



# Incidence of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt (TIPS) according to its severity and temporal grading classification

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## Abstract

**Objectives** To evaluate hepatic encephalopathy (HE) incidence after transjugular intrahepatic portosystemic shunt (TIPS) and classify by gravity and frequency.

**Methods** This is a retrospective study of 75 patients with no previous episodes of HE who underwent TIPS between 2008 and 2014 with clinical follow-up after 6 and 12 months. Patient risk factors evaluated include age, INR (international normalized ratio), creatinine, bilirubin, and MELD score (Model for End-of-stage Liver Disease). HE was reported using two classifications: (1) gravity divided in moderate (West-Haven grades I–II) and severe (III–IV); (2) frequency divided in episodic and recurrent/persistent.

**Results** Overall HE incidence was 36% at 6 months, with 12 month incidence significantly decreased to 27% ( $p = 0.02$ ). 13/75 (17%) patients had one episode of moderate HE, while 3/75 (4%) patients had severe recurrent/persistent HE. Age was the only pre-TIPS risk predictor. Post-TIPS bilirubin and INR showed variations from basal values only in the presence of diagnosed HE. Bilirubin significantly increased ( $p = 0.03$ ) in correlation to HE

severity, whereas INR changes correlated with temporal frequency ( $p = 0.04$ ). HE distribution classified for severity is similar at 6 and 12 months, whereas when classified for frequency shows significant differences ( $p = 0.04$ ).

**Conclusions** A classification by gravity and frequency attests post-TIPS HE as a manageable risk. Monitoring of bilirubin and INR may help on clinical management risk stratification.

**Keywords** Radiology · Interventional · Portosystemic shunt · Transjugular intrahepatic · Hepatic encephalopathy · Liver · Liver cirrhosis

## Abbreviations

TIPS	Transjugular intrahepatic portosystemic shunt
HE	Hepatic encephalopathy
INR	International normalized ratio
MELD	Model for end-of-stage liver disease
FU	Follow-up
ROC	Receiver-operating characteristic
AUC	Area under the curve

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## Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) proved to be an effective treatment for complications of portal hypertension, as rescue treatment when medical or endoscopic treatment fails in contrasting gastro-esophageal variceal bleeding and as the first-line treatment for patients with refractory ascites, when frequent paracentesis is needed. [1–3].

The most common complication of TIPS is the development of hepatic encephalopathy (HE), occurring in 30–60% of patients within 1 year [2, 4–6]. The development of HE represents an important drawback of this otherwise valuable and life-prolonging intervention [2, 5, 7], being associated with significant morbidity and increased mortality [8, 9]. HE post-TIPS is typically attributed to the portosystemic shunt, but can be precipitated by abrupt changes in portal perfusion, shunt dysfunction, multiple hepatic re-interventions, and recurrent gastrointestinal bleeding or ascites [6]. Patients' factors which might have an impact on the onset and features of HE are age, international normalized ratio (INR), serum creatinine, serum bilirubin, and the model for end-of-stage liver disease (MELD) score obtained from the latter three variables [7], which is an excellent predictor of survival in patients with end-stage liver disease.

The classification of HE as minimal, moderate, and severe was standardized in 1998 [10] and recently reviewed in 2014 in a more comprehensive classification [11]. Despite this, in the radiological literature, there is heterogeneity of results regarding the incidence and impact of post-TIPS HE on clinical practice and quality of life. Some studies considered the overall episodes of HE, whereas others considered only the new or worsened HE episodes; some investigators selected the episodes that occurred without an evident precipitating cause [9], and others, those leading to hospitalization [5]; overt/covert differentiation was rarely used, while in most cases, moderate/severe classification is widely accepted [4]. Moreover, even if the diagnosis of severe HE is relatively straightforward on clinical grounds, it requires exclusion of other neuropsychiatric disorders that can be responsible for similar clinical findings. Particularly, the diagnosis of minimal HE requires formal neuropsychological assessment and testing. The reporting heterogeneity and the fact that only a few studies have a long-term follow-up also affects the available meta-analyses [7].

An alternative HE classification based on the temporal occurrence and recurrence patterns of HE after TIPS was proposed in recent guidelines [11], but, as far as we know, it has not yet been used by radiologists.

The open questions are as follows:

1. Is it possible to identify pre-TIPS indicators (biomarkers) of the middle (6 months) and long-term (1 year) post-TIPS outcome? For instance, how are the patient's risk factors associated with the HE onset, features, and resolution?
2. What is the incidence of HE in its various forms at 6 and 12 months?
3. Which extra information can be derived using both severity and time pattern classification?

Herein, we report and discuss the outcome of a retrospective evaluation of incidence, features, and evolution of HE in a cohort of cirrhotic patients treated with TIPS in our unit and followed for at least 1 year by the hepatology reference centre of our hospital. The goal of our study was to obtain a representation of the scenario at 6 and 12 months after the procedure based on both HE classifications (severity and temporal pattern grading).

## Materials and methods

### Study population

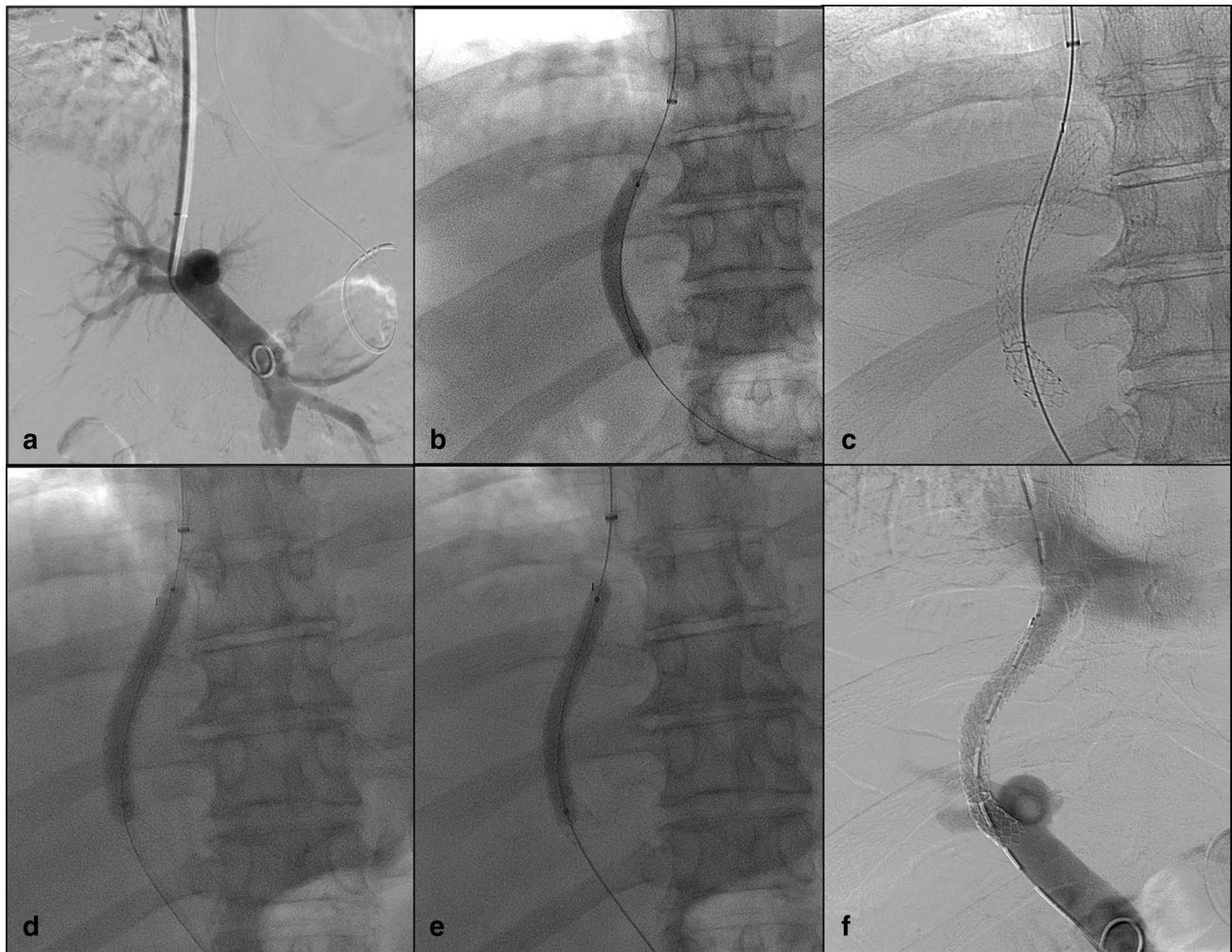
We retrospectively analyzed the radiological and clinical records of all consecutive cirrhotic patients who underwent a technically successful TIPS procedure in our unit from January 2008 to November 2014 and completed a 12 month follow-up (FU) period. The initial study sample included 276 patients. Exclusion criteria were: lack of complete clinical information (112), liver transplantation during FU (43), death during FU (21), and pre-TIPS encephalopathy, since it might introduce a non-controllable bias (25). The final sample thus included 75/276 (27%) patients.

We chose to analyze the patients' status as determined by our hepatology reference centre at 6 and 12 months as the best representative of the middle and long-term post-TIPS evolution.

The study was conducted in good clinical practice according to the Helsinki Declaration of 1975 and subsequent modifications. Institutional review board approval was not required because of its retrospective nature. Written informed consent was obtained from all patients before TIPS.

### TIPS protocol

TIPS was performed according to conventional methods (Fig. 1) [2, 12]. Venous access was gained through the right jugular vein. A catheter was accessed into an hepatic vein, the right one for 56/75 patients (75%), and a Rosch–Uchida transjugular liver access set (Cook Medical Co.,



**Fig. 1** TIPS procedure: **a** ultrasound-guided creation of shunt between the right hepatic vein and the right branch of the portal vein, **b** dilation of the parenchymal tract of the shunt, **c** Viatarr covered-

stent grafts deployment, **d, e** 8 mm balloon catheter is used to dilate the stent graft, and **f** final portography control

Bloomington, IN, USA) with ultrasound guide was used to penetrate the liver for access to the portal vein. The shunt was created with the right branch of the portal vein in 64 patients (85%), with the left branch in 8 (11%) and in the bifurcation in 3 (4%). The stents were 11 Wallstent bare-metal stents (Boston Scientific, Natick, MA, USA) (used from 2008 to 2010), 63 Viatarr covered-stent grafts (W. L. Gore & Associates, Flagstaff AZ, USA) (used from 2010 to 2014), and 1 Luminexx (Bard, Tempe, AZ, USA) (used in 2009).

To optimize the shunt, the stent was performed with a dilation balloon catheter of various sizes. In 71 patients, a single dilation was sufficient; when using the Viatarr stent, the dilation was performed with balloon catheters of maximum nominal diameter between 8 and 12 mm, while for patients with Luminexx or Wallstent stents, dilation ranged

between 8 and 14 mm. Balloon dilation was followed by shunt venography.

In five cases (7%), the procedure was completed by embolization of the varicose periesophageal or perigastric circles, highlighted on pre-procedural diagnostic angiography. After catheterization, the pressure before and after the balloon dilatation of the hepatic parenchymal tract was evaluated.

Following TIPS procedures, patients underwent inpatient monitoring for 48–72 h and were then followed as outpatients in the reference centre for liver failure and transplantation. Medication and diet of 75 patients after TIPS was the same—we recommended low-protein intake within 3 months after TIPS, especially the first month, and patients are always asked to keep good bowel movement. No patients were treated with anticoagulant therapy.

## HE classification

We followed the HE classification proposed in 2014 by the AASLD/EASL [11], adopting two different classifications:

1. Severity classification, the most used in radiological literature [4, 13, 14], divided into moderate (Grade I–II West-Haven) and severe (Grade III–IV). We did not consider the minimal grade, for the uncertainties connected with its diagnosis.
2. Time pattern classification, often used in gastroenterology [11, 15–17], but generally neglected by radiologists, divided into episodic occurrence and recurrent (bouts of HE occurring within 6 months or less) or persistent (always present with intermittent episodes of overt HE) occurrence.

## Statistical analysis

Continuous variables were tested for normality with the Shapiro–Wilks test. When normality was accepted (age), the data were presented as mean  $\pm$  standard deviation; when normality was rejected (other risk factors), the data were presented as median and interquartile range (IQR). Comparisons employed non-parametric tests for  $k$  distributions—Mann–Whitney test for  $k = 2$  and Kruskal–Wallis test for  $k > 2$  independent distributions; Wilcoxon test for  $k = 2$ ; and Friedman test for  $k > 2$  correlated distributions.

The ability to differentiate between healthy and pathological conditions was tested with the receiver operating characteristic (ROC) curve procedure; the quality of discrimination was quantified by the area under the curve (AUC), ranging from 0.5 (chance) to 1 (excellent). The threshold between the two conditions was set at the value which maximized Jouden's index  $J$  and the harmonic mean (HM) of sensitivity (SNS) and specificity (SPC) while minimizing the distance  $D$  of the curve from the (0, 1) upper left vertex. SNS and SPC were used to determine the likelihood ratio of a positive test LR+, i.e., the likelihood that a positive test result would be expected in a patient with disease compared to the likelihood that the same result would be expected in a patient without disease.

Categorical variables, reported as counts and percentages, were arranged in  $r \times c$  tables studied with the Chi-square test (with Yates' correction for  $2 \times 2$  tables) or with Fisher's exact test. McNemar's test was used to assess the difference between two correlated proportions.

Statistical significance was set at two-tails  $p < 0.05$ .

The analysis was carried out with open source softwares (<http://www.openepi.com> and <http://www.vassarstats.net>) and Statplus:Mac version v6 (AnalystSoft, Walnut, USA). All statistical procedures were run on at least two different packages.

The statistical power of the study in some comparisons suffered from the low sample sizes, so some borderline values of  $p > 0.05$  may actually hide significances that the test could not evidence; however, all results reported as significant originate from 80% power tests.

## Results

### HE incidence and risk factors

Table 1 shows the liver disease etiology and indication for TIPS for the 75 patients as assessed through the available clinical records.

At 6 months after TIPS, 27/75 (36%) patients were diagnosed with at least one episode of HE. Between 6 and 12 months, 4 patients without HE at 6 months developed HE, while 11 patients with HE at 6 months recovered—the rate of patients affected by HE at 12 months was thus down to 20/75 (27%), with a significant 11% difference ( $p = 0.02$ ).

We checked whether the presence of at least one HE episode during the FU could be procedure-related, i.e., associated with values of the portal pressure gradient during TIPS. All data are summarized in Table 2 and agree on the lack of significant differences between absence and presence of HE. The results were confirmed by the outcome of the logistic regression.

We considered the four patient-related risk factors—MELD score, INR, creatinine, and bilirubin, and the presence of a large volume of ascites on the day of TIPS procedure. We did not evaluate the presence of gastro-esophageal variceal for lack of information in the patients' files and the albumin serum values for the high iatrogenic variations (for this last reason we did not calculate retrospectively the Child-Pugh score).

**Table 1** Liver disease etiology and indication for TIPS

Liver disease etiology	
Viral	34 (45%)
Exotoxic	16 (21%)
Cryptogenic	9 (12%)
Others	16 (21%)
Indications for TIPS	
Refractory ascites	31 (41%)
Acute gastro-esophageal variceal bleeding	7 (9%)
Recurrent gastro-esophageal variceal bleeding	19 (25%)
Massive portal vein thrombosis	12 (16%)
Hepato-renal syndromes type II	4 (5%)
Budd-Chiari syndrome	2 (3%)

**Table 2** HE and portosystemic pressure gradient during TIPS procedure

Variable	Patients without HE diagnosis	Patients with HE diagnosis	p
Caval pressure before TIPS (mmHg)	10.5 ± 6.3	11.6 ± 3.6	0.41
Portal pressure before TIPS (mmHg)	33.7 ± 8.1	36.5 ± 6.7	0.14
Portal pressure gradient before TIPS (mmHg)	24.1 ± 6.1	24.1 ± 6.7	>0.99
Caval pressure after TIPS (mmHg)	18.0 ± 6.3	19.4 ± 5.0	0.32
Portal pressure after TIPS (mmHg)	25.7 ± 7.0	27.0 ± 5.2	0.44
Portal pressure gradient after TIPS (mmHg)	8.4 ± 2.6	7.9 ± 2.3	0.46
Difference in portal pressure gradient before and after TIPS (mmHg)	15.8 ± 5.3	15.8 ± 5.9	0.98

**Table 3** pre-TIPS conditions and HE post-TIPS

	Patients without HE diagnosis	Patients with HE diagnosis	p
Patients	44	31	
Males	30 (61%)	19 (68%)	0.71
Age (years)	52.9 ± 9.4	59.1 ± 9.5	<b>0.01</b>
MELD <sup>a</sup> score	12 (9.7–15)	12 (11–16)	0.31
INR <sup>b</sup>	1.3 (1.2–1.5)	1.4 (1.2–1.5)	0.23
Creatinine (mg/dL)	0.88 (0.71–1.0)	0.95 (0.84–1.2)	0.09
Bilirubin (mg/dL)	1.65 (1–2.35)	1.5 (1.2–1.95)	0.51
Abscites <sup>c</sup>	31	23	0.73

<sup>a</sup> Model for end-stage liver disease

<sup>b</sup> International normalized ratio

<sup>c</sup> Large abscesses on the day of TIPS procedure

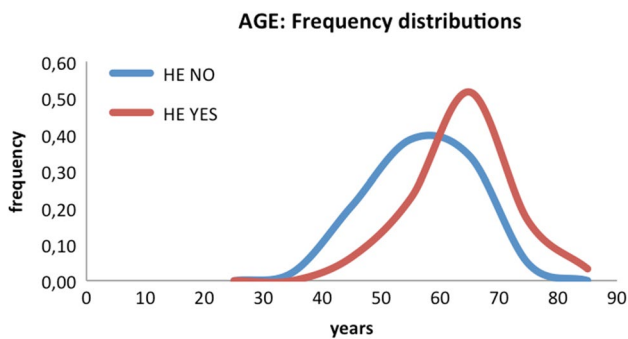
**Fig. 2** Age and frequency distributions on the two samples

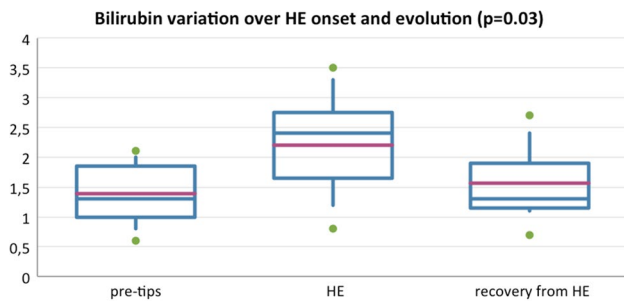
Table 3 compares the pre-TIPS values for the 31 patients who at different times were diagnosed with HE and the 44 patients who did not have HE in the entire FU year. The only variable showing a significant difference between the two samples of patients is age. We tested its discrimination ability by studying the frequency distributions of the two samples and the associated ROC curve. The frequency distributions overlap over a substantial region of age values (Fig. 2), crossing at 60 years. The ROC curve has AUC = 0.70, which stands for a moderate-to-fair discriminating ability; the ROC curve

diagnostic parameters indicate age  $\geq 60$  years as threshold for possible onset of HE (sensitivity = 71%, specificity = 61.4%, likelihood Ratio-LR+ = 1.8).

To investigate the role of the other risk factors in determining the onset of HE, we studied their evolution in the follow-up period.

The 44 patients free from HE diagnosis over the entire 1-year FU had similar values at pre-TIPS, 6-month and 12-month tests for MELD ( $p = 0.47$ ), INR ( $p = 0.49$ ), creatinine ( $p = 0.38$ ), and bilirubin ( $p = 0.17$ ).

For the 31 patients who instead had HE either at 6 months or at 12 months, we compared the pre-TIPS conditions to the conditions corresponding to the HE diagnosis (27 at 6 months and 4 at 12 months). The comparison clearly indicated that the onset of HE was associated with a significant increase of bilirubin from the pre-TIPS value ( $p = 0.003$ ). Such association was confirmed by the results relative to the 11 patients who at the 12-month check-up had recovered from the HE diagnosed at 6 months— recovery corresponded to a significant ( $p = 0.03$ ) decrease of bilirubin from HE to a value very close ( $p = 0.58$ ) to the pre-TIPS one. Figure 3 illustrates the evolution of bilirubin over the three stages: pre-TIPS, HE, and recovery. The values of INR and creatinine showed no significant variation.



**Fig. 3** Evolution of bilirubin over the three stages— pre-TIPS, HE, and recovery

### HE classification

The 31 patients who suffered from HE had a total of 47 HE diagnoses (27 at the 6-month check-up and 20 at the 12-month check-up). Table 4 shows how they fit the two classifications—in horizontal, the severity grading; in vertical, the time recurrence pattern; and in bold, the two conditions that combine a high level of severity with a high frequency of recurrence, i.e., the worst to manage and those seriously damaging the quality of life of the patients. One patient was affected by

severe recurrent/persistent HE both at the 6-month and 12-month check-ups.

### Severity grading and temporal pattern grading

At 6 months, there were 23 patients with moderate HE and four with severe HE, whereas at 12 months, there were 18 moderate HE and two severe HE, with a similar distribution between moderate and severe ( $p = 0.46$ ). The main features of the 47 HEs observed at 6 and 12 months (41 moderate and six severe) are reported in Table 5 (left side).

At 6 months, there were 13 patients with episodic HE and 14 with recurrent/persistent HE; at 12 months, there were three episodic HEs and 17 recurrent/persistent HEs. Interestingly, the distribution according to the temporal pattern was significantly different at the two check-ups, with the episodic HEs decreasing and the more fastidious recurrent/persistent ones increasing ( $p = 0.04$ ). Seven patients with Episodic HE at 6 months recovered, three remained stable and four worsened to recurrent/persistent; at the same time, one patient with recurrent/persistent HE improved to episodic. The main features of the 47 HEs observed at the two checkpoints of 6 and 12 months (overall 16 Episodic, 31 Recurrent/Persistent) are reported in Table 5 (right side).

**Table 4** Details of the 47 diagnosed HEs

6 months	HE		27/75 (36%)
	Moderate	Severe	
Episodic	11	2	13 (17%)
Recurrent/persistent	12	<b>2</b>	14 (19%)
	23 (31%)	4 (5%)	
12 months	HE		20/75 (27%)
	Moderate	Severe	
Episodic	2	1	3 (4%)
Recurrent/persistent	16	<b>1</b>	17 (22%)
	18 (24%)	2 (3%)	
Pooled	41	6	47

**Table 5** Details of the 47 diagnosed HEs using the severity grading (left side) and the temporal pattern grading (right side)

Variable	HE			Episodic ( $n = 16$ )	Recurrent/persistent ( $n = 31$ )	$p$
	Moderate HE ( $n = 41$ )	Severe HE ( $n = 6$ )	$p$			
Age	58.8 ± 9.6	63.3 ± 9.1	0.25	60.2 ± 9.3	59.2 ± 8.7	0.65
MELD	13 (11–15)	18 (13–20)	0.11	14 (1.7–15)	13 (12–16)	0.73
INR	1.44 (1.27–1.59)	1.36 (1.3–1.4)	0.70	1.29 (1.18–1.48)	1.46 (1.4–1.6)	<b>0.04</b>
Creatinine (mg/dL)	0.88 (0.78–0.99)	1.12 (1.0–1.5)	0.09	0.87 (0.82–1.01)	0.90 (0.78–1.03)	0.77
Bilirubin (mg/dL)	1.7 (1.1–2.5)	3.7 (2.1–4.7)	<b>0.03</b>	2.4 (1.7–3.5)	1.65 (0.95–2.5)	0.10

Bold values indicate statistical significance  $P$  values ( $p < 0.05$ )

## Discussion

The results of our study sketch a picture of the onset and evolution of HE at 6 and 12 months after the TIPS procedure from two different points of view— severity grading—the most generally used—and temporal pattern grading—recently emphasized by the AASLD-EASL, but until now, scarcely adopted in the radiological environment.

The main results of our study are—

- the overall HE incidence significantly decreased from 27/75 (36%) at 6 months to 20/75 (27%) at 12 months, ( $p = 0.02$ ). 44/75 (59%) patients enjoyed complete freedom from HE, and 13/75 (17%) had only one episode of moderate HE— overall, the procedure may be considered safe for 57/75 (76%) patients. The procedure was cause of heavy distress (severe recurrent/persistent HE) only for 3/75 (4%) patients;
- among all pre-TIPS risk factors, age  $\geq 60$  years was identified as a fair indicator of increased probability of post-TIPS HE;
- the onset of HE was associated with a significant increase in the bilirubin value ( $p = 0.003$ ), just as recovery from HE was associated with a significant decrease to the basal value. In addition, the increasing severity of HEs was significantly associated with increasing values of bilirubin ( $p = 0.03$ ), whereas the increasing frequency of HEs was associated with increasing values of INR ( $p = 0.04$ );
- the HE distribution, classified according to severity, was similar at 6 and 12 months ( $p = 0.46$ ), whereas when classified according to the temporal pattern grading, it showed significant differences ( $p = 0.04$ ), due to the decrease of episodic HEs and increase of persistent HEs.

### Comprehensive incidence of HE

The overall incidence of patients with HE at 6 months (36%) of our series is at the bottom of the range of values present in the literature (from 30 to 60%). [7, 18, 19] Considering both severity and temporal pattern grading, we obtain that a large percentage of patients (76%) had no HE or had a single moderate episode that was easily managed. The worst condition, a severe recurrent/persistent HE, was, indeed, a rare situation (4%). The risks associated with post-TIPS morbidity are not negligible, but they must be balanced against its potential benefits, being aware that untreatable variceal hemorrhage and refractory ascites have in 30–50% of cases a survival time of about 2 years [20, 21].

## Predictive factors

In our series, age was the only pre-TIPS variable significantly associated with HE onset ( $p = 0.01$ ), with patients above 60 years, the most probable candidates. The likelihood ratio for a positive test is 1.8, increasing to 4.2 for ages  $\geq 70$  years. This is consistent with the results by Bai [7], who demonstrated that older patients were usually accompanied by a higher post-TIPS HE risk and those by Hassoun [22], who hypothesized that the aging brain may be more susceptible to the toxic effects of substances such as ammonia involved in pathogenesis of HE.

### Bilirubin associated with HE onset and severity grading

We assessed a significant increase of bilirubin from the pre-TIPS value ( $p = 0.003$ ) to the onset of HE, with values higher for severe than for moderate HEs ( $p = 0.03$ ). Accordingly, the recovery corresponded to a significant decrease of bilirubin to basal values ( $p = 0.58$ ).

The increase in serum bilirubin is a well-known direct indicator of hepatocyte dysfunction, especially in the days following the shunt creation. Casadaban [23] described an acute (within 7 days) two- to three-fold increase in bilirubin, typically resolved within 2 weeks, remaining far from the baseline value only for patients with 90-day mortality. The transient nature of these alterations is explained by the sudden decrease of hepatic flow; the subsequent arterial perfusion compensation (“the hepatic arterial buffer response” [24, 25]) may allow relative normalization of laboratory test results after TIPS. Although the authors do not describe any correlation between hepatobiliary enzymatic elevation and HE, we can assert that the more compromised is the liver function (e.g., longer is bilirubin elevation), the higher is the risk of HE. It is the precisely timed association: HE presence—high bilirubin versus HE absence—basal bilirubin that prevents bilirubin to be used as pre-TIPS predictor.

### INR associated with HE temporal pattern grading

In contrast to bilirubin, the value of INR was not significantly associated with HE onset and severity grading; however, when considering the data in the temporal pattern frame, we evidenced a significant association between increasing frequency of HE episodes and increasing values of INR ( $p = 0.04$ ).

This difference in behavior according to the classification method is intriguing. INR is a marker of liver function which is known to usually increase in the latest stages [26, 27] of liver disease, when presumably patients may suffer from more frequent HE episodes. Indeed,

Pomier-Layrargues [26] described that the first sign of liver failure is a progressive increase in the serum bilirubin, followed by a rise in INR, onset of encephalopathy, and death due to multiorgan failure.

### HE incidence at 6 and 12 months

The 12-month FU witnessed a significant 11% decrease ( $p = 0.016$ ) in the number of patients affected by HE compared to the 6-month FU. When considering the severity grading, the distribution between moderate and severe was essentially similar ( $p = 0.46$ ) at the two checkpoints. Instead of considering the temporal criteria, we recognized a significant change ( $p = 0.04$ ) in the ratio of episodic to recurrent/persistent occurrences— at 6 months, there was a prevalence of episodic HEs, whereas at 1 year, the ratio was turned over with prevalence of recurrent/persistent occurrences. The prevalence of episodic HEs at 6 months is most probably due to the temporary changes caused by TIPS, possibly due to the suddenly increased shunt flow. More difficult to explain is the reason underlying the long-term evolution from episodic to the more devastating recurrent/persistent form, also because of the small number of patients involved ( $n=4$ ).

### Limitations

This study has several limitations: (1) data were collected retrospectively and, hence, non-randomized; (2) patient treatment spanned over 7 years, with consequent differences in their treatment; (3) development of HE was determined subjectively by the hepatologists and knowledge about HE features were limited to information available in patient files. We did not evaluate HE incidence according to the stent type for the high predominance of PTFE-covered stent used. We could not evaluate 3-month (short-term) HEs according to the existence of precipitating factors nor use the overt/covert classification for lack of information in the patient's files.

### Conclusions

Our study determines an overall HE incidence of 36% at 6 months, decreasing to 27% at the 1-year FU. The comprehensive (severity and temporal) classification of HE evidenced that the more devastating form of severe recurrent/persistent HE struck only 4% of the patients.

Age can be considered as pre-TIPS risk predictor, advising a careful evaluation of patients over 60 years for their significantly higher probability of HE. Furthermore, bilirubin is closely associated with the level of severity

characterizing the HE, whereas INR is associated with the temporal occurrence of HE.

Although our study involves one of the biggest single institution series [7], a reliable test of the validity of the “cross-classification” matching severity and frequency will require a specifically designed prospective study, possibly a well-coordinated multicenter study to collect large numbers in a short period of time, guaranteeing the necessary homogeneity of treatment. In conclusion, our study underlines the need for a standardization of the reporting criteria of post-TIPS HE to better compare data within the radiological community and interact with other specialists.

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### Compliance with ethical standards

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Ethical standards** Institutional Review Board approval was not required because of its retrospective nature. The study was conducted in good clinical practice according to the Helsinki Declaration of 1975 and subsequent modifications.

**Informed consent** Written informed consent was obtained from all patients in this study. Methodology: retrospective, observational, and performed at one institution.

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