Research Article
Cirrhosis and Liver Failure

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Episodic overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt does not increase mortality in patients with cirrhosis

Authors

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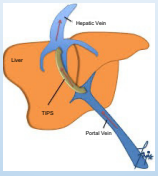
Graphical abstract

Patients and methods

614 patients submitted
to TIPS for variceal bleeding or refractory
ascites in 3 Italian centers



A multicenter non-inferiority observational
study to evaluate the mortality rate
at 30 months in patients with
and without OHE after TIPS, using competing
risk analysis

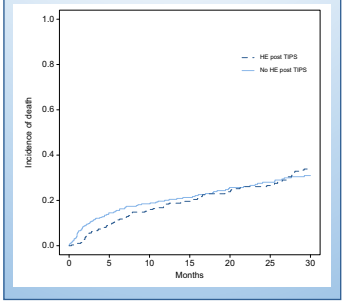
Study population

	No OHE post TIPS (n = 321)	OHE post TIPS (n = 293)	*p* value
Sex (M/F)	222/99	198/95	0.738
Age (y)	59 (50-67)	64 (57-71)	<0.001
Aetiology (virus/alcohol/other)	139/110/72	145/84/64	0.245
MELD score	10 (9-13)	11 (8-14)	0.195
Child-Pugh class (A/B/C)	90/197/34	66/190/37	0.263
Child-Pugh score	7 (6-9)	8 (7-9)	0.101
Previous OHE (no/yes)	292/29	248/45	0.023
Bilirubin (mg/dl)	1.3 (0.9-2.1)	1.3 (0.9-2.1)	0.892
Albumin (g/dl)	3.3 (2.9-3.6)	3.1 (2.8-3.5)	0.023
INR	1.3 (1.2-1.4)	1.3 (1.1-1.4)	0.663
Sodium (mEq/L)	138 (134-140)	137 (133-140)	0.006
TIPS indication (bleeding/ascites)	191/130	165/128	0.473

Results

Multivariable analysis showed that age
[sHR 1.04 (1.02 -1.05),
p <0.001] and MELD
[sHR 1.09 (1.05;1.13), *p* <0.001],
but not post-TIPS OHE, were associated
with a higher mortality rate.

Episodic OHE after TIPS does not
increase mortality in patients
undergoing TIPS



Highlights

- In patients with cirrhosis outside the setting of TIPS, the development of OHE negatively impacts survival.
- OHE is considered a major complication in patients treated with TIPS.
- We show that post-TIPS episodic OHE does not increase the risk of death in patients undergoing TIPS, irrespective of the indication.
- This finding alleviates concerns regarding the impact of this complication on survival after TIPS.

Impact and implications

Overt hepatic encephalopathy (OHE) is a common complication in patients with advanced liver disease and it is particularly frequent following transjugular intrahepatic portosystemic shunt (TIPS) placement. In patients with cirrhosis outside the setting of TIPS, the development of OHE negatively impacts survival, regardless of the severity of cirrhosis or the presence of acute-on-chronic liver failure. In this multicenter, non-inferiority, observational study we demonstrated that post-TIPS OHE does not increase the risk of mortality in patients undergoing TIPS, irrespective of the indication. This finding alleviates concerns regarding the weight of this complication after TIPS. Intensive research to improve patient selection and risk stratification remains crucial to enhance the quality of life of patients and caregivers and to avoid undermining the positive effects of TIPS on survival.

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Episodic overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt does not increase mortality in patients with cirrhosis

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Background & Aims: Overt hepatic encephalopathy (OHE) is a major complication of transjugular intrahepatic portosystemic shunt (TIPS) placement, given its high incidence and possibility of refractoriness to medical treatment. Nevertheless, the impact of post-TIPS OHE on mortality has not been investigated in a large population.
Methods: We designed a multicenter, non-inferiority, observational study to evaluate the mortality rate at 30 months in patients with and without OHE after TIPS. We analyzed a database of 614 patients who underwent TIPS in three Italian centers and estimated the cumulative incidence of OHE and mortality with competitive risk analyses, setting the non-inferiority limit at 0.12.
Results: During a median follow-up of 30 months (IQR 12-30), 293 patients developed at least one episode of OHE. Twenty-seven (9.2%) of them experienced recurrent/persistent OHE. Patients with OHE were older (64 [57-71] vs. 59 [50-67] years, p <0.001), had lower albumin (3.1 [2.8-3.5] *vs.* 3.25 [2.9-3.6] g/dl, p = 0.023), and had a higher prevalence of pre-TIPS OHE (15.4% *vs.* 9.0%, p = 0.023). Child-Pugh and MELD scores were similar. The 30-month difference in mortality between patients with and without post-TIPS OHE was 0.03 (95% CI -0.042 to 0.102). Multivariable analysis showed that age (subdistribution hazard ratio 1.04, 95% CI 1.02–1.05, p <0.001) and MELD score (subdistribution hazard ratio 1.09, 95% CI 1.05–1.13, p <0.001), but not post-TIPS OHE, were associated with a higher mortality rate. Similar results were obtained when patients undergoing TIPS for variceal re-bleeding prophylaxis (n = 356) or refractory ascites (n = 258) were analyzed separately. The proportion of patients with persistent OHE after TIPS was significantly higher in the group of patients who died. The robustness of these results was increased following propensity score matching.
Conclusion: Episodic OHE after TIPS is not associated with mortality in patients undergoing TIPS, regardless of the indication.

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is an increasingly and widely used non-surgical radiological interventional procedure aimed at treating complications of portal hypertension. TIPS establishes a communication between the portal and hepatic veins to divert blood flow directly from the portal circulation into the systemic vascular bed, effectively decompressing the portal venous system by lowering the portosystemic pressure gradient. Since its introduction in the late 1980s, TIPS has become an established therapy for patients with complications of portal hypertension, mainly in the management of variceal re-bleeding and recurrent or refractory ascites.[1–3] In these conditions, TIPS has been shown to improve patient survival, with some differences according to the studies.[4–9]

Overt hepatic encephalopathy (OHE) is a major shunt-related complication following TIPS placement. The incidence of post-TIPS OHE in patients with cirrhosis has been reported to be as high as 35-50% within the first year after the procedure, and up to 8% of patients treated with TIPS may experience a persistent form of OHE,[10–14] which, in selected cases, needs to be managed by reducing the stent diameter.[14,15] These findings have prompted numerous studies aimed at identifying risk factors for the development of post-TIPS OHE, to improve patient selection, as well as studies exploring pharmacological strategies to prevent post-TIPS OHE. Older age, high model for end-stage liver disease (MELD) or Child-Pugh scores, previous history of overt or minimal HE, sarcopenia, impaired renal function, large shunt diameter, and lower post-derivative portosystemic pressure

Keywords: overt hepatic encephalopathy; TIPS; liver cirrhosis; portal hypertension.
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gradient, have been shown to increase the likelihood of developing post-TIPS OHE.[14,16–22] Accordingly, the available guidelines encourage a selection of patients for TIPS based on the above reported factors, whenever possible.[1–3] Administration of pharmacological agents for the prophylaxis of post-TIPS OHE is still debated.[23,24]

In patients with cirrhosis outside the setting of TIPS, the development of OHE negatively impacts survival, regardless of the severity of cirrhosis or the presence of acute-on-chronic liver failure.[25] In patients awaiting liver transplantation (LT), the occurrence of at least one episode of OHE increases 6-month mortality and significantly improves the predictive value of the MELD score.[26] However, whether increased mortality is also observed in patients who develop OHE after TIPS has not been specifically addressed. Several scores, such as the Child-Pugh score, the MELD score, the FIPS (Freiburg index of post-TIPS survival) score, and the recently published ExPeCT score have been proposed to identify patients at high risk of poor prognosis after TIPS.[27–30] However, these scores do not consider post-TIPS OHE as a potential factor affecting survival, and the impact of post-TIPS OHE on mortality rate has not yet been investigated in a large population.[31]

Whether the occurrence of post-TIPS OHE increases the mortality rate in patients with TIPS is still uncertain. Thus, we designed a multicenter, non-inferiority, observational study to compare the mortality rate in a large population of patients with TIPS divided according to the occurrence of post-TIPS OHE.

Patients and methods

We analyzed an anonymized database shared by the participating centers, as part of a multicenter Italian survey (RI-TIPS, Italian Registry of TIPS), including patients with cirrhosis who received a TIPS for refractory ascites or for secondary prophylaxis of variceal bleeding. The patients were prospectively followed-up in three Italian tertiary referral centers (University Hospitals of Modena, Florence and Rome) with high expertise in TIPS placement. Inclusion criteria were a diagnosis of cirrhosis, based on clinical history, imaging, or histology, and TIPS placement for refractory ascites or secondary prophylaxis of variceal bleeding. Exclusion criteria were TIPS placement in the preemptive or rescue setting, hepatocellular carcinoma, and non-cirrhotic portal hypertension. Absolute contraindications to TIPS placement were severe liver failure, heart failure, severe porto-pulmonary hypertension (mean pulmonary artery pressure >45 mmHg at right heart catheterization), severe renal failure (serum creatinine >3 mg/dl), recurrent or persistent OHE despite adequate treatment, and uncontrolled sepsis, as reported elsewhere.[2] In patients with only one previous episode of OHE precipitated by variceal hemorrhage and ameliorated after the control of bleeding, TIPS was not contraindicated. All patients underwent TIPS placement using VIATORR stent-grafts (W.L. Gore SRL, Flagstaff, AZ).[32] The TIPS procedure was performed as previously described.[17,21,30] In two centers (Firenze and Modena) a routinely 5 to 6 mm diameter non-compliant angioplasty balloon catheter was used to dilate the parenchymal tract before deploying the endoprosthesis. In the remaining center (Roma) the balloon was used to dilate the parenchymal tract and the stent-graft to either 8 mm or 10 mm nominal diameters.

Embolization of spontaneous porto-systemic shunts was not performed before TIPS in any of our patients.

Written informed consent for the collection of demographic and clinical data was obtained from each patient. The "Sapienza" University of Rome Ethical Committee approved the collection of patient data for prognostic studies (Ref. 1720/01.10.09).

Patients were evaluated and followed by the same medical team in each center, following a prospective, predefined diagnostic work-up and surveillance strategy. At baseline, none of the patients received any pharmacological treatment to prevent the occurrence of OHE. After TIPS, patients remained hospitalized for approximately 1 week and were then followed-up in the outpatient clinic every 3 months for the first 6 months. Subsequently, the patients were evaluated every 6 months. Moreover, both the patients and their caregivers were instructed about the importance of an immediate referral to the medical staff should any alteration in mental state occur between scheduled visits. In particular, caregivers were instructed to report the occurrence of lethargy, apathy, obvious personality change, inappropriate behavior, or disorientation for time and space. In such cases, OHE evaluation was conducted by the medical staff to confirm and grade it. A grade II or higher score on the West-Heaven scale was considered to adjudicate an episode of OHE[33] and was censored as OHE+. Recurrent OHE was defined as two or more episodes of hepatic encephalopathy requiring hospitalization in the previous 6 months, in the absence of an evident precipitating factor and despite continuous treatment with non-absorbable disaccharides. Persistent OHE was defined as the presence of a continuously detectable altered mental state without recovery to a normal/baseline neuropsychiatric performance despite appropriate treatment.

Patients with an episode of OHE were then managed in an in- or outpatient setting, depending on the severity of the episode. These patients were treated with oral administration of non-absorbable disaccharides and/or non-absorbable antibiotics according to the guidelines available at the time of occurrence of the OHE episode. All potential precipitating factors were treated and, when possible, removed.

Statistical analysis

A sample size of 307 patients in each group achieved 90% power for comparing the estimated difference in the proportion of mortality at 30 months post-TIPS in patients with or without OHE. This sample size was based on a two-group test for equivalence of proportions with a significance level of 0.05 (2-sided) assuming a post-TIPS mortality rate of 0.30 in each group and a non-inferiority margin of 0.12. The non-inferiority margin of 0.12 was set as a clinically relevant difference in mortality between the groups by consensus among the investigators, based on clinical judgment and available data at the time of study design.[31]

Data are expressed as mean (SD) or median (IQR) for continuous variables, based on their distribution and as counts and percentages for categorical variables. Comparison

between treatment groups was performed using the chi-squared test, the Student's *t* test or the Mann-Whitney *U* test, as appropriate.

Patient outcomes considered in the statistical analysis were the first episode of OHE, LT and death. Post-TIPS mortality was defined as the probability of death for any cause, in the absence of LT. Patients who were alive and had not undergone LT at the time of the last follow-up were censored at this date. Mortality and the incidence of OHE post-TIPS were analyzed in a competing risks framework using the cumulative incidence estimator and the Gray test for univariable analysis, as well as Cox proportional hazards regression for analysis of cause-specific hazards. The competing risk events considered were LT for mortality and either death or LT for the incidence of OHE after TIPS placement.

To remove the effects of confounding factors in estimating the effects of post-TIPS OHE on mortality, a propensity score was estimated through a multivariable logistic regression model. Therefore, pairs of patients with and without post-TIPS OHE were matched using the propensity score with a caliper width equal to 0.2 of the SD of the logit of the propensity score.[34] Covariate balance between the two groups was assessed by a standardized difference with a threshold of 0.10 for significant imbalance.[35]

All *p* values were two-sided and *p* values <0.05 were considered significant. All analyses were performed using R software (version 4.0.2).

Results

Six hundred and fourteen patients who had received TIPS were enrolled, 258 for refractory ascites and 356 for re-bleeding (bleeding individuals were derived in the context of recurrent variceal bleeding, *i.e*. following the failure of standard of care therapy). No patients receiving TIPS within 72 h from index bleeding (preemptive TIPS) were enrolled. During a median follow-up of 30 months after TIPS placement, the cumulative incidence of OHE at 30 months was 47% (95% CI 43-51), considering LT and death as competitive risks. The mean time between TIPS placement and occurrence of OHE was 2.4±4.7 months and the mean duration of the episode was 3.3±2.5 days. Grade 2 OHE was detected in 61% of patients, grade 3 in 34% and grade 4 in 5%. Among the 293 patients who experienced at least one episode of OHE, 58 patients (19.7%) had multiple episodes of OHE (two episodes in 48%, three episodes in 42%, four episodes in 5%, and five or more episodes in 5%). The main precipitants of OHE were dehydration (40%), infections (31%), constipation (13%), gastro-intestinal bleeding unrelated to portal hypertension (5%), use of benzodiazepines (5%), or other causes (6%). None of the patients had a recurrence of ascites or bleeding after TIPS. The incidence of OHE was not associated with a deterioration in liver function, as MELD scores at the time of the OHE episode were similar to baseline values.

Comparison of baseline characteristics between the patients with or without incident OHE after TIPS is reported in Table 1. At the time of TIPS placement, there were no significant differences between the two groups in terms of sex, etiology, severity of liver disease (Child-Pugh and MELD scores), nominal diameter of the stent-graft, and pre- and immediate post-TIPS portosystemic pressure gradient presented as continuous variables. At the time of TIPS, patients who eventually developed post-TIPS OHE were older and had significantly lower levels of albumin and serum sodium. A previous history of OHE was significantly more common in the group of patients with post-TIPS OHE (15% *vs*. 9%, $p = 0.023$). Moreover, the proportion of patients with under-dilated stent-grafts (in which the dilatation balloon used was <8 mm) was significantly higher in patients without post-TIPS OHE (39.9% *vs*. 27%; $p < 0.001$). Persistent OHE was observed in 27 patients (9%), 15 of whom (56%) required stent-graft caliber reduction, resulting in a significant improvement in their mental state. Importantly, the causes of death in patients submitted to caliber reduction were not related to recurrence of complications of portal hypertension. Although 55% of patients developed ascites after reduction of the endoprosthesis, this was responsive to diuretic treatment. No patients required endoprosthesis occlusion.

According to EASL guidelines,[33] after the first episode of OHE, 73% of patients received lactulose (obtaining 2-3 bowel

Table 1. Comparison of demographic, clinical and hemodynamic characteristics between patients with and without post-TIPS OHE.

	No post-TIPS OHE (n = 321)	Post-TIPS OHE (n = 293)	*p* value
Sex (male/female)	222/99	198/95	0.738
Age (years)	59 (50-67)	64 (57-71)	<0.001
Etiology (virus/alcohol/other)	139/110/72	145/84/64	0.245
MELD score	10 (9-13)	11 (8-14)	0.195
Child-Pugh class (A/B/C)	90/197/34	66/190/37	0.263
Child-Pugh score	7 (6-9)	8 (7-9)	0.101
Previous OHE (no/yes)	292/29	248/45	0.023
Bilirubin (mg/dl)	1.3 (0.9-2.1)	1.3 (0.9-2.1)	0.892
Albumin (g/dl)	3.3 (2.9-3.6)	3.1 (2.8-3.5)	0.023
INR	1.3 (1.2-1.4)	1.3 (1.1-1.4)	0.663
Sodium (mEq/L)	138 (134-140)	137 (133-140)	0.006
TIPS indication (bleeding/ascites)	191/130	165/128	0.473
Stent-grafts nominal diameter (8 mm/10 mm)	187/134	167/126	0.806
Pre-TIPS PSPG (mmHg)	21.8 (5.34)	22.4 (5.18)	0.072
Post-TIPS PSPG (mmHg)	10.0 (4.62)	10.1 (4.46)	0.737
Under-dilated stent-grafts (<8 mm)	128 (39.9%)	79 (27.0%)	<0.001

Data are expressed as mean (SD) or median (IQR) for continuous variables, based on their distribution and as counts and percentages for categorical variables. Comparison between treatment groups was performed using the chi-squared test, the Student's *t* test or the Mann-Whitney *U* test, as appropriate. All *p* values were two-sided and *p* values <0.05 were considered significant.

INR, international normalized ratio; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; PSPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

movements per day) and 27% received non-absorbable antibiotics. The combination of both drugs as secondary prophylaxis was prescribed in patients with a second episode of OHE within 6 months from the first one.

During a median follow-up of 30 months (IQR 12-30), 168 (27%) patients died, and 64 (10%) underwent transplantation. The main causes of death were: acute-on-chronic liver failure (36%), infections and sepsis (32%), heart failure (15%), hepatocellular carcinoma (7%) and other causes not related to liver disease (10%). Patients who died were older and had more severe liver disease, as expressed by Child-Pugh and MELD scores, compared to surviving patients (Table 2). There were no significant differences in terms of sex, history of previous OHE and other biochemical parameters between the two groups. As expected, a higher mortality was observed in the patients submitted to TIPS for refractory ascites compared to those treated because of variceal bleeding. The proportion of patients with post-TIPS OHE was also similar between the two groups. The number of patients with post-TIPS OHE was also similar between the two groups. However, the number of hospitalizations and the proportion of patients with persistent OHE was significantly higher in the group of patients who died (8% *vs.* 3%). In particular, in patients with persistent OHE, MELD and Child-Pugh scores were significantly higher than in patients without OHE (MELD 13.6±4.2 *vs*. 11.5±4.1; p <0.01 and Child-Pugh 9.9±0.7 *vs*. 7.8±0.6; p <0.01, respectively), as were the number of hospitalizations during follow-up (2.4±0.6 *vs.* 0.5±0.8; p <0.01, respectively).

The estimate of mortality post-TIPS, accounting for LT as a competing risk, was similar among patients with and without post-TIPS OHE (Fig. 1). The mortality rate and 95% CI at 30 months were 0.34 (0.28–0.40) and 0.31 (0.25–0.37) in the group of patients with or without post-TIPS OHE, respectively. The difference in mortality rate at 30 months and 95% CI between patients with and without OHE was 0.03 (-0.042 to 0.102). Thus, the upper limit of the CI (0.102) was lower than the prespecified non-inferiority confidence limit of 0.12. On this basis, the mortality rate post-TIPS in patients with OHE can be considered as non-inferior to the mortality post-TIPS in patients without OHE. The incidence of HE was not significantly different among the three centers.

Multivariable analysis identified age (subdistribution hazard ratio [sHR] 1.04) and MELD score (sHR 1.09), but not post-TIPS OHE (sHR 0.81), as factors independently associated with a higher mortality rate after TIPS (Table 3). Similar results were obtained by propensity score analysis (Table S1 and Fig. S1) and when separately considering patients undergoing TIPS for prophylaxis of variceal re-bleeding (n = 356; Table S2) or refractory ascites (n = 258; Table S3).

To identify predictors of post-TIPS OHE within the cohort during the entire follow-up, a further competing risk multivariable analysis was conducted. Age (sHR 1.02, 95% CI 1.01–1.03, p <0.001), history of previous OHE (sHR 1.90, 95% CI 1.32–2.74, p = 0.001), serum sodium (sHR 0.96, 95% CI 0.94-0.98, p = 0.005) and stent-graft dilation diameter ≥8 mm (sHR 1.66, 95% CI 1.20-2.27, p = 0.002) were independently associated with the risk of post-TIPS OHE (Table S4).

Discussion

The main finding of this large non-inferiority study, which included 614 patients with cirrhosis undergoing elective TIPS, is that the development of episodic OHE after TIPS is not associated with an increased risk of mortality, unlike in patients with cirrhosis not undergoing TIPS.[25,36] Remarkably, there was no excess of mortality even when the population was separately analyzed according to TIPS indication, *i.e.* prevention of re-bleeding or refractory ascites. Conversely, the multivariate analysis identified age and MELD score as independent factors associated with higher mortality. Our analysis is in agreement with the observation of Mamiya *et al.*[31] in a much smaller cohort (87 patients), mainly submitted to TIPS for the prevention of variceal re-bleeding (77%) and before the introduction of covered stent-grafts.

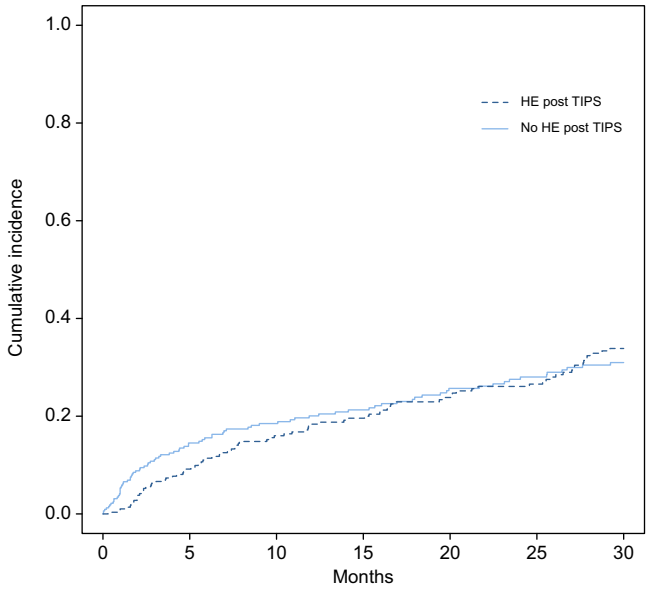
Similar to other studies that included patients treated with VIATORR® stent-grafts,[17,21,30] in our cohort the incidence of

Table 2. Comparison of demographic, clinical and hemodynamic characteristics between survived and dead patients.

	Alive (n = 446)	Dead (n = 168)	*p* value
Sex (male/female)	305/141	115/53	0.98
Age (years)	59 (52-67)	66.5 (59-72)	<0.001
Etiology (virus/alcohol/other)	207/145/94	77/49/42	0.525
MELD score	10 (8-13)	12 (10-15)	<0.001
Child-Pugh class (A/B/C)	134/270/42	22/117/29	<0.001
Child-Pugh score	7 (6-8)	8 (7-9)	<0.001
Previous OHE (no/yes)	397/49	143/25	0.237
Bilirubin (mg/dl)	1.2 (0.9-1.8)	2 (1.1-2.8)	<0.001
Albumin (g/dl)	3.2 (2.9-3.6)	3.1 (2.7-3.5)	0.187
INR	1.3 (1.2-1.4)	1.3 (1.1-1.4)	0.278
Sodium (mEq/L)	138 (134-140)	137 (133-140)	0.185
TIPS indication (bleeding/ascites)	273/173	83/85	0.011
OHE post-TIPS (no/yes)	237/209	84/84	0.546
Number of hospitalizations	1.27 (1.13-1.40)	1.55 (1.37-1.72)	0.015
Persistent OHE (no/yes)	432/14	155/13	0.013
Stent-grafts nominal diameter (8 mm/10 mm)	218/148	141/107	0.506
Pre-TIPS PSPG (mmHg)	22.2 (5.42)	21.6 (4.94)	0.349
Post-TIPS PSPG (mmHg)	9.9 (4.55)	10.5 (4.62)	0.158

Data are expressed as mean (SD) or median (IQR) for continuous variables, based on their distribution and as counts and percentages for categorical variables. Comparison between treatment groups was performed using the chi-squared test, the Student's *t* test or the Mann-Whitney *U* test, as appropriate. All p values were two-sided and p values <0.05 were considered significant.

INR, international normalized ratio; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; PSPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.



N° at risk				
HE post TIPS	293	201	148	111
No HE post TIPS	321	194	143	109

Fig. 1. The estimate of mortality post-TIPS, accounting for liver transplantation as a competing risk, among patients with and without post-TIPS OHE. OHE, overt hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt.

post-TIPS OHE was approximately 50%. As previously described,[10,13–16,21,30] most cases of post-TIPS OHE occurred within the first 3 months after the procedure and were managed by medical therapy and removal or correction of precipitating factors. The reduced incidence of post-TIPS OHE over time may be explained by the improvement or disappearance of other risk factors for encephalopathy such as hyponatremia, kidney dysfunction and sarcopenia. In particular, improvement of the nutritional status and sarcopenia after TIPS might enhance ammonia clearance by the skeletal muscle.[37,38]

In the present study, persistent OHE was observed in only 9% of patients, among whom reducing the TIPS caliber significantly improved mental status in more than half. However, the prevalence of persistent OHE after TIPS was significantly higher in patients who died (8% *vs*. 3%). This increased mortality could be explained by a more advanced liver disease in this group of patients or by the more frequent hospitalizations during follow-up.

Table 3. Results of multivariate analyses predicting mortality in all patients.

	sHR	95% CI	*p* value
Sex (female *vs*. male)	0.96	0.68–1.35	0.81
Age	1.04	1.03–1.05	<0.001
MELD score	1.09	1.05–1.13	<0.001
Post-TIPS OHE (yes *vs*. no)	0.81	0.59–1.13	0.22
TIPS indication (bleeding *vs*. ascites)	1.30	0.92–1.83	0.14
Albumin (g/dl)	0.88	0.64–1.22	0.46
Sodium (mEq/L)	0.98	0.95–1.02	0.38
Previous OHE (no/yes)	1.11	0.69–1.77	0.67

Mortality post-TIPS analyzed in a competing risks framework using the cumulative incidence estimator and the Gray test for univariable analysis, as well as Cox proportional hazards regression for analysis of cause-specific hazards. All *p* values were two-sided and *p* values <0.05 were considered significant.
MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; sHR, subdistribution hazard ratio; TIPS, transjugular intrahepatic portosystemic shunt.

In any case it should be stressed that persistent OHE after TIPS, although occurring in a minority of patients (9% in the present series), is a very important complication of the TIPS procedure that not only reduces patients' quality of life and burdens caregivers but also adversely affects survival outcomes.

A pharmacologic strategy to prevent post-TIPS OHE remains an important unmet need, because evidence of efficacious prophylactic treatments is extremely limited.[23,24,39] In fact, our data underline that episodic OHE remains a significant problem after TIPS, and that careful selection of the most appropriate candidates is crucial. In potentially more frail patients, some additional precautions may be advised, including a thorough cardiologic work-up, placement of an undersized TIPS, withdrawal of psychoactive therapies, and consideration of less strict hemodynamic targets. Our study confirmed that older age, lower serum sodium, and previous history of OHE before TIPS are associated with the appearance of OHE after TIPS.[2,3] In contrast, stent-graft nominal diameters and immediate post-TIPS portosystemic pressure gradient were not associated with either OHE or death after TIPS.

The finding that patients with cirrhosis who develop post-TIPS OHE have similar mortality rates compared to patients without OHE is somehow surprising considering data previously reported in patients with cirrhosis without TIPS, where OHE was associated with higher mortality.[25,36] One hypothesis that can be put forward to explain this result is that patients who underwent TIPS placement at our centers had been strictly selected and those with severe hepatic failure were excluded. Moreover, all patients were closely monitored, given the potential for complications. A regular clinical and laboratory assessment provided to these patients and the empowerment of their caregivers are likely to have contributed to prompt detection and management of

episodes of post-TIPS OHE, limiting their impact on mortality. This highlights the importance of rapid intervention and personalized management of complications associated with TIPS and portal hypertension.

Some limitations of our study must be acknowledged. As an observational study, there may be inherent biases that could have influenced the results. However, possible incomplete recognition of OHE episodes is very unlikely, considering the prospective design of the study and careful instructions provided to caregivers about the detection of potential OHE. It is possible that the selection of patients for TIPS procedures could have influenced the overall mortality rate of the population under study. Furthermore, the patients enrolled in this study had advanced liver disease and a higher risk of mortality even before TIPS placement, thus attenuating the additional impact of post-TIPS OHE on mortality rates. Moreover, some relevant variables, such as sarcopenia, were not captured in the present study and should be included in future research on this topic. Another point to be noted is the exclusion of patients submitted to preemptive TIPS. This choice was discussed before the study design because preemptive TIPS is known to be associated with reduced mortality and an incidence of OHE similar to pharmacological and endoscopic combined treatments. Therefore, the inclusion of patients submitted to preemptive TIPS may have altered *per se* the impact of OHE on survival[40]

In conclusion, our analysis demonstrates that episodic OHE after TIPS is not associated with increased mortality, irrespective of the indication for shunting. Despite this observation, episodic OHE remains a significant problem, particularly in patients submitted to elective TIPS, due to its detrimental effects on patients' quality of life and morbidity. Persistent OHE, although infrequent after TIPS, remains an important complication associated with increased mortality. Thus, intensive research to improve patient selection and risk stratification remain crucial to ameliorate the quality of life of patients and caregivers and to avoid undermining the positive effects of TIPS on survival.

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Abbreviations

LT, liver transplantation; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; sHR, subdistribution hazard ratio; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflict of interest

The authors of this study declare that they do not have any conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

S. Nardelli: acquisition of data, analysis, and interpretation of data; manuscript preparation. V. Adotti, D. Bellafante, M. Rosi, T. Guasconi, D. Roccarina, M. Bianchini, F. Indulti: acquisition of data. A. Spagnoli: statistical analysis and interpretation of data; manuscript preparation. L. Ridola, M. Merli, D. Saltini and S. Gioia: critical discussion and support, manuscript revision of the manuscript for important intellectual content. C. Caporali, F. Fanelli: acquisition of radiological data. O. Riggio, F. Vizzutti, F. Marra and F. Schepis: study concept and design, analysis and interpretation of data; manuscript preparation; final drafting of the manuscript; study supervision.

Data availability statement

Data used for this work are unavailable to access because they are confidential.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.11.033.

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