Cognitive Impairment Predicts The Occurrence Of Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt

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OBJECTIVES: **Hepatic encephalopathy (HE) is a major problem in patients treated with TIPS. The aim of the study was to establish whether pre-TIPS covert HE is an independent risk factor for the development of HE after TIPS.**

METHODS: **Eighty-two consecutive cirrhotic patients submitted to TIPS were included. All patients underwent the PHES to identify those affected by covert HE before a TIPS. The incidence of the first episode of HE was estimated, taking into account the nature of the competing risks in the data (death or liver transplantation).**

RESULTS: **Thirty-five (43%) patients developed overt HE. The difference of post-TIPS HE was highly significant (*P*=0.0003) among patients with or without covert HE before a TIPS. Seventy-seven percent of patients with post-TIPS HE were classified as affected by covert HE before TIPS. Age: (sHR 1.05, CI 1.02–1.08, *P*=0.002); Child–Pugh score: (sHR 1.29, CI 1.06–1.56, *P*=0.01); and covert HE: (sHR 3.16, CI: 1.43–6.99 *P*=0.004) were associated with post-TIPS HE. Taking into consideration only the results of PHES evaluation, the negative predicting value was 0.80 for all patients and 0.88 for the patients submitted to TIPS because of refractory ascites. Thus, a patient with refractory ascites, without covert HE before a TIPS, has almost 90% probability of being free of HE after TIPS.**

CONCLUSIONS: **Psychometric evaluation before TIPS is able to identify most of the patients who will develop HE after a TIPS and can be used to select patients in order to have the lowest incidence of this important complication.**

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INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is currently used for the treatment of complications of portal hypertension, mainly variceal rebleeding and refractory ascites (1–9). This procedure involves a major drawback: hepatic encephalopathy (HE). This complication has been reported in 30–55% (10–15) of cirrhotic patients within the first year, and up to 10% of patients treated with a TIPS may experience a severe form of HE that is refractory to standard treatments and will need to be resolved by reducing the shunt diameter (13). Unfortunately, no pharmacological treatment has yet proved to be able to reduce the incidence of post-TIPS HE. The only randomized controlled trial carried out with this aim failed to show any beneficial effect of drugs commonly used in the treatment of HE (16). More recently, a randomized controlled trial was performed to assess the efficacy of polytetrafluoroethylene-covered stents of different diameters (10 vs. 8 mm) on the incidence of post-TIPS HE. Unfortunately, the trial was stopped because the stents with the smaller diameter were unable to control the complications of portal hypertension (17). Thus, the selection of patients remains the only method to try to reduce the incidence of post-TIPS HE, and many studies have attempted to identify the predictors of this complication in order to select for TIPS only those patients with the lowest incidence. The factors identified as the most robust predictors of

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post-TIPS HE were previous HE, age, a low porto-caval pressure gradient, and a high Child–Pugh score (13,18–20). Further factors were high creatinine levels (13) and low serum sodium concentration (21). Despite the exclusion of patients with previous HE and advanced liver disease, the incidence of post-TIPS HE still remains fairly high (22); thus, other factors are involved.

In cirrhotic patients without TIPS, the presence of subclinical cognitive impairment, also known as covert HE (23), has been shown to be a strong predictor of the occurrence of overt HE (24). Correspondingly, alterations in psychometric performance detected in a TIPS candidate before the procedure may help identify the patients at risk of HE after the procedure. Actually, in our randomized controlled trial (16), post-TIPS HE developed more frequently in patients with an abnormal psychometric test (Trail Making Test A) before TIPS, and, more recently, Berlioux P. *et al.* showed in 54 patients submitted to a TIPS that the incidence of HE increased in those with abnormal critical flicker frequency before a TIPS (25). However, in both studies, the relationship between psychometric performance and post-TIPS HE was present only at the univariate analysis, and thus the role of cognitive impairment as a risk factor for HE after a TIPS remains uncertain.

The aim of the present study was to establish whether pre-TIPS covert HE is an independent risk factor for the development of HE and whether the psychometric evaluation before a TIPS may be used for selecting patients in order to have the lowest rate of HE after a TIPS.

METHODS

From January 2011 to December 2014, all consecutive cirrhotic patients undergoing TIPS were considered eligible for the study. In our Center, exclusion criteria for TIPS placement are age >75 years, bilirubin levels >5 mg/dl, creatinine levels >3 mg/dl, a serious cardiac or pulmonary dysfunction, a Child–Pugh's score >11 (except for patients who were candidates for early TIPS), a model end-stage liver disease score >18, the presence of portal thrombosis, a diagnosis of hepatic carcinoma, sepsis, and spontaneous bacterial peritonitis. Present HE or previous spontaneous/recurrent HE is also a contraindication to TIPS; however, patients with only one episode of HE precipitated by variceal bleeding and ameliorated after the bleeding was controlled are not excluded. Other exclusion criteria were alcohol/psychoactive drugs intake (positive alcoholaemia and/or benzodiazepines or opioid urine metabolites) at the moment of evaluation, unrelated neurological disease including dementia (mini mental state <26), and lack of compliance with psychometric evaluation because of language barriers or reduced visual acuity.

The purpose of the study, the enrollment, and the details of the TIPS operation were clearly explained to all the patients before obtaining their written informed consent. The "Sapienza" University of Rome Ethical Committee approved the collection of data of the patients for prognostic studies (Rif.1720/01.10.09).

All TIPS procedures were carried out by the same radiology team, using polytetrafluoroethylene-covered stents of 10 mm diameter. The anesthesiological procedure (4,26) and the technical details of TIPS with polytetrafluoroethylene-covered stent-graft implantation were previously described (27,28). All the subjects were evaluated and followed by the same medical team by a prospective protocolled diagnostic work-up and a surveillance strategy.

The day before the procedure, a basal evaluation of HE, including an examination and grading of the patients' mental state, asterixis, and psychometric performance, as well as the determination of venous blood ammonia, were carried out. The evaluation of the degree of HE was based on the alteration of the patient's mental state using modifications of the West Haven Criteria (29). The mental state was assessed in each patient by the same investigator using standardized tests and questions, as previously described (30). All patients also underwent the psychometric HE score (PHES) battery of tests, including the digit-symbol-test, the trail-making-test A and B, the serial-dotting-test, and the line-tracing-test. Each test was scored against age and education-adjusted norms for the Italian population. The PHES is the sum of integer scores of each test computed from the adjusted Z-values, as follows: score=−3 for $Z \leq -3$, score −2 for $-3 < Z \leq -2$, score −1 for $-2 < Z \leq -1$, score 0 for $-1 < Z < 1$, score 1 for $Z \geq 1$. The PHES ≤−4 was considered abnormal (30). Blood samples from a peripheral vein were collected in iced tubes for the determination of ammonia, which was performed immediately after using the Ammonia Checker II (Menarini, Florence, Italy), as previously described (31).

None of the patients received any pharmacological treatment to prevent the occurrence of HE. After TIPS, the patients remained hospitalized for 1 week and then were followed up once a week in the outpatient department for the first month. The patients were then seen every 3 months and also contacted by phone every month for the first 6 months. Thereafter, the patients were seen every 6 months. Moreover, both the patients and their families were instructed about the importance of an immediate contact with the medical staff should any alteration in their mental state occur between the scheduled visits. In particular, the family was instructed to refer the occurrence of lethargy, apathy, obvious personality changes, inappropriate behavior, or disorientation to time and space (corresponding to a grade-II alteration of the patients' mental state). In this case, the HE evaluation, including the psychometric performance, was repeated to confirm and stage the degree of HE. A grade II HE or higher was considered an episode of overt HE (23), and the patients were censored as HE+ patients. The occurrence of a recurrent HE (defined as at least three episodes of non precipitant-induced severe encephalopathy requiring hospitalization in the last 3 months despite continuous treatment with non-absorbable disaccharides) or a persistent HE (defined as the presence of a continuously detectable altered mental state with further episodic deterioration despite protein restriction and treatment with non-absorbable disaccharides) was also recorded, and the patients were considered affected by refractory HE. Those patients with an overt episode of HE were then managed either as in- or outpatients, depending on the severity of the HE episode. Once developed, HE was treated with the oral administration of non-absorbable disaccharides or non-absorbable antibiotics. All potential HE precipitating events were treated and, when possi-

ble, avoided. The patients' outcomes considered for the statistical analysis were the first episode of HE, liver transplantation (LT), and death.

Statistical analysis

The data are reported as mean±s.d. Comparisons between groups were performed by unpaired Student's *t*-test or χ^2-test. We estimated the cumulative incidence of the first episode of HE during the first 6 months of follow up, taking into account the nature of the competing risks in the data (HE before LT, death, and LT are competing events). As the study is estimating outcomes other than all-cause mortality, a method based on multistate disease models was selected. The usual Cox regression model in this context might be severely biased (32) and the sub-distribution model of Fine and Gray was selected. The conditional sub-distribution hazard at multivariate analysis was evaluated using the model of Fine and Gray (33). We therefore report on the sub-distribution hazard ratios (sHRs) rather than the usual HR, but the former have similar interpretations to the latter. The factors associated with the development of HE were initially evaluated by univariate models (using univariate Fine and Gray models) and then included in a multivariate analysis (according to multivariate Fine and Gray models). The final multivariate model was chosen in a forward manner by minimizing the Bayesian Information Criterion.

In order to build a score for the prediction of HE post TIPS, we built an event-history analysis model allowing for competing risks, therefore predicting the risk of the event. The maximum likelihood coefficients of the optimal model were used as weights for the new score. A time-dependent ROC curve (34) for censored data at 6 months of follow-up was estimated using the NN estimation method, whereas significance tests and confidence intervals were assessed through the non-parametric bootstrap. Sensitivity, specificity, positive predictive value, and negative predictive value were based on the estimated relative operating characteristic at 6 months. Software R version 3.0.2 (Stanford University, CA) was used for all computations.

RESULTS

The demographic, clinical, and biochemical characteristics of the patients are reported in **Table 1**.

During the whole follow-up, 35 of the 82 (43%) patients developed at least one episode of overt HE. In 3 of them, HE persisted and was refractory to standard treatment, needing the reduction in the stent calibre to ameliorate. This procedure was carried out 5, 6, and 8 months after TIPS and led to the resolution of HE symptoms in all patients. During the whole follow-up, 13 patients died and 5 were transplanted.

The comparison between the 35 patients with overt HE and the 47 patients who did not develop HE after a TIPS is reported in **Table 2**. At the time of the TIPS placement, there were no significant differences between the two groups in gender, etiology and severity of liver disease (Child–Pugh and model end-stage liver disease score) and most biochemical parameters. However, age (55 vs. 62 years) was significantly higher and serum sodium (138 vs. 135 mEq/ml) significantly lower in patients with post-TIPS HE. The porto-systemic gradient measured immediately after the shunt opening was 6.9±3.9 in the HE patient group and 5.9±3.2 in the patients who did not develop HE after a TIPS (NS). In the group of patients with HE after a TIPS, there was a higher prevalence of patients in whom TIPS was indicated because of refractory ascites, but the difference did not reach statistical significance (P=0.08). As far as the pre-TIPS evaluation of the patients' cognitive function is concerned, according to our exclusion criteria, no patients had signs of HE at inclusion and only a few of them (11 patients, 13%) experienced one episode of precipitated HE before a TIPS.

Table 1. Demographic and clinical characteristics of the patients included in the study

	Patients (n=82)
Sex (M/F)	57/25
Age (y)	57.9±10.1 (25–78)
Etiology (virus/alcohol/other)	34/29/19
MELD	11.4±3.3 (6–23)
Child–Pugh class (A/B/C)	17/53/12
Child–Pugh score	7.6±1.5 (5–11)
TIPS indication (bleeding/refractory ascites)	37/45
Previous HE (no/yes)	71/11
Covert HE (PHES ≤–4)(no/yes)	40/42
Bilirubin (mg/dl)	1.5±0.8 (0.5–4)
Albumin (g/dl)	3.3±0.5 (2.1–4.5)
INR	1.3±0.1 (0.9–1.9)
Sodium (mEq/l)	136.8±4.6 (124–145)
NH3 (microg/dl)	51.9±24.4 (10–146)
Gradient pre TIPS (mm Hg)	20.5±6.2 (11–41)
Gradient post TIPS (mm Hg)	6.3±3.5 (4–22)

F, female; HE, hepatic encephalopathy; INR, international normalized ratio; M, male; MELD, model end-stage liver disease; PHES, psychometric hepatic encephalopathy score; TIPS, transjugular intrahepatic portosystemic shunt; Y, years. Mean±s.d.

Seventy-seven percent of the patients with post-TIPS HE were classified as affected by covert HE before a TIPS according to the PHES evaluation. The corresponding figure in the group without HE was 32% and the difference was highly significant (P=0005). The cumulative incidence of HE after TIPS, taking into consideration LT and death as risks competing with HE development, is reported in **Figure 1**. The difference in the incidence of post-TIPS HE was highly significant (P=0.0003) among patients with or without covert HE detected by PHES before a TIPS. This difference, however, was at the limit of statistical significance, if only the 37 patients operated because of variceal bleeding are considered (58 vs. 28%; P=0.07), whereas it was highly significant in the 45 patients submitted to a TIPS because of refractory ascites (87 vs. 36%; P=0.0001). Moreover, all the 3 patients with refractory HE belonged to the group of ascitic patients.

Table 2. Demographic and clinical characteristics of the patients with or without HE after TIPS placement

	Post-TIPS hepatic encephalopathy		*P* value
	Absent (*n*=47)	Present (*n*=35)	
Sex (M/F)	32/15	25/10	NS
Age (y)	54.8±10.4 (25–77)	61.9±8.9 (45–78)	0.001
Etiology (virus/ alcohol/other)	20/17/10	14/12/9	NS
MELD	10.8±3.6 (6–23)	11.7 ±3.6 (6–18)	NS
Child–Pugh class (A/B/C)	13/29/5	4/24/7	NS
Child–Pugh score	7.4±1.4 (5–10)	7.9±1.5 (5–11)	NS
TIPS indication (bleeding/refractory ascites)	25/22	12/23	NS
Previous HE (no/yes)	43/4	28/7	NS
Covert HE (PHES ≤–4) (no/yes)	32/15	8/27	<0.0005
Bilirubin (mg/dl)	1.4±0.8 (0.5–3.8)	1.8±1.5 (0.5–4.5)	NS
Albumin (g/dl)	3.4±0.5 (2.1–4.3)	3.3±0.5 (2.2–4.5)	NS
INR	1.3±0.17 (1–1.9)	1.2±0.17 (0.9–1.6)	NS
Sodium (mEq/l)	138±4.3 (124–145)	135±4.9 (125–143)	0.009
NH3 (microg/dl)	51±27 (10–146)	53±20 (10–85)	NS
Gradient before	20.5±5.8 (11–36)	20.4±6.8 (11–41)	NS
Gradient after	5.9±3.2 (4–11)	6.9±3.9 (3–22)	NS

F, female; HE, hepatic encephalopathy; INR, international normalized ratio; M, male; MELD, model end-stage liver disease; NS, not significant; PHES, psychometric hepatic encephalopathy score; TIPS, transjugular intrahepatic portosystemic shunt; Y, years.
Mean±s.d.

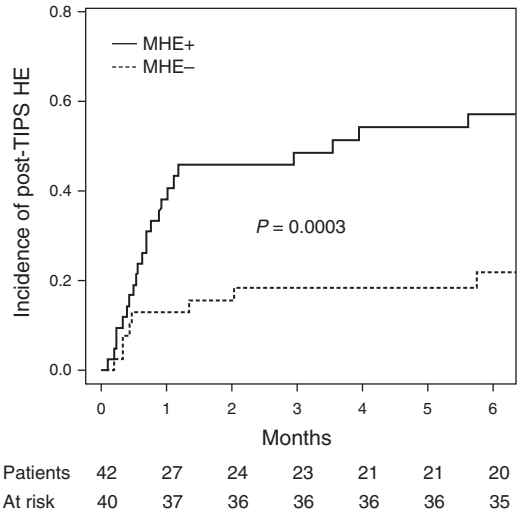

Figure 1. Cumulative incidence of HE post TIPS for patients with and without MHE, taking into account two additional competing risks: OLT and Death. HE, hepatic encephalopathy; MHE, minimal hepatic encephalopathy; OLT, orthotopic liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt.

Age, severity of liver disease (Child–Pugh/model end-stage liver disease), TIPS indication (varices/ascites), and covert HE were included in the Fine and Gray multivariate model analysis. Age: (sHR 1.05, CI 1.02–1.08, *P*=0.0022); Child–Pugh score: (sHR 1.29, CI 1.06–1.56, *P*=0.0110); and covert HE: (sHR 3.16 CI: 1.43–6.99 *P*=0.0045) were independently associated with post-TIPS HE development. On the basis of these results, a model was developed as follows: Age/10+Child–Pugh score+4.88 if covert HE is present with an AUC of 0.75. With a cutoff of 17, sensitivity was 0.77 (0.72–0.82), specificity 0.75 (0.70–0.80), PPV 0.64 (0.59–0.69), and NPV 0.83 (0.79–0.87). If age and the Child–Pugh score are excluded and only the presence of covert HE before a TIPS is considered, the corresponding values are sensitivity 0.74 (0.69–0.79), specificity 0.63 (0.58–0.68), PPV 0.55 (0.50–0.60), and NPV 0.80 (0.76–0.84). The NPV was 0.78 (0.71–0.85) in the group of patients submitted to TIPS to prevent variceal rebleeding and 0.88 (0.83–0.93) in patients operated on because of refractory ascites.

DISCUSSION

The identification of the risk factors for the development of HE after a TIPS is a relevant problem. In fact, post-TIPS HE is very frequent and, although in a minority of patients, it may be persistent and refractory to medical treatment, thus affecting deeply the patients' quality of life. The problem is, in our opinion, particularly relevant in patients submitted to a TIPS because of refractory ascites. In fact, at variance with the TIPS performed for the prevention of variceal rebleeding, which can be life saving and without therapeutic alternatives, a patient with refractory ascites may be treated with a TIPS or repeated large volume paracentesis with a fairly similar efficacy at least in terms of survival. The lack of preventive measures, whether pharmacological or based on the optimization of the porto-systemic gradient reached after the procedure, makes the optimal selection of patients particularly crucial. Previous HE with the exception of that precipitated by variceal bleeding, especially if recidivant, aging and advanced liver failure are the most robust risk factors for post-TIPS HE (35), and today most protocols and clinical studies consider the presence of these factors as a contraindication to TIPS. Nevertheless, the incidence of post-TIPS HE continues to be regrettably high, suggesting that other factors may be important.

The working hypothesis of the present paper was that the subclinical cognitive impairment, also known as covert HE, may be a predictive factor for overt HE development after a TIPS. This hypothesis is supported by the fact that covert HE is one of the strongest predictors of the occurrence of overt HE in the follow-up in cirrhotic

patients (24) and by the observation that trail-making-test A, one of the tests included in the PHES, the standard for the identification of patients affected by covert HE, as well as the critical flicker frequency, was significantly correlated with post-TIPS HE at least at univariate analysis. Our results support the hypothesis, as the incidence of post-TIPS HE was significantly different among patients with or without covert HE before a TIPS. Our results are particularly solid because they were obtained in a group of patients already selected for TIPS on the basis of the known risk factors for HE development (see inclusion criteria). Moreover, post-TIPS HE was detected using the PHES, which is considered the standard method (23), and statistically analyzed taking into consideration the risks competing with HE during the patients' follow-up (32), such as death and LT. Finally, at variance with previous observations, covert HE before a TIPS was a predictor independently of a number of clinical and laboratory variables, age and the Child–Pugh score at the multivariate analysis. The model derived from the results (including age, Child–Pugh score, and covert HE) showed a fairly good sensitivity and specificity in identifying patients with overt HE after a TIPS. On the basis of the above results, we tried to calculate the possible applicability of the detection of covert HE before a TIPS as a criterion for the selection of patients. If only the results of the PHES evaluation (i.e., not considering age and Child–Pugh score) are taken into consideration, the negative predicting value was 0.80 for all patients and 0.88 for the patients submitted to TIPS because of refractory ascites. This means that a patient with refractory ascites, without covert HE according to PHES before a TIPS, has almost 90% probability of being free of HE after a TIPS. In our opinion, this observation may help choose the use of TIPS in patients particularly susceptible to severe HE and with treatment alternatives.

A limitation of the present observation is inherent to the use of the PHES, which is based on 5 paper and pencil psychometric tests and on *Z*-scores obtained in a reference population that are available only in Germany, Italy, Spain, India, and Korea. Another limitation of our study is that we were not able to identify the risk factors for refractory HE, which is the most relevant problem in these patients. This was due to the fact that, fortunately, only 3 patients developed this complication during the follow-up, limiting the possibility to analyze these data statistically.

In conclusion, the psychometric evaluation before a TIPS is able to identify most of the patients who will develop HE after a TIPS and can be useful to select patients in order to have the lowest incidence of this important complication.

CONFLICT OF INTEREST

Guarantor of the article: Oliviero Riggio, MD.

Specific author contributions: Silvia Nardelli: acquisition of data, analysis and interpretation of data; manuscript preparation; Stefania Gioia, Chiara Pasquale, Ilaria Pentassuglio, Leandra Nikolli, Valeria Nicoletti, Francesca Greco, and Sabrina Torrisi: acquisition of data; Manuela Merli: critical discussion and support, manuscript revision of the manuscript for important intellectual content; Filippo Maria Salvatori: TIPS placement, acquisition of data; Alessio Farcomeni: statistical analysis and interpretation of data; manuscript preparation; Oliviero Riggio: study concept and design, analysis and interpretation of data; manuscript preparation; final drafting of the manuscript; study supervision.

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LIVER

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