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Shunt magnitude is a key determinant of overt hepatic encephalopathy in patients undergoing TIPS

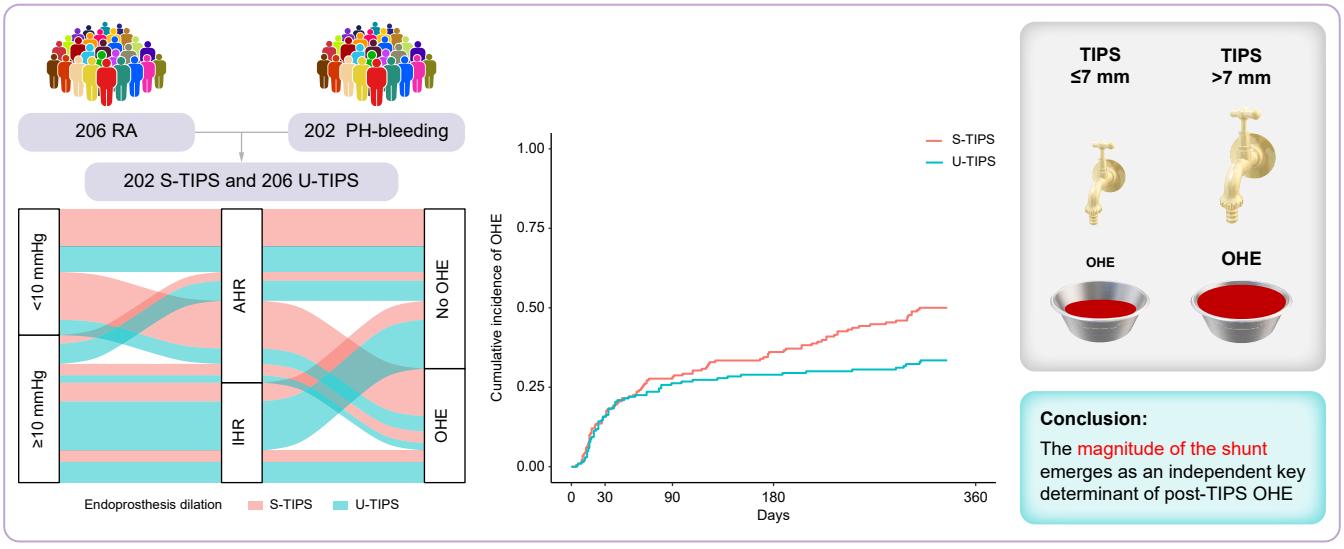
Authors

Davide Roccarina, Dario Saltini, Marco Senzolo, …, Sara Montagnese, Filippo Schepis, Francesco Vizzutti[1†]

Correspondence

francesco.vizzutti@unifi.it (F. Vizzutti).

Graphical abstract



Highlights:

- TIPS carries a significant risk of overt hepatic encephalopathy.
- Low portosystemic pressure gradient and larger shunt diameter have been reported to increase the risk of overt hepatic encephalopathy.
- TIPS under-dilation reduces overt hepatic encephalopathy occurrence while effectively controlling portal hypertension complications even without meeting established hemodynamic targets.
- Thus, the TIPS dilation diameter represents an independent key determinant of post-TIPS overt hepatic encephalopathy.

Impact and implications:

TIPS carries a significant risk of overt hepatic encephalopathy. Low portosystemic pressure gradient and larger shunt diameter have been reported to increase the risk of overt hepatic encephalopathy. The TIPS dilation diameter represents an independent key determinant of post-TIPS overt hepatic encephalopathy. Thus, TIPS under-dilation reduces overt hepatic encephalopathy occurrence while effectively controlling portal hypertension complications even without meeting established hemodynamic targets.

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Research article

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Shunt magnitude is a key determinant of overt hepatic encephalopathy in patients undergoing TIPS

Davide Roccarina[1,2], Dario Saltini[3], Marco Senzolo[4], Silvia Nardelli[5], Martina Rosi[1], Valentina Adotti[1], Marcello Bianchini[3], Lara Biribin[4], Stefania Gioia[5], Cristian Caporali[6], Lucia Ragozzino[1], Tomas Guasconi[3], Margherita Falcini[1], Federico Casari[6], Antonio Piscopo[3], Francesco Pindozzi[1], Stefano Gitto[1], Silvia Aspite[1], Gianmarco Falcone[7], Angelica Ingravallo[1], Melania Gaggini[8], Kymentie Ferdinande[4], Umberto Arena[1], Manuela Merli[9], Lorenzo Ridola[10], Oliviero Riggio[5], Fabrizio Fanelli[7], Chiara Mangini[11], Fabio Marra[1], Sara Montagnese[11], Filippo Schepis[3,†], Francesco Vizzutti[1,12,†,*]

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Background & Aims: Under-dilated transjugular intrahepatic portosystemic shunts (U-TIPS) has been proposed to reduce the risk of overt hepatic encephalopathy (OHE) while effectively treating portal hypertension (PH) complications. In this study we assessed how end-procedural porto-caval pressure gradient (PCPG), obtained in sedated patients, and endoprosthesis dilation affect the risk of OHE after TIPS.

Methods: Consecutive patients with cirrhosis receiving TIPS for refractory ascites or recurrent PH-related bleeding were enrolled. OHE within 1-year was analyzed using a competing risk model, accounting for death and liver transplantation. Adequate hemodynamic response (AHR) was defined as post-TIPS PCPG <12 mmHg or reduction ≥60% in refractory ascites, and <12 mmHg or reduction ≥50% in PH-related bleeding. PCPG values outside of the above criteria were considered as inadequate response. U-TIPS was defined as endoprosthesis dilation ≤7 mm, as opposed to standard TIPS (S-TIPS).

Results: Among 408 patients enrolled, 50% received U-TIPS, 63% achieved AHR, and 46% had a PCPG <10 mmHg. One-year cumulative incidence of OHE was 33% and 50% in U-TIPS and S-TIPS, respectively (p <0.001). In the univariable analysis, both AHR and PCPG <10 mmHg, and S-TIPS were associated with higher cumulative incidence of OHE. In a model comprising age, previous history of OHE, TIPS indication, liver disease severity and endoprosthesis dilation, only S-TIPS along with older age, previous history of OHE and Child-Pugh class B and C, were statistically significantly associated with OHE.
Subgroup analysis stratified by U-TIPS *vs.* S-TIPS confirmed that AHR and PCPG <10 mmHg were not associated with OHE within either TIPS group.

Conclusions: The magnitude of the shunt emerges as an independent key determinant of post-TIPS OHE.

Introduction

The transjugular intrahepatic portosystemic shunt (TIPS) is an effective procedure for the management of complications of cirrhotic portal hypertension (PH), enhancing survival in patients with both PH-related bleeding and refractory ascites (RA).[1–5] Yet, the procedure is associated with a high incidence of post-TIPS overt hepatic encephalopathy (OHE).[6,7] The pathogenesis of post-TIPS OHE involves multiple factors, with a significant contribution attributed to a reduction of the porto-caval pressure gradient (PCPG).[6–8] Furthermore, the extent of portosystemic shunt significantly contributes to the development of this complication.[9–11] Indeed, under-dilation of endoprostheses to a diameter of ≤7 mm has shown to reduce the incidence of post-TIPS OHE, while still effectively controlling portal hypertension-related complications,[11] independently of the achievement of the hemodynamic targets currently recommended by the guidance.[12]

To disentangle the impact of endoprosthesis diameter from the reduction of PCPG, we evaluated the role of end-procedural PCPG in the development of OHE among patients who received under-dilated TIPS (U-TIPS) and standard TIPS (S-TIPS). Our findings confirm a significantly lower cumulative incidence of OHE in patients receiving U-TIPS, independently of the achievement of guidance-recommended hemodynamic targets obtained at the end of TIPS in sedated patients,[13–19] and further support the TIPS under-dilation approach.

Patients and methods

We conducted a multicenter retrospective study to evaluate OHE incidence according to immediate post-TIPS PCPG

* Corresponding author. Address: Portal Hypertension Departmental Unit, Department of Experimental and Clinical Medicine, University of Florence, Viale Morgagni 85, Florence, I-50134, Italy.
E-mail address: francesco.vizzutti@unifi.it (F. Vizzutti).
† Shared senior authorship.
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values in patients with cirrhosis treated with S- or U-TIPS. The cohort was identified from the Italian TIPS registry (RI-TIPS) and included patients who received TIPS for RA or secondary prophylaxis of PH-related bleeding between October 2010 and October 2022 at four Italian tertiary centers (Florence, Modena, Padua, and Rome) with expertise in TIPS and hepatic hemodynamic measurements. The RI-TIPS database complies with the principles reported in the Declaration of Helsinki and Istanbul and it was approved by Ethics Committee of all participating centers. All patients provided written informed consent for recording their data at the time of TIPS.

U-TIPS was defined as endoprosthesis balloon dilation ≤7 mm within the intraparenchymal tract of the endoprosthesis, involving both hepatic and portal vein walls. All other cases were classified as S-TIPS. Initially introduced to reduce OHE, in our centers U-TIPS has become the standard of care for both indications well before the introduction of controlled-expansion devices.[11] During the study period, patients were treated with the first-generation VIATORR endoprosthesis (Gore, Flagstaff, AZ, USA) until 2018, followed by new generation endoprostheses.

Inclusion criteria were: (a) cirrhosis of any etiology based on clinical, histological, or imaging findings; (b) TIPS placed for RA or prevention of recurrent PH-related bleeding. Exclusion criteria included: (a) preemptive, salvage, or rescue TIPS for acute variceal bleeding; (b) grade 2–3 acute-on-chronic liver failure; (c) non-cirrhotic portal hypertension; (d) hepatocellular carcinoma beyond Milan criteria; (e) contraindications to TIPS as per RI-TIPS protocol such as severe liver failure (Child-Pugh >11, serum bilirubin >5 mg/dl, model for end-stage liver disease [MELD] >18), severe organic renal failure (serum creatinine >3 mg/dl), heart failure, moderate/severe pre- or post-capillary pulmonary hypertension (mean pulmonary artery pressure >35 mmHg at right heart catheterization), recurrent or persistent OHE despite adequate treatment, and uncontrolled sepsis; (f) active alcohol use per addiction center criteria; (g) loss to 1-year follow-up, unless liver transplant (LT) or death occurred.

Before TIPS, patients were treated with nonselective beta-blockers according to international guidelines.[13] The PCPG was measured upon portal vein access and again at the end of the procedure, in accordance with both Italian[14] and international guidelines.[13] All TIPS including hemodynamic measurements were performed under deep sedation using remifentanil and midazolam.

In agreement with the commonly adopted threshold,[13,15–22] in patients treated for secondary prophylaxis of PH-related bleeding, an adequate hemodynamic response (AHR) was defined as a post-TIPS PCPG <12 mmHg or a PCPG reduction of at least 50% from the basal value, while in patients with RA, AHR was defined as a post-TIPS PCPG <12 mmHg or a PCPG reduction of at least 60% from the basal value. When the above hemodynamic targets were not met, the hemodynamic outcome was deemed inadequate (inadequate hemodynamic response [IHR]). All hemodynamic values refer to those obtained at the end of the procedure.

Patients were followed according to the RI-TIPS protocol, with visits scheduled at 1, 3, and 6 months post-TIPS, then every 6 months or as clinically indicated, until death or LT. At each visit, the same medical team assessed all patients for OHE, defined as grade II or higher on the West-Haven scale. Only patients who developed post-TIPS OHE started on pharmacological prophylaxis according to international guidance.[23] Based on the RI-TIPS protocol, no patients received primary prophylaxis for OHE before or after TIPS.

Follow-up included physical exams and laboratory tests. Patients and their caregivers were thoroughly educated on the early recognition of OHE with clear guidance to promptly notify the medical team and proceed with hospitalization upon confirmation of OHE.

Doppler ultrasound was performed at 2 weeks, 3 months and 6 months post-TIPS, and every 6 months thereafter, or earlier if PH complications arose.

Data were collected at the moment of TIPS using a standardized, anonymized Excel™-based form (Microsoft, Redmond, WA, USA) shared among centers. Collected variables included demographics, cirrhosis etiology, OHE history, labs (bilirubin, albumin, creatinine, sodium, international normalized ratio [INR], platelets), Child-Pugh class, MELD score, ongoing pharmacological treatments, TIPS indication, PCPG values (pre- and post-TIPS), and dilation diameter.

This investigation builds upon findings from our recent publication,[12] where patients who achieved an IHR showed a lower occurrence of OHE. Notably, this group also had a significantly higher proportion of patients with a U-TIPS, potentially confounding the relationship between PCPG reduction, endoprosthesis dilation and OHE development. Therefore, the aim of the study was to assess whether the cumulative incidence of OHE within the first year after TIPS was associated with the degree of end-procedural PCPG reduction (AHR *vs.* IHR) in patients receiving U-TIPS or S-TIPS. In addition, we also considered post-TIPS PCPG values lower or higher than 10 mmHg based on previous data suggesting that values below this threshold may significantly increase the risk of developing OHE.[6–8]

Statistical analysis

Descriptive statistics were used to summarize the study population's demographics. Quantitative variables were reported as medians and IQRs, while qualitative variables were summarized as counts and percentages. Group comparisons for quantitative variables were performed using the Wilcoxon rank sum test or Kruskal–Wallis test; qualitative variables were compared using X^2 or Fisher's exact test, as appropriate.

To assess the association between hemodynamic targets (AHR *vs.* IHR; PCPG <10 mmHg vs. ≥10 mmHg), S-TIPS and the 1-year risk of OHE post-TIPS, a two-step analysis was used. First, a binary logistic regression analysis was performed to explore predictors of OHE as an initial screening regardless of the time of occurrence. This included univariable analyses followed by a multivariable model if hemodynamic targets were found to be significantly associated with OHE. Variables for multivariable model were selected based on literature, clinical relevance, and univariable analysis (p <0.1), ensuring a covariate-to-event ratio ≤1:10 to prevent overfitting. Only baseline variables available at the time of TIPS were included. To avoid multicollinearity, candidate variables were assessed for collinearity using the variance inflation factor (VIF), with a conservative threshold of <2 considered acceptable. In case of

collinearity (VIF ≥2), the variable deemed less clinically informative was excluded from the final model. In cases where two collinear variables were both deemed clinically relevant, they were tested in separate models, and the version with the best model fit (based on the lowest Akaike Information Criterion [AIC]) was retained. In addition, to further confirm the stability and robustness of variables selected in the final model, a Ridge penalized logistic regression was performed, which shrinks coefficients without excluding variables.

Subsequently, to obtain a more realistic assessment of the cumulative incidence of the event of interest, a time-to-event analysis was carried out using a multivariable competing risks model based on Fine and Gray's method,[24] including the covariates assessed in the logistic regression and accounting for death and LT as competing events.

Cumulative incidence function curves were plotted for categorical variables significantly associated with OHE, and group differences tested using Gray's test. Time-to-event analyses were conducted in the overall cohort and in subgroups stratified by endoprosthesis dilatation.

All analyses were performed in R (v4.2.2, R Foundation for Statistical Computing, Vienna, Austria) using gtsummary, dplyr, and tidycmprsk packages. Two-sided p values <0.05 were considered significant.

Results

A total of 408 patients with cirrhosis undergoing TIPS for either RA (206, 50%) or failure of secondary prophylaxis for PH-related bleeding (202, 50%) were included. Baseline characteristics for the overall cohort and comparisons across different hemodynamic targets, AHR *vs.* IHR, and post-TIPS PCPG <10 mmHg *vs.* ≥10 mmHg, are summarized in Table 1.

Overall, 188 patients (46%) achieved a post-TIPS PCPG <10 mmHg. An AHR was observed in 259 patients (63%). Half of the patients (206, 50%) received a U-TIPS. Sixty-nine (17%) patients had at least one previous episode of non-recurrent OHE (triggered 15% and non-triggered 2%), after which a treatment with only non-absorbable disaccharides was started. Pre-TIPS OHE was well balanced across the evaluated subgroups (no significant differences, Tables 1 and 2). During the first year following TIPS, 47 patients (12%) died and five (1%) underwent LT. A total of 170 patients (42%) experienced at least one episode of OHE, with 108 (64%) having their first episode within the first 3 months. The median time to the first OHE episode was 46 days (IQR: 19–176). Liver function remained stable during the first year after TIPS, as indicated by stable MELD scores at 1, 3, 6, and 12 months (data not shown).

As illustrated by the alluvial plot (Fig. 1), which maps the transition of patients with different endoprosthesis dilations from post-TIPS pressure gradient and hemodynamic response to the occurrence of OHE, patients who developed OHE within the first year, compared with those who did not, were significantly more likely to have achieved an AHR (72% *vs.* 58%, p = 0.004), to have reached a post-TIPS PCPG <10 mmHg (55% *vs.* 39%, p = 0.002), and to have received a S-TIPS (63% *vs.* 41%, p <0.001).

In the univariable binary logistic regression, both AHR and PCPG <10 mmHg, and S-TIPS were significantly associated with an increased risk of OHE, along with age, previous history of OHE and liver disease severity as defined by Child-Pugh class B and C. Because of the significant correlation observed among AHR, PCPG <10 mmHg, and S-TIPS, we assessed their potential multicollinearity using VIFs. Moderate collinearity was detected only for AHR and PCPG <10 mmHg, as indicated by VIF values between 2 and 5. To address this, two alternative multivariable models were built: one including AHR (AIC = 519.4) and another including PCPG <10 mmHg (AIC = 520.8). In both models, all VIF values were <2. Given the lower AIC, the model including AHR was selected.

In this multivariable model, adjusted for sex, age, endoprosthesis dilation, previous history of OHE, indication for TIPS and liver disease severity as defined by Child-Pugh class, AHR was not statistically significantly associated with OHE. Predictors of OHE were S-TIPS (OR 2.20, 95% CI 1.42–3.42, p <0.001) along with older age (OR 1.02, 95% CI 1.01–1.05, p = 0.035), Child-Pugh class C (OR 3.44, 95% CI 1.41–8.80, p = 0.008) and previous history of OHE (OR 2.50, 95% CI 1.39–4.50, p = 0.002).

To further assess the potential impact of multicollinearity between covariates included in the chosen multivariable model, we also performed a Ridge logistic regression including the same covariates as in the standard model. The penalized regression coefficients were consistent with those obtained from the standard logistic regression. In particular, both S-TIPS and AHR retained non-zero coefficients after penalization (0.57 and 0.36, respectively), confirming that multicollinearity did not meaningfully distort their individual associations with the outcome. Replacing AHR with PCPG <10 mmHg in the multivariable model yielded similar results. These findings were further confirmed by time to OHE analysis accounting for LT and death as competing events. The cumulative incidence of OHE 1 year after TIPS was significantly higher in patients who achieved an AHR compared to IHR (45% *vs.* 35%, respectively, Gray's test = 0.013) and those with a post-TIPS PCPG <10 mmHg compared with ≥10 mmHg (49% *vs.* 35%, respectively, Gray's test = 0.002), and in patients who received S-TIPS compared to U-TIPS. In the multivariable model adjusted for sex, age, endoprosthesis dilation, previous history of OHE, indication for TIPS and basal Child-Pugh class, AHR and PCPG <10 mmHg, included in two separated models, were not statistically significantly associated with OHE. Predictors of a higher cumulative incidence of OHE were S-TIPS along with older age, Child-Pugh class B and C, and previous history of OHE (Table 3). The cumulative incidence of OHE progressively increased over time across endoprosthesis dilation groups. At 12 months, patients with S-TIPS had a significantly higher incidence of OHE compared to those with U-TIPS (50% *vs.* 33%, Gray's test p <0.001) (Fig. 2).

In subgroup analyses, the lack of association between hemodynamic targets and OHE risk persisted when patients were stratified by S-TIPS *vs.* U-TIPS. The two groups were well matched for age and liver disease severity (Table 2). Within both S-TIPS and U-TIPS groups, the cumulative incidence of OHE did not significantly differ between patients with AHR *vs.* IHR, or between those with post-TIPS PCPG <10 mmHg *vs.* ≥10 mmHg (Table 4).

Subgroup analyses by endoprosthesis generation did not change the overall findings (data not shown).

No statistically significant differences emerged between the two subgroups stratified by endoprosthesis dilation regarding

Table 1. Baseline demographic, clinical-laboratory and hemodynamic characteristics of the overall population and of the groups according to the end-procedural hemodynamics targets.

Variable	Overall N = 408 Median (IQR) or number (%)	Adequate hemodynamic response (n = 259) Median (IQR) or number (%)	Inadequate hemodynamic response n = 144 Median (IQR) or number (%)	*p* value*	PCPG <10 mmHg n = 220 Median (IQR) or number (%)	PCPG ≥10 mmHg n = 180 Median (IQR) or number (%)	*p* value*
Sex				**0.093**			**0.020**
Female	292 (72)	178 (69)	114 (77)		168 (76)	124 (66)	
Male	116 (28)	81 (31)	35 (23)		52 (24)	64 (34)	
Age (years)	60 (54–69)	62 (54–70)	59 (53–68)	0.084	59 (52–68)	62 (55–70)	**0.007**
Etiology				0.477			0.945
Alcohol	138 (34)	88 (33)	50 (34)		73 (33)	65 (35)	
MASLD	76 (19)	47 (17)	31 (21)		43 (20)	33 (18)	
Other	54 (13)	39 (15)	15 (10)		28 (13)	26 (14)	
Viral	140 (34)	87 (34)	53 (36)		76 (35)	64 (34)	
BMI (kg/m^2)	25.0 (22.6–28.3)	24.7 (22.5–28.1)	25.4 (22.8–28.6)	0.287	25.0 (22.4–28.3)	24.8 (22.8–28.3)	0.887
Indication to TIPS				**0.164**			0.116
Refractory ascites	206 (50)	124 (48)	82 (55)		119 (54)	87 (46)	
Variceal bleeding	202 (50)	135 (52)	67 (45)		101 (46)	101 (54)	
OHE last year, n (%)	69 (17)	44 (17)	27 (18)	0.676	32 (17)	34 (18%)	0.673
Albumin (g/dl)	3.3 (2.9–3.7)	3.3 (2.9–3.6)	3.3 (2.9–3.8)	0.325	3.3 (2.9–3.7)	3.3 (3.0–3.6)	0.700
Total bilirubin (mg/dl)	1.20 (0.80–1.80)	1.30 (0.80–1.89)	1.10 (0.77–1.56)	0.067	1.2 (0.80–1.68)	1.24 (0.80–1.80)	0.399
INR	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	0.152	1.3 (1.2–1.4)	1.2 (1.2–1.4)	**0.02**
Creatinine (mg/dl)	0.95 (0.72–1.29)	0.94 (0.71–1.24)	0.96 (0.75–1.33)	0.570	0.95 (0.72–1.31)	0.94 (0.73–1.23)	0.626
Na (mEq/L)	138 (134–140)	138 (134–140)	137 (134–140)	0.697	138 (134–140)	138 (134–140)	0.551
Child-Pugh class before TIPS				0.714			0.846
A	114 (28)	70 (27)	46 (31)		66 (30)	53 (28)	
B	265 (65)	168 (65)	94 (63)		141 (64)	122 (65)	
C	29 (7)	21 (8)	9 (6)		13 (6)	13 (7)	
MELD before TIPS	12 (10–14)	11 (10–14)	12 (10–14)	0.535	12 (10–14)	11 (9–14)	0.087
Endoprosthesis dilatation (mm)	7.0 (6.0–8.0)	8.0 (6.0–10.0)	6.0 (6.0–8.0)	**<0.001**	6.0 (6.0–8.0)	8.0 (6.0–10.0)	**<0.001**
Endoprosthesis dilation				**<0.001**			**<0.001**
S-TIPS	205 (50)	157 (61)	45 (30)		75 (34%)	127 (68%)	
U-TIPS	206 (50)	102 (39)	104 (70)		145 (66%)	61 (32%)	
PCPG before TIPS (mmHg)	21.5 (19.0–25.3)	20.0 (17.5–23.8)	23.4 (21.5–27.0)	**<0.001**	23.0 (20.3–26.5)	19.0 (16.3–23.0)	**<0.001**
PCPG after TIPS (mmHg)	10.0 (7.0–14.0)	8.0 (6.0–10.0)	15.0 (13.0–16.0)	**<0.001**	13.1 (11.0–16.0)	7.0 (5.0–8.0)	**<0.001**
PCPG reduction (mmHg)	10.6 (8.0–15.0)	12.0 (9.0–16.0)	9 (6.0–11.0)	**<0.001**	9.0 (7.0–12.3)	13.0 (10.0–16.4)	**<0.001**
PCPG reduction (%)	50.0 (38.9–64.3)	60.7 (50.7–69.6)	36.8 (29.4–44.0)	**<0.001**	41.9 (31.6–47.6)	65.0 (56.7–75.0)	**<0.001**

Adequate hemodynamic response is defined as post-TIPS PCPG <12 mmHg or PCPG reduction ≥50% for bleeding secondary prophylaxis, and post-TIPS PCPG <12 mmHg for refractory ascites. If these criteria are not met, the hemodynamic response is defined inadequate. U-TIPS is defined as endoprosthesis dilatation ≤7 mm while S-TIPS is defined as endoprosthesis dilation >7 mm. Values in bold denote statistical significance. INR, international normalized ratio; MASLD, metabolic-dysfunction associated steatotic liver disease; MELD, model of end-stage liver disease; Na, sodium; OHE, overt hepatic encephalopathy; PCPG, porto-caval pressure gradient; S-TIPS, standard TIPS; TIPS, transjugular intrahepatic portosystemic shunt; U-TIPS, under-dilated TIPS. *Pearson's X^2 test; Wilcoxon rank sum test; Fisher's exact test.

the need for endoprosthesis diameter reduction or occlusion to control OHE. This intervention was required in only one and two patients treated with U-TIPS and S-TIPS, respectively.

Discussion

The efficacy of TIPS in controlling the complications of cirrhotic PH and improving survival suggests that an increasing number of patients will be candidates for, and benefit from, TIPS.[1–5] However, changes in portal pressure and in the amount of portal blood shunted following TIPS can negatively impact clinical outcomes in cirrhotic patients. Indeed, this procedure currently has two main drawbacks, the occurrence of OHE[6,7] and the development of heart failure.[25–27]

OHE is well known to complicate the clinical course of patients with cirrhosis undergoing TIPS, with incidence rates reported as high as 50%.[6,7] Although data on the prognostic impact of this complication, particularly with regard to episodic events, remain controversial,[28–30] the development of OHE clearly impairs patients' and caregivers' quality of life, increases hospitalization rates, and adds costs to the health-care system.[31]

TIPS endoprostheses with larger diameters, as well as spontaneous portosystemic shunts (SPSSs) with greater total cross-sectional area[32] or SPSS equivalent diameter,[33] are associated with a higher degree of portosystemic shunting and consequently an increased risk of OHE.[34–36] Moreover, the volume of blood flow through the TIPS has been shown to positively correlate with the development of OHE,[9,10] and the extent of portosystemic shunting has emerged as the main determinant of the risk of post-TIPS OHE in a cohort of patients with cirrhosis without severe impairment of hepatocellular function.[9] Furthermore, embolization of SPSS has been shown to reduce the recurrence rate of OHE.[37] The relationship between PCPG values and the development of OHE is also well established. Indeed, lower post-TIPS PCPG values were associated with higher rates of OHE.[6,8,38]

To reduce the incidence of post-TIPS OHE, under-dilation of the endoprosthesis at the intraparenchymal tract has been proposed.[11] This strategy has proven to be effective in

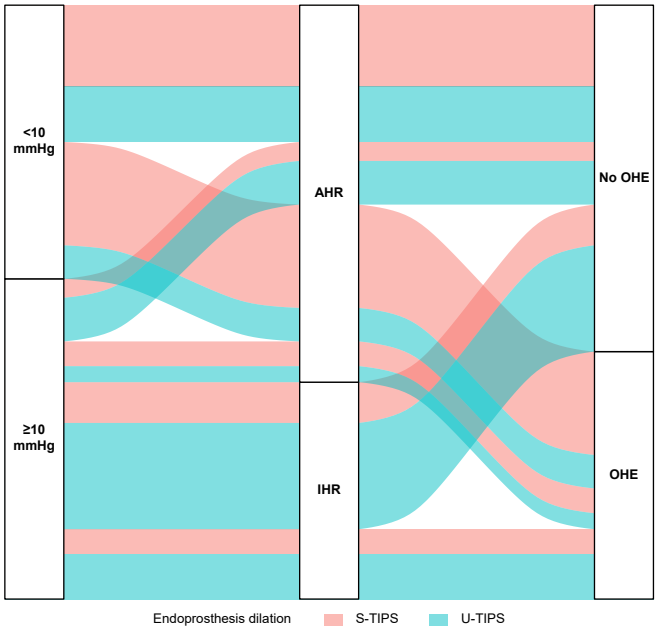
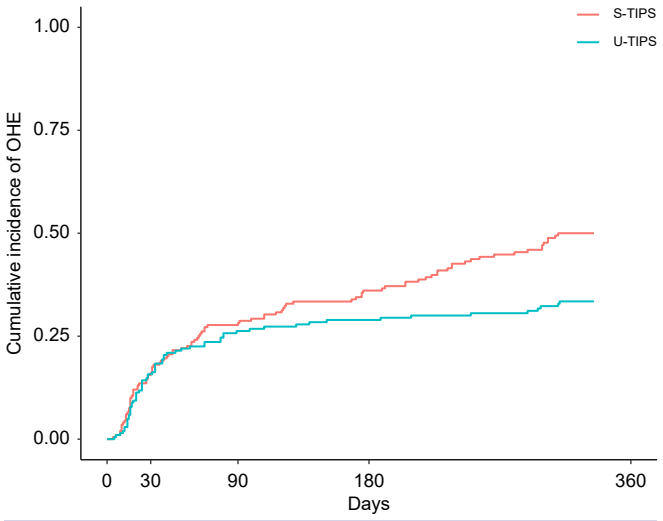


Fig. 1. An alluvial plot illustrating the flow of patients with different endoprosthesis dilation (U-TIPS and S-TIPS) across post-TIPS PCPG values (PCPG <10 mmHg and PCPG ≥10 mmHg), hemodynamic response (AHR and IHR) and OHE occurrence. AHR is defined as post-TIPS PCPG <12 mmHg or PCPG reduction ≥50% for bleeding secondary prophylaxis indication, and post-TIPS PCPG <12 mmHg or PCPG reduction ≥60% for refractory ascites. If these criteria are not met, the hemodynamic response is defined inadequate (IHR). U-TIPS is defined as endoprosthesis dilatation ≤7 mm while S-TIPS is defined as endoprosthesis dilation >7 mm. AHR, adequate hemodynamic response; IHR, inadequate hemodynamic response; OHE, overt hepatic encephalopathy; PCPG, porto-caval pressure gradient; S-TIPS, standard TIPS; U-TIPS, under-dilated TIPS.



S-TIPS					
At risk	202	168	141	120	86
Events	0	32	56	71	96
U-TIPS					
At risk	206	171	138	132	109
Events	0	32	52	57	65

Fig. 2. Overall cumulative incidence of OHE, in the presence of liver transplant and death considered as competing events, in the first year after TIPS in patients with U-TIPS *vs.* S-TIPS endoprosthesis. U-TIPS is defined as endoprosthesis dilatation ≤7 mm while S-TIPS is defined as endoprosthesis dilation >7 mm. OHE, overt hepatic encephalopathy; S-TIPS, standard TIPS; TIPS, transjugular portosystemic shunt; U-TIPS, under-dilated TIPS.

containing the incidence of OHE while maintaining efficacy in controlling PH complications.[11,12,35,39,40]

It has also been demonstrated that U-TIPS independently predicts a lower rate of post-TIPS OHE suggesting that lower endoprosthesis diameter may protect from OHE by mechanism other than PCPG degree of reduction.[11] Recently, we have demonstrated that failure to achieve post-TIPS recommended hemodynamic targets does not affect control of PH-related complications or patient survival, while an IHR reduces the incidence of post-TIPS OHE independently of TIPS indication. Moreover, IHR was more prevalent among individuals with U-TIPS[12] thereby introducing a potential bias in assessing the relationship between the degree of PCPG reduction, endoprosthesis diameter and OHE occurrence.

In the present study, we provide evidence that the dilation of the endoprosthesis predicts the risk of developing OHE independently of end-procedural PCPG obtained in sedated patients. In line with previous studies,[6,7] advanced age, Child-Pugh class B and C, previous history of OHE and S-TIPS, were independently associated to an increased cumulative incidence of OHE in our cohort. Importantly, the distribution of pre-TIPS OHE across the considered subpopulations was well balanced. Indeed, the cumulative incidence of OHE was confirmed significantly lower in patients with U-TIPS. Remarkably, a sub-analysis in patients stratified by S-TIPS and U-TIPS did not show significant differences in the cumulative incidence of OHE regardless of whether an end-procedural AHR or PCPG ≤10 mmHg were achieved. These findings indicate that when patients are analyzed according to the TIPS dilation diameter, the magnitude of the shunt emerges as a major determinant of OHE.

The relationship between the hemodynamic outcome of TIPS and post-TIPS clinical events, though defined by literature data burdened by objective limitations,[41–43] influences the need to pursue a very narrow range of PCPG values to ensure effectiveness in controlling PH complications and reducing the incidence of OHE. Therefore, this makes the relationship between post-TIPS PCPG and subsequent clinical events a challenge and the U-TIPS approach may facilitate it. The data presented herein further support a pragmatic approach that does not focus, primarily in patients treated for RA,[18] on achieving specific PCPG values to predict the outcome of TIPS but it is aimed to control the complications of cirrhotic PH and to limit the incidence of OHE simply through the implantation of U-TIPS. Indeed, in our cohort, end-procedural PCPG values measured in sedated patients did not allow the identification of those at higher risk of developing OHE, regardless of whether a S-TIPS or U-TIPS was implanted.

However, data from the present study are not sufficiently robust to support the same approach in the secondary prevention of PH-related bleeding. Furthermore, in the individual patient, other factors, beyond endoprosthesis dilation and post-TIPS PCPG, could be hypothesized to influence TIPS outcome and the incidence of OHE, primarily including the impact on systemic hemodynamics. The weight of additional factors such as comorbidities, sarcopenia, frailty, systemic inflammatory status, and intestinal microbiota should also be taken into account, possibly using, in the future, innovative

Table 2. Baseline demographic, clinical, laboratory, and hemodynamic characteristics of the groups according to the endoprosthesis dilation.

Variable	S-TIPS n = 202 Median (IQR) or number (%)	U-TIPS n = 206 Median (IQR) or number (%)	*p* value*
Sex			0.316
Female	140 (69)	154 (74)	
Male	63 (31)	54 (26)	
Age (years)	60 (54–68)	62 (54–70)	0.093
Etiology			**0.006**
Alcohol	83 (41)	55 (27)	
MASLD	27 (13)	49 (24)	
Other	25 (12)	29 (14)	
Viral	67 (33)	73 (35)	
BMI (kg/m^2)	24.7 (22.8–27.9)	25.1 (22.5–28.4)	0.659
Indication to TIPS			0.998
Refractory ascites	102 (50)	104 (50)	
Variceal bleeding	100 (50)	102 (50)	
OHE prior to TIPS	34 (17%)	37 (18%)	0.900
Albumin (g/dl)	3.3 (3.0–3.6)	3.3 (2.9–3.8)	0.249
Total bilirubin (mg/dl)	1.20 (0.80–1.80)	1.20 (0.80–1.80)	0.703
INR	1.3 (1.2–1.4)	1.3 (1.2–1.4)	0.993
Creatinine (mg/dl)	0.95 (0.75–1.20)	0.94 (0.71–1.33)	0.925
Na (mEq/L)	137 (134–140)	138 (135–140)	**0.037**
Child-Pugh class before TIPS			0.079
A	48 (24)	68 (33)	
B	139 (69)	126 (61)	
C	15 (7)	12 (6)	
MELD before TIPS	11 (9–14)	12 (10–14)	0.478
Endoprosthesis dilatation (mm)	8.0 (8.0–10.0)	6.0 (6.0–6.0)	**<0.001**
PCPG before TIPS (mmHg)	21.0 (18.0–25.0)	22.0 (19.0–25.5)	0.367
PCPG after TIPS (mmHg)	8.0 (5.8–11.0)	12.0 (9.0–15.0)	**<0.001**
PCPG reduction (mmHg)	12.6 (9.5–16.0)	9.0 (7.0–12.1)	**<0.001**
PCPG reduction (%)	60.7 (46.7–72.0)	43.1 (32.2–54.3)	**<0.001**
Hemodynamic response			**<0.001**
Adequate hemodynamic response	160 (79)	109 (53)	
Inadequate hemodynamic response	42 (21)	97 (47)	
PCPG 10 mmHg			**<0.001**
PCPG ≥10 mmHg	75 (37)	145 (70)	
PCPG <10 mmHg	127 (63)	61 (30)	

Adequate hemodynamic response is defined as post-TIPS PCPG <12 mmHg or PCPG reduction ≥50% for bleeding secondary prophylaxis, and post-TIPS PCPG <12 mmHg for refractory ascites. If these criteria are not met, the hemodynamic response is defined inadequate. U-TIPS is defined as endoprosthesis dilatation ≤7 mm while S-TIPS is defined as endoprosthesis dilation >7 mm *Pearson's X^2 test; Wilcoxon rank sum test; Fisher's exact test. Values in bold denote statistical significance. INR, international normalized ratio; MASLD, metabolic-dysfunction associated steatotic liver disease; MELD, model of end-stage liver disease; Na, sodium; PCPG, porto-caval pressure gradient. S-TIPS, standard endoprosthesis TIPS; TIPS, transjugular intrahepatic portosystemic shunt; U-TIPS, under-dilated endoprosthesis TIPS.

strategies such as artificial intelligence to better assess patient risk and guide therapeutic decisions.

We also confirmed that OHE has a high incidence within the first months following TIPS, and this occurred irrespective of the endoprosthesis dilation diameter. Notably, the overlapping cumulative incidence curves of OHE in U-TIPS and S-TIPS patients during the initial 2 months of follow-up underscore the need to identify and integrate additional prognostic factors beyond the hemodynamic outcome and endoprosthesis diameter in predicting OHE development. Indeed, the aforementioned co-factors are likely to exert a predominant influence during the early post-TIPS phase, thereby accounting for the delayed separation of OHE cumulative incidence curves. Consequently, the clinical impact of U-TIPS is expected to become more evident as the contribution of these determinants progressively diminishes.

Regrettably, sufficient data regarding the presence and persistence of SPSS after TIPS were not available in our cohort. Likewise, data on the persistence of orthograde portal blood flow distal to the endoprosthesis, as a rough indirect marker of lower portosystemic shunting, are lacking. Therefore, further studies that measure, ideally directly, the proportion of portosystemic shunt and integrate assessments of systemic hemodynamics with the abovementioned factors, will be essential for an accurate pathophysiological definition.

The present study has inherent limitations, notably its retrospective design and the immediate post-procedural measurement of PCPG in sedated patients.[44,45] Indeed, it remains unclear whether hemodynamic assessment in awake individuals would yield different prognostic accuracy or alter conclusion regarding endoprosthesis dilation. Therefore, specifically designed clinical studies are warranted to dissect this interaction. However, potential bias associated with end-procedural PCPG measurement has been limited by excluding pre-emptive, salvage, and rescue TIPS, patients with grade 2–3 acute-on-chronic liver failure, and cases where inotropic or vasoactive agents were ongoing. The relatively high rates of OHE observed in our cohort may be explained by

Table 3. Results of univariable and multivariable analysis predicting overall cumulative incidence of OHE within 1 year after TIPS, analyzed in a competing risks framework considering liver transplant and death as competing events.

	Multivariable		
Characteristic	**sHR[1]**	**95% CI**	***p* value**
Sex			
Female	—	—	
Male	1.00	0.71, 1.39	>0.9
Age	1.01	1.00, 1.03	**0.046**
Previous of OHE prior to TIPS	2.12	1.18, 3.81	**0.012**
Indication to TIPS			
Refractory ascites	—	—	
Variceal bleeding	1.11	0.80, 1.53	0.5
Child-Pugh class before TIPS			
A	—	—	
B	1.48	1.01, 2.15	**0.042**
C	2.19	1.27, 3.80	**0.005**
Endoprosthesis dilation			
U-TIPS	—	—	
S-TIPS	1.72	1.26, 2.35	**<0.001**
Hemodynamic response			
Inadequate hemodynamic response	—	—	
Adequate hemodynamic response	1.30	0.79, 2.12	0.29
^PCPG 10 mm Hg			
PCPG above 10 mm Hg	—	—	
PCPG below 10 mm Hg	1.28	0.93, 1.76	0.13

^This variable was included in the multivariable model separately from hemodynamic response due to assessed collinearity. The table refers to the model including hemodynamic response. When the multivariable was performed using instead the PCPG 10 mm Hg threshold, the significance of other variables did not change.
Values in bold denote statistical significance.
CI, confidence interval; OHE, overt hepatic encephalopathy; PCPG, porto-caval pressure gradient; sHR: sub distribution Hazard Ratio, TIPS, transjugular intra-hepatic porto-systemic shunt.
[1]sHR: sub distribution Hazard Ratio.

Table 4. Cumulative incidence of overt hepatic encephalopathy within the first year after TIPS according to different end-procedural hemodynamic targets in patients stratified by the endoprosthesis dilation.

	Days 30	Days 90	Days 180	Days 360	*p* value*
U-TIPS					
Hemodynamic response					0.6
AHR	17% (10%, 25%)	30% (21%, 39%)	32% (23%, 42%)	36% (26%, 45%)	
IHR	15% (8.5%, 22%)	23% (15%, 31%)	26% (18%, 35%)	32% (23%, 41%)	
End-procedural PCPG					0.2
<10 mmHg	23% (14%, 35%)	36% (24%, 48%)	36% (24%, 48%)	40% (27%, 52%)	
≥10 mmHg	13% (7.8%, 19%)	22% (16%, 29%)	26% (19%, 34%)	31% (23%, 39%)	
S-TIPS					
Hemodynamic response					0.12
AHR	19% (13%, 25%)	30% (23%, 38%)	38% (31%, 46%)	53% (45%, 61%)	
IHR	17% (10%, 24%)	28% (20%, 36%)	36% (27%, 45%)	49% (40%, 58%)	
End-procedural PCPG					0.2
<10 mmHg	19% (13%, 26%)	30% (22%, 38%)	39% (30%, 47%)	54% (44%, 62%)	
≥10 mmHg	11% (5.1%, 19%)	25% (15%, 35%)	32% (21%, 43%)	44% (32%, 55%)	

AHR is defined as post-TIPS PCPG <12 mmHg or PCPG reduction ≥50% for bleeding secondary prophylaxis indication, and post-TIPS PCPG <12 mmHg or PCPG reduction ≥60% for refractory ascites. If these criteria are not met, the hemodynamic response is defined as inadequate (IHR). U-TIPS is defined as endoprosthesis dilatation ≤7 mm while S-TIPS is defined as endoprosthesis dilation >7 mm *Grey's test. AHR, adequate hemodynamic response; IHR, inadequate hemodynamic response; PCPG, porto-caval pressure gradient. S-TIPS, standard endoprosthesis TIPS; TIPS, transjugular intrahepatic portosystemic shunt; U-TIPS, under-dilated endoprosthesis TIPS.

the thorough instructions provided to patients and caregivers to promptly report any changes in mental status, combined with a predefined surveillance protocol. This approach likely minimized the risk of underdiagnosing OHE, particularly grade 2 episodes. Moreover, a substantial number of older adults was included in the study. Lastly, the administration of secondary prophylaxis for OHE in 69 patients may have influenced post-TIPS outcomes; however, these patients were evenly distributed across the subgroups under investigation.

In conclusion, this study shows that the lower incidence of OHE in patients receiving U-TIPS is independently determined by the magnitude of the shunt.

Affiliations
[1]*Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;* [2]*Sheila Sherlock Liver Unit and UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK;* [3]*Severe Liver Diseases Departmental Unit (M.E.C.), AOU Policlinico of Modena, University of Modena and Reggio Emilia, Modena, Italy;* [4]*Unit of Vascular Liver Diseases and Treatment of Portal Hypertension, Gastroenterology, Department of Surgery, Oncology and Gastroenterology,*

University Hospital of Padua, Padua, Italy; [5]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; [6]Interventional Radiology Unit, AOU Policlinico of Modena, University of Modena and Reggio Emilia, Modena, Italy; [7]Department of Radiology, Interventional Radiology Unit, Careggi Hospital, Florence, Italy; [8]Institute of Clinical Physiology, National Research Council, Via G. Moruzzi 1, 56124 Pisa, Italy; [9]Dipartimento di Scienze Biotecnologiche Medico Chirurgiche, Sapienza University of Rome, Rome, Italy; [10]Department of Integrated Diagnostic Services DIDAS, University Hospital of Padua, Padua, Italy; [11]Department of Medicine (DIMED), University of Padova, Padova, Italy; [12]Portal Hypertension Departmental Unit, Dipartimento Oncologico e di Chirurgia ad Indirizzo Robotico, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

Abbreviations

AHR, adequate hemodynamic response; AIC, Akaike Information Criterion; IHR, inadequate hemodynamic response; INR, international normalized ratio; LT, liver transplant; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; PCPG, porto-caval pressure gradient; PH, portal hypertension; RA, refractory ascites; RI-TIPS, Italian TIPS registry; SPSSs, spontaneous portosystemic shunts; S-TIPS, standard TIPS; TIPS, transjugular portosystemic shunt; U-TIPS, under-dilated TIPS; VIF, variance inflation factor.

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Conflicts of interest

FV, FS, OR, FM, and FF have received lecture fees and FS has received research grant support from Gore. All other co-authors have nothing to declare.

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

Authors' contributions

Contributed to the conduct of the study: all authors. Data collection: all authors. Data interpretation: DR, DS, MS, SN. Statistical analysis: DR. Collaborated in drafting the manuscript: DR, DS, MS, SN. Approved the final version of the submitted manuscript: all authors.

Supplementary data

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Author names in bold designate shared co-first authorship

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