms requiring additional medical and/or interventional treatment.

Clinical relapse is defined as reoccurrence of massive ascites, refractory to medical treatment after TIPS-creation.

In case of grade 3 and 4 hepatic encephalopathy, refractory to medical management, a reduction stent or stent-graft was inserted. Note that reduction stents are available on the market since 1996.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation when normally distributed, if not then expressed as median, 25% and 75%. Statistical analysis performed were Chi-square test for qualitative data and T-test for quantitative data if normally distributed, if not Mann-Whitney Rank Sum Test was performed. A Kaplan-Meier curve was calculated in order to evaluate

the survival of the ncs-TIPS patients vs. the cs-TIPS patients and the Cox proportional-hazard regression allowed to identify the significantly related variables with the survival.

Multivariate regression analysis was performed to examine the relationship between independent pre- and post TIPS variables and the corresponding independent effects on survival with special attention to covered / uncovered stents and the drop in portosystemic pressure gradient as pre- and post TIPS variables.

A two-sided p value of less than 0.05 was considered to be significant. The software programme used in this study was the SAS software, version 9.2 of SAS Systems for Windows (SAS Institute, Cary, NC, USA).

Results

The baseline characteristics are given in Table 1. The total group consisted of 222 patients : 68% (n = 150) from University Hospitals Leuven and 32% (n = 72) from Erasme Hospital, Brussels. Patients predominantly were male, middle age and suffering from alcoholic cirrhosis. Around 20% were still active drinkers at the moment of TIPS placement. Nineteen patients (8%) had an associated hydrothorax. The mean Child-Pugh and MELD scores were respectively 9 and 15.

Two patients were lost to follow-up after 2 months and 4 months in the ncs-TIPS group and were excluded for the analysis. There was no statistically significant difference in parameters between patients who received a ncs-TIPS and a cs-TIPS, except that in the ncs-TIPS group more patients were still active drinking and in the cs-TIPS group there were more male patients and the bilirubin was higher.

TIPS placement was possible in all patients with an early mortality (first week post TIPS) of 3% (n = 4) of the ncs-TIPS vs. 5% (n = 5) in the cs-TIPS (p = 0.67). One patient who received a ncs-TIPS developed a haemoperitoneum and one patient had a subcapsular hematoma after placement of a cs-TIPS.

The mean portosystemic pressure gradient (PSPG) before shunt creation was 17 ± 5 mmHg in the ncs-TIPS patients vs. 20.3 ± 11.1 mmHg in the cs-TIPS (p = 0.0031) (Table 1). In all cases, direct portography after TIPS placement showed a fully patent shunt without evidence of focal shunt stenosis. The portosystemic gradient after TIPS was 8 ± 3 mmHg in the ncs TIPS patients vs. 6.3 ± 2.8 mmHg in the cs-TIPS patients (p<0.0001). No anticoagulation therapy was administered during or after the procedure. Ischemic hepatitis, defined as a flare-up of ALT > 5 baseline value with a concomitant increase of bilirubin, occurred in 6% (n = 8) of the ncs-TIPS patients vs. 3% (n = 3) of the cs-TIPS patients (p = 0.36).

In case of clinical response after TIPS (no more need for regular paracenteses), no more diuretics were prescribed ; in case of persistent refractory ascites after

Table 1. — **Characteristics of the 222 patients who received a transjugular intrahepatic porto-systemic shunt (TIPS) procedure for refractory ascites**

	Non-covered stent TIPS n = 126		**Covered stent TIPS n = 96**		**P-value**
	n	**%**	**n**	**%**	
Age (yrs)	55 ± 11 (38-78)		56 ± 10 (37-81)		0.360
Male Gender	76	59	70	73	**0.0469**
Cause of cirrhosis					
Alcoholic	*94*	*74*	*77*	*80*	*0.2683*
Viral	*16*	*13*	*7*	*7*	*0.2672*
Other	*16*	*13*	*12*	*13*	*0.873*
Active alcohol intake	32	25	12	13	**0.0265**
Haemoglobin (gr/dL)	11.2 ± 1.9		10.8 ± 1.9		0.1204
Total bilirubin (mg/dL)	1.5 ± 3.6		2.5 ± 2.7		**0.0234**
ALT (IU/L)	24 ± 25		55.7 ± 231.9		0.1260
Creatinine (mg/dL)	1.1 ± 1.3		1.2 ± 0.6		0.4849
Albumin (gr/dL)	3.2 ± 0.6		3.1 ± 5.4		0.8346
Prothrombin Time (%)	61 ± 20		65.9 ± 18.6		0.0629
INR	1.45 ± 0.36		1.4 ± 0.3		0.2711
Child-Pugh class					
B	*81*	*63*	*64*	*67*	*0.6721*
C	*47*	*37*	*32*	*33*	*0.6721*
Mean ± Std Dev	*9 ± 2.0*		*9.2 ± 1.3*		*0.3942*
MELD score	15 ± 6		15 ± 4.9		1.0000
Porto-systemic gradient (mmHg)					
Before TIPS	*17 ± 5*		*20.3 ± 11.1*		***0.0031***
After TIPS	*8 ± 3*		*6.3 ± 2.8*		***< 0.0001***

succesful TIPS-placement, the medical treatment, including the same diuretics as before TIPS-placement was continued. Clinically significant residual ascites 1 month after TIPS placement remained present in 70 patients treated with a ncs-TIPS (55.6%) and in 34 patients treated with a cs-TIPS (35.5%). The difference in ascites control within the first month after TIPS-placement is statistically significant between the two groups (p = 0.003).

Shunt dysfunction within one year

Shunt dysfunction is given in Table 2 : 49% (n = 63) of the ncs-TIPS developed shunt dysfunction which was significantly more than in 19% (n = 18) of cs-TIPS patients (p < 0.0001). Onset of dysfunction was at a median of 3.3 months (*25%, 75%* : 1.7m ; 7.6m) in the ncs-TIPS patients vs. at a median of 2 months (*25%, 75%* : 1m ; 4m) in the cs-TIPS patients (p = 0.075). First signs of TIPS dysfunction were detected by angiography in 30% (n = 38) of the ncs-TIPS patients vs. 19% (n = 18) of the cs-TIPS (p = 0.075) and clinical relapse occurred only in the ncs-TIPS patients [20% (n = 25)] (p < 0.0001). In 17% (n = 21) of the ncs-TIPS patients the occluded shunt was recanalized and relined with a bare stent with a median of 2 stents (range : 1-3) versus 7% (n = 7) with a median of 2 stents (range : 1-3) in the cs-TIPS patients (p = 0.0601) and TIPS dilatation was only necessary in the ncs-TIPS patients [33% (n = 42)] with a median of 1 TIPS dilatation (range : 1-3) (p < 0.0001).

Rate of post TIPS encephalopathy within one year

The encephalopathy grade 3 or 4 post TIPS placement (Table 2) occurred in 56% (n = 70) of the ncs-TIPS patients vs. 22% (n = 22) of the cs-TIPS patients p < 0.0001. The majority of the patients were managed medically but in the cs-TIPS group 10/22 patients (10%) needed a reduction stent (p = 0.0007).

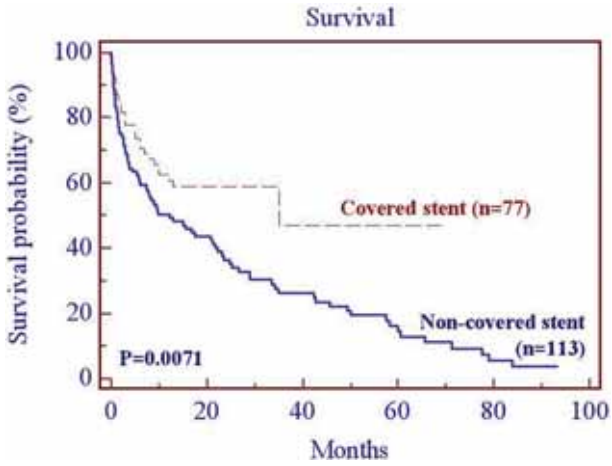

Figure 1. — Overall survival after TIPS placement for refractory ascites : covered versus non-covered stent. The overall survival is significantly better in the cs-TIPS patients (p = 0.0071)

Overall survival

End of follow-up was due to liver transplantation in 10% (n = 13) of the ncs-TIPS patients after a median of 3.7 months (*25%, 75%* : 2 m ; 10.2 m) vs. in 20% (n = 19) of the cs-TIPS patients after a median of 3 months (*25%, 75%* : 2 m ; 6 m). Fig. 1 shows the overall survival of patients excluding those who received a liver transplantation. The overall survival is significantly better in the cs-TIPS patients (p = 0.0071) : the overall survival at 6 months and 1 year is 73.2% (n = 65) - 65.5% (n = 51) and 62.8% (n = 74) – 55.0% (n = 63) for the cs-TIPS and ncs-TIPS group, respectively. The cause of death was : predominantly liver failure which occurred in 65% (56/86) of the ncs-TIPS patients after a median of 3.1 months (*25%, 75%* : 25 days ; 14.1 m) vs. 83% (25/30) of the cs-TIPS patients after a median of 3

Table 2. — **Number of patients who developed stent dysfunction and TIPS induced encephalopathy within one year**

	Non-covered TIPS		Covered TIPS		P-value
	n	%	n	%	
Overall TIPS dysfunction	63	49	18	19	< **0.0001**
Onset of dysfunction *median (25% ; 75%)*	3.3 m (1.7 m ; 7.6 m)		2 m (1 m ; 4 m)		0.075
First signs of TIPS dysfunction					
Angiographic TIPS stenosis	38	30	18	19	0.075
Clinical relapse	25	20	0	0	< **0.0001**
Intervention					
TIPS dilatation	42	33	0	0	< **0.0001**
New TIPS due to obstruction	21	17	7	7	0.0601
Encephalopathy post TIPS	70	56	22	22	< **0.0001**
Need for stent reduction	0	0	10	10	**0.0007**

months (*25%, 75%* : 27 d ; 6.3 m). Non-liver related death were : undetermined death cause in 16% (n = 20) of the ncs-TIPS patients after 24.3 months (*25%, 75%* : 9.5 m ; 38.8 m) ; high gastrointestinal bleeding in 3% (n = 4) of the ncs-TIPS patients after 2.5 months (*25%, 75%* : 1.6 m ; 4.7 m) ; heart failure in 2% (n = 2) of the cs-TIPS patients after 1.5 months ; other reasons in 2% (n = 3) of the ncs-TIPS patients after 58.2 months (*25%, 75%* : 15.5 m ; 72.6 m). Finally, malignancies in 3% (n = 4) of the ncs-TIPS patients (1 patient with hepatocellular carcinoma) after 60.5 months (*25%, 75%* : 27.9 m ; 75 m) vs. 3% (n = 3) of the cs-TIPS patients after 9 months (*25%, 75%* : 6m ; 28.5m). The hazard ratio for overall survival comparing patients with covered and uncovered stents equals 0.524 (p = 0.002, 95% CI : 0.349 ; 0.786). After correction for the difference in drop of PSPG, the hazard ratio hardly changes and remains significant : hazard ratio 0.510 (p = 0.002, 95% CI : 0.334 ; 0.780). Consequently the difference in PSPG drop does not explain the difference in overall survival between the covered and uncovered stent group. Note also that there is no evidence for a relation between portosystemic pressure gradient drop and overall survival (p = 0.63 and p = 0.65 in univariable and multivariable setting respectively).

Risk factors of death

Baseline

A poorer survival occurred in patients with Child-Pugh class C (p = 0.0042) and MELD score >16 (p < 0.0001).

After TIPS

The survival gain in favour of covered stent occurred in the group of patients with MELD score <16 (p < 0.0001) (Fig. 2). Post TIPS encephalopathy, the need for TIPS dilatation and/or insertion of a new stent and the type of stent (non-covered) were the only risk factors directly related with a poor survival (p = 0.0249, p = 0.0001 ; p = 0.0098 ; respectively). In multivariate analysis the independent factors of poor outcome were post TIPS encephalopathy and ncs-TIPS respectively (p < 0.0001 and p = 0.015).

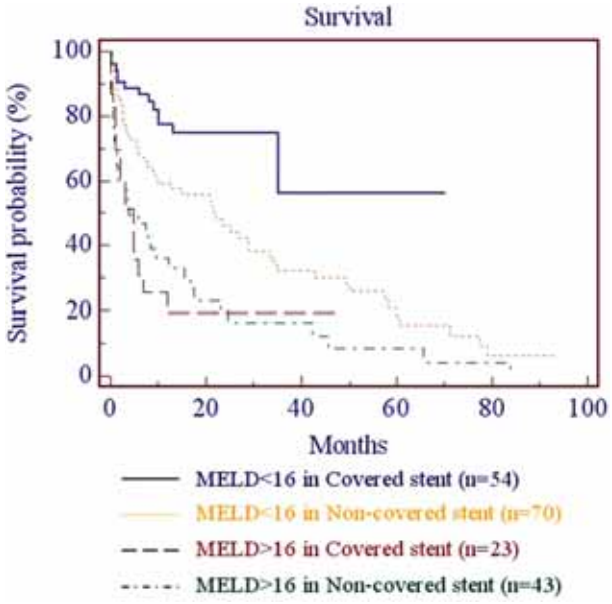

Figure 2. — Survival according Child-Pugh and MELD scores system after TIPS placement for refractory ascites. The survival gain in favour of covered stent occurred in the group of patients with MELD score <16 (p < 0.0001)

Discussion

This analysis demonstrates that cirrhotic patients suffering from refractory ascites will present less symptomatic relapses of their ascites during post-TIPS follow-up and, more importantly, will have a better survival if they are treated with a TIPS using an e-PTFE covered stent compared to an uncovered, vascular stent. These observations confirm the findings of Angermayr *et al.* (10) and Bureau *et al.* (14) : both authors demonstrated that patients treated with a TIPS using e-PTFE-covered stents will have less symptomatic relapses of portal hypertension-related symptoms and have a better survival than in case a bare, uncovered vascular stents was implanted. However, both studies included both patients with a medical history of variceal bleeding as well as refractory ascites as the main indication for performing TIPS. The presented study focused only on patients with refractory ascites as the most important symptom of portal hypertension and in this specific subgroup of cirrhotic patients e-PTFE covered stents should be used instead of bare, vascular stents, not only to obtain less symptomatic relapses, but also to obtain better survival. Avoiding relapses of ascites production and subsequently avoiding all potential complications of refractory ascites might explain why patients with an e-PTFE-covered stent have a better survival.

This study is a non-randomized, retrospective study, comparing two patient groups treated with TIPS in a different time period. However, the two study groups are quite equal, and the patient sample is large (n = 222) with a very low number of patients excluded for further evaluation because of incomplete follow-up (n = 2). The same, strict clinical and radiological follow-up protocol was used for both study groups without substantial change over time, including the medical management of cirrhotic patients with refractory ascites. No procedure-related deaths were noted in both groups and no difference in patient death was noted in the first week after TIPS-creation, although the patients treated with uncovered stents were treated in the beginning of the experience with TIPS. Finally, the cs-TIPS patient group had a better clinical outcome and overall survival, although they presented with a higher pre-TIPS portosystemic gradient and a significant higher baseline total bilirubin level, parameters which have a negative effect on survival as reported by Gerbes *et al.* (21).

The presented results also confirm that cirrhotic patients with refractory ascites, but with a poor MELD score, do worse after TIPS. If a cut-off of MELD score < 16 is taken, a significant better survival is noted. These results are in analogy with Montgomery *et al.* (17) who evaluated patients undergoing an elective TIPS-procedure mainly by inserting a bare vascular stent. In these cases, a thorough evaluation of potential advantages versus potential complications due to TIPS should be made before the portosystemic shunt is created, stressing the need for careful patient selection.

Finally, creation of durable TIPS potentially can result in effective and sustained derivation of splanchnic venous blood from the liver and subsequently in a higher systemic ammonia level and in a higher number of patients suffering from post-TIPS hepatic encephalopathy. However, this study could not demonstrate a significant increase in hepatic encephalopathy in case of sustained shunt patency owing to the implantation of a covered stent. On the contrary, a reduced risk of post-TIPS hepatic encephalopathy was observed, confirming the same observations as Bureau *et al.* (14) in a randomized trial including cirrhotic patients mainly presenting with variceal bleeding.

In conclusion, this retrospective study suggests that e-PTFE-covered stents should be used for TIPS, not only in patients presenting with refractory variceal bleeding, as previously demonstrated, but also in cirrhotic patients suffering from refractory ascites to obtain a sustained symptomatic control and better overall survival. Additionally, this survival benefit will become more important if the MELD score pre-TIPS is equal to 16 or less. Finally, use of e-PTFE-covered stents in TIPS will not result in a higher incidence post-TIPS hepatic encephalopathy.

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