Predicting overt hepatic encephalopathy after TIPS: Value of three minimal hepatic encephalopathy tests

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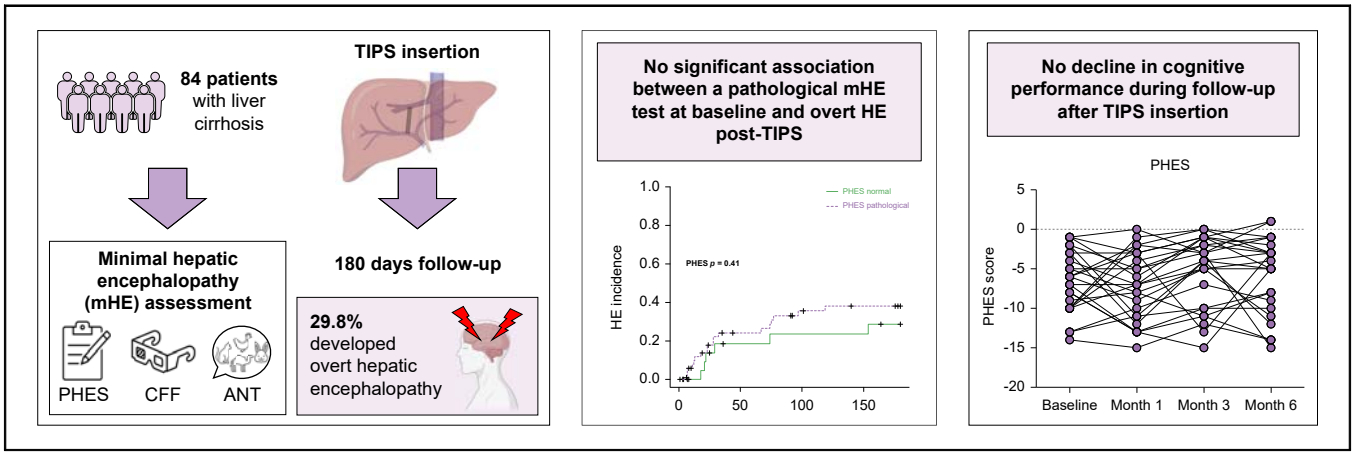
Graphical abstract



Highlights

- A total of 84 patients with cirrhosis underwent a minimal hepatic encephalopathy assessment before TIPS insertion.
- After TIPS insertion, they were monitored for 180 days for the development of overt hepatic encephalopathy.
- There was no significant association between pathological test results and overt hepatic encephalopathy post-TIPS.
- Patients were re-evaluated with all minimal hepatic encephalopathy tests at Months 1, 3, and 6 after TIPS insertion.
- Neurological performance remained stable during follow-up.

Impact and implications

This prospective observational study compared three diagnostic tests for mHE and showed the limited value of these tests for predicting overt HE in patients with cirrhosis undergoing TIPS insertion. In addition, the results suggest that cognitive performance generally remains stable after TIPS insertion. These results are important for physicians and researchers involved in the management of patients with cirrhosis undergoing TIPS procedures. The study's findings serve as a starting point for further investigations on the development of more effective strategies for predicting and managing post-TIPS HE.

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Research article

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Predicting overt hepatic encephalopathy after TIPS: Value of three minimal hepatic encephalopathy tests

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Background & Aims: Hepatic encephalopathy (HE) is a frequent and severe complication in patients after transjugular intrahepatic portosystemic shunt (TIPS) insertion. However, risk factors for post-TIPS HE remain poorly defined. Minimal HE (mHE) is a well-known risk factor for overt HE in patients with cirrhosis without TIPS. We aimed to evaluate three tools frequently used for diagnosing mHE for their dynamic changes and their predictive value for overt HE after TIPS.
Methods: We prospectively recruited 84 consecutive patients before TIPS insertion and monitored them for 180 days for post-TIPS HE. Before TIPS insertion, the patients underwent the portosystemic encephalopathy (PSE) syndrome test, the animal naming test (ANT), and the critical flicker frequency (CFF). Patients were retested after TIPS insertion.
Results: The majority of patients were male (67.9%), and the predominant indication for TIPS was refractory ascites (75%). Median age was 59 years, model for end-stage liver disease score was 12, and 66.3%, 64.6%, and 28.4% patients had evidence for mHE according to the PSE syndrome test, ANT, and CFF, respectively. Overall, 25 patients developed post-TIPS HE within 180 days after TIPS insertion. Post-TIPS incidence of overt HE was 22.2, 28.6, 45.5, and 55.6% in those with no, one, two, and three pathological tests at baseline, respectively. However, none of the three tests was significantly associated with post-TIPS HE. Of note, mean performance in all tests remained stable over time after TIPS insertion.
Conclusions: PSE syndrome test, ANT and CFF, which are frequently used for diagnosing mHE have limited value for predicting HE after TIPS insertion. We could not find evidence that TIPS insertion leads to a psychometric decline in the long term.
Impact and implications: This prospective observational study compared three diagnostic tests for mHE and showed the limited value of these tests for predicting overt HE in patients with cirrhosis undergoing TIPS insertion. In addition, the results suggest that cognitive performance generally remains stable after TIPS insertion. These results are important for physicians and researchers involved in the management of patients with cirrhosis undergoing TIPS procedures. The study's findings serve as a starting point for further investigations on the development of more effective strategies for predicting and managing post-TIPS HE.
Clinical trial number: ClinicalTrials.gov NCT04801290.

Introduction

The development of portal hypertension-related complications represents a hallmark in the natural course of patients with liver cirrhosis.[1,2] An effective and causal treatment of cirrhosis-associated portal hypertension is the insertion of a transjugular intrahepatic portosystemic shunt (TIPS).[3] TIPS insertion significantly reduces the risk for variceal bleeding, can lead to permanent ascites control, and even increases the transplant-free survival.[4–7] However, some important complications of TIPS treatment need to be considered when selecting suitable patients. The development of clinically significant, overt hepatic encephalopathy (HE) is one of the most frequent complications after TIPS insertion affecting approximately 35–50% of patients.[8] Moreover, the development of early-recurrent overt HE after TIPS insertion is associated with poor survival.[9] Recurrent and persistent HE is one of the main reasons for TIPS diameter reduction and occlusion.[10–13] Therefore, a careful evaluation of the patients before TIPS insertion is crucial.

To date, there are no established risk scores or tests that can reliably predict the occurrence of overt HE after TIPS insertion. In patients with cirrhosis without TIPS, the presence of minimal HE (mHE) is a well-known risk factor for the development of overt

Keywords: Liver cirrhosis; Hepatic encephalopathy; Transjugular intrahepatic portosystemic shunt; TIPS; PSE syndrome test; Animal naming test; Critical flicker frequency.
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HE.[14,15] The portosystemic encephalopathy (PSE) syndrome test yielding the psychometric hepatic encephalopathy score (PHES) is currently considered as the gold standard for diagnosing mHE.[16] In routine clinical practice, the applicability of the PSE syndrome test is limited by the requirement of trained staff and the time needed for testing. In recent years, other tests such as the animal naming test (ANT) or the critical flicker frequency (CFF) assessment have been suggested as faster and easier, but also less accurate tools for initial screening for HE.[17,18] However, the predictive role of mHE in general and the specific value of dedicated diagnostic tests in patients undergoing TIPS insertion remains poorly investigated, so far.[19–21] In turn, it also remains controversial whether TIPS therapy necessarily leads to cognitive impairment. Although the increase in the portosystemic shunt volume certainly has the potential to worsen HE, this might be balanced by positive effects such as the reduction of hypertensive gastrointestinal bleeding and the improvement of sarcopaenia.[5,22] The overall impact of TIPS on long-term cognitive performance has not been investigated in detail and thus remains uncertain so far.

The aim of this study was to evaluate the PSE syndrome test, ANT, and CFF for their predictive value for overt HE development after TIPS insertion and the impact of TIPS on the test performances over time.

Patients and methods

Study cohort

Between August 2019 and April 2022, we prospectively recruited 120 consecutive patients who underwent TIPS insertion at Hannover Medical School. Patients with insufficient evidence for liver cirrhosis (n = 10), with previous organ transplantation (n = 4), severe neurological comorbidities (n = 3), or chronic renal impairment requiring haemodialysis (n = 1) were excluded from the analysis. From the 102 patients without exclusion criteria, 84 patients underwent mHE assessment at baseline and therefore were available for further evaluation. The remaining patients declined testing or could not be tested for organisational or staffing reasons (Fig. 1).

Assessment of mHE

The mHE assessment included the PSE syndrome test, ANT, and CFF.

The PSE syndrome test battery yielding the psychometric hepatic encephalopathy score (PHES) (version 2.0; 2020)[23] includes five sub-tests: the digit symbol test, the number connection tests A and B, the serial dotting test, and the line tracing test. The test battery was performed in all patients, as previously described. The standardised and validated test is currently considered as the gold standard and was therefore used to determine mHE in our study (cut-off: -4 points).[24]

In the ANT, patients are asked to name as many animals as possible in 1 min. Following Labenz *et al.*[25] we set 23 animals per minute as the cut-off value for the German population.[26]

The CFF was determined using the HEPAtonorm™-Analyzer. Eight measurements were completed, and the mean and SD were calculated. If the SD was >1, we added and replaced runs until the SD was <1, as suggested by the inventor of CFF for mHE diagnosis. The cut-off was set at 39 Hz.[27]

Assessment of clinical data

According to the predefined protocol, patients' data were collected from their medical records and by questioning them personally during their hospital stay before TIPS insertion as well as 1, 3, and 6 months after TIPS insertion during their fixed outpatient appointments. Development of overt HE was defined according to the West Haven and ISHEN (International Society on Hepatic Encephalopathy and Nitrogen Metabolism) criteria,[28] and recurrent HE was defined as previously defined by the 2022 EASL guidelines[8] with at least two HE episodes within 6 months.

TIPS insertion

The Department of Diagnostic and Interventional Radiology at Hannover Medical School performed TIPS insertion according to institutional standard operating procedures in all patients.[29,30] The procedure was conducted under general anaesthesia using only polytetrafluoroethylene-covered stents grafts (GORE® VIATORR® TIPS Endoprosthesis, Flagstaff, Arizona, AZ, USA) with a stent diameter of 6 mm (n = 31), 8 mm (n = 52), and 10 mm (n = 1). The indications for the insertion of a 6 mm TIPS were cardiac impairment, impaired liver function, and history of HE in 18 (58.1%), 9 (29.0%), and 5 (16.1%) patients, respectively (Table S1).

Study design

The primary endpoint of this study was the development of overt HE within 180 days after TIPS insertion. For determining the predictive value of PHES, ANT, and CFF results, patients performed all three tests at baseline, and the results were evaluated for the prediction of HE after TIPS insertion.

For the evaluation of the test performance after TIPS insertion, patients were examined again 1, 3, and 6 months after the procedure during their outpatient appointments. A subgroup of 25 patients had continuous and complete mHE test results of all their outpatient appointments after TIPS insertion and were therefore available for further analyses for the evolution of mHE after TIPS.

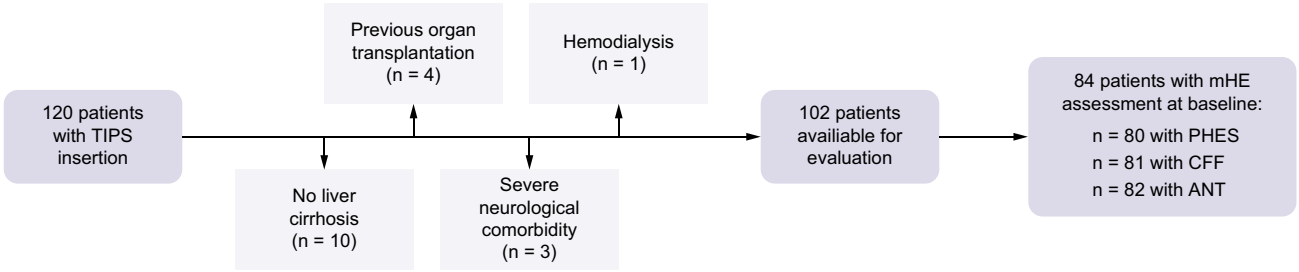

Fig. 1. Patient selection. ANT, animal naming test; CFF, critical flicker frequency; mHE, minimal hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; TIPS, transjugular intrahepatic portosystemic shunt.

Table 1. Baseline characteristics.

Baseline characteristics	All patients	No HE development after TIPS	HE development after TIPS	*p* value
Number of patients	84	59	25	
Age*	59 (52–66)	59 (52–64)	62 (52–72)	**0.039**
Sex male†	57 (67.9%)	43 (72.9%)	14 (56%)	0.130
Sex female†	27 (32.1%)	16 (27.1%)	11 (44%)	0.130
Aetiology of cirrhosis†				
Alcohol related	57 (67.9%)	43 (72.9%)	14 (56%)	0.130
NASH	18 (21.4%)	14 (23.7%)	4 (16%)	0.430
Viral	5 (6%)	4 (6.8%)	1 (4%)	0.623
TIPS indication (multiple selection possible)†				
Refractory ascites	63 (75%)	43 (72.9%)	20 (80%)	0.491
Bleeding	28 (33.3%)	20 (33.9%)	8 (32%)	0.866
PSG before TIPS (mmHg)*	15 (13–18)	15 (13–18)	15 (13–20)	0.734
PSG after TIPS (mmHg)‡	6 (4–9)	6 (4–9)	7 (4–8)	0.992
Stent diameter 6 mm†	31 (36.9%)	23 (39%)	8 (32%)	0.544
Diabetes at baseline†	33 (39.3%)	20 (33.9%)	13 (52%)	0.120
History of HE†	23 (27.4%)	14 (23.7%)	9 (36%)	0.249
PHES*	-6.0 (-9 to -3)	-5 (-9 to -3)	-6 (-10 to -4)	0.501
PHES pathological†	53 (66.3%)	35 (62.5%)	18 (75%)	0.279
CFF (Hz)*	41.4 (38.7–47.4)	43.4 (39.0–48.8)	40.4 (37.0–46.0)	0.065
CFF pathological†	23 (28.4%)	14 (24.6%)	9 (37.5%)	0.238
ANT (animals/min)‡	20 (16–26)	21 (16–27)	19 (17–24)	0.631
ANT pathological†	53 (64.6%)	35 (61.4%)	18 (72%)	0.356
Sodium (mmol/L)*	135 (131–138)	135 (131–138)	136 (132–138)	0.750
Creatinine (μmol/L)‡	99 (77–147)	98 (77–141)	110 (79–157)	0.273
CHE (kU/L)*	2.5 (1.8–3.8)	2.5 (1.8-3.9)	2.4 (1.8–3.9)	0.793
Bilirubin (μmol/L)‡	18 (11–27)	19 (12–27)	14 (10–27)	0.502
Albumin (g/L)*	32 (28–36)	32 (28–37)	30 (27–35)	0.127
Haemoglobin (g/dl)*	10.1 (8.1–11.5)	10.2 (11.5)	9.9 (8.2–11.4)	0.895
Platelets (tsd/μl)‡	111 (72–176)	116 (72–197)	106 (68–146)	0.633
INR*	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	0.168
Ammonia (μmol/L)‡	47 (36–66)	47 (35–69)	47 (41–63)	0.860
MELD*	12 (9–14)	12 (9–14)	12 (8–15)	0.993
FIPS score‡	-0.21 (-0.54 to 0.26)	-0.21 (-0.54 to 0.15)	-0.10 (-0.53 to 0.37)	1.000
Child–Pugh score‡	8 (7–9)	8 (7–9)	8 (7–9)	0.850
HE prophylaxis at discharge†				
Lactulose§	70 (83.3%)	51 (86.4%)	19 (76%)	0.240
Rifaximin¶	48 (57.1%)	36 (61%)	12 (48%)	0.270
L-ornithine L-aspartate**	14 (16.7%)	12 (20.3%)	2 (8%)	0.165

Median and IQR for all continuous variables, and frequencies and percentages for nominal data.
Values of p <0.05 are highlighted in bold font.
ANT, animal naming test; CFF, critical flicker frequency; CHE, cholinesterase; FIPS, Freiburg index of post-TIPS survival; HE, hepatic encephalopathy; INR, international normalised ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PHES, psychometric hepatic encephalopathy score; PSG, portosystemic gradient; TIPS, transjugular intrahepatic portosystemic shunt.
* *t* test for normative values.
† Chi-square test for nominal data.
‡ Mann–Whitney *U* test for not normal distributed values.
§ Dose: up-titrating dose until two to three bowel movements per day.
¶ Dose: 1,100 mg/day.
** Dose: 9–18 g/day.

Statistics

We performed all statistical analyses using Microsoft Excel™ (Microsoft Corp., Redmond, WA, USA), IBM SPSS Statistics (version 27, SPSS Inc., Chicago, IL, USA), and R (version 4.2.0).[31] Within R, we used the packages 'cmprsk',[32] 'RCmdr',[33] 'RcmdrPlugin.EZR',[34] and 'RcmdrPlugin.KMggplot2'.[35]

All continuous variables are presented as median with IQR. Normal distribution of continuous data was tested using the Kolomogorov–Smirnov test. For comparing normally distributed variables, we used *t* tests, and for comparing not normally distributed variables, we used the Mann–Whitney *U* test. Categorical variables are presented as numbers and percentages. For comparing categorical variables, we used the Chi-square test. Moreover, we analysed the correlation between parameters using the Spearman rho test.

In addition, association with HE development was tested using the time-dependent Fine–Gray model for competing risk analysis treating death or liver transplantation as competitor. First, we evaluated pathological test results in PHES, CFF, and ANT as risk factors for HE development in a univariable analysis. Then, we applied two different multivariable models with the pathological psychometric test results:

- Model 1: adjusting for all values with p <0.05 in univariable analysis (age).
- Model 2: with preselected factors, namely, Freiburg index of post-TIPS survival (FIPS),[36] rifaximin intake,[37] and stent diameter.[38]

We did not adjust for ammonia levels in the multivariable models, as there were lacking values in 28 patients.

Furthermore, we performed repeated measures ANOVA for normally distributed values and the Friedman test for not normally distributed values to detect statistically significant changes

of the mHE tests during follow-up.[39–41] We used the Mauchly test to check sphericity and the Bonferroni correction for multiple testing. Values of p <0.05 were considered statistically significant results.

Ethics

All patients gave written informed consent to participate in this prospective study. The local ethics committee of Hannover Medical School approved this study (protocol identification number: Nr. 8498_BO_S_2019), and it was carried out according to the principles of the Declaration of Helsinki.

Results

Baseline characteristics of the study cohort

The majority of patients were male (67.9%), and the predominant indication for TIPS was refractory ascites (75%). Median age was 59 (IQR 52–66) years, model for end-stage liver disease (MELD) score 12 (IQR 9–14), FIPS score -0.21 (IQR -0.54 to 0.26), and Child–Pugh score 8 (IQR 7–9). None of the patients presented with overt HE at baseline, and 23 (27.4%) patients had a history of HE. At baseline, advanced age was the only parameter that showed a statistically significant difference between those patients who later developed HE and those who did not. We found no statistically significant difference regarding laboratory values, comorbidities, and other assessed clinical parameters (Table 1).

PHES, ANT, and CFF results at baseline

PHES results at baseline were pathological in 66.3% of patients with a median score of -6 (IQR -9 to -3). Similarly, ANT yielded pathological results in 64.6% of patients with a median number of 20 (IQR 16–26) animals per minute. In contrast, CFF measurements were considered pathological in 28.4% of patients with a median of 41.4 (IQR 38.7–47.4) Hz.

Baseline values of PHES and ANT results correlated strongly (r = 0.521, p <0.001), and those of ANT and CFF correlated modestly (r = 0.260, p = 0.021), but there was no significant correlation between PHES and CFF (r = 0.176, p = 0.120) (Table 2).

Development of HE during follow-up

Median follow-up time amounted 187 (IQR 74–371) days after TIPS insertion. During the first 180 days, 25 patients (29.8%) developed at least one episode of overt HE. Seven patients developed a recurrent HE. However, the majority of patients (64%) with overt HE developed only a single episode. The median time interval between TIPS placement and onset of overt HE was 28 (IQR 16–74) days. Precipitants for HE development could be identified in 15 (60%) patients. Most identified triggers for were postinterventional HE development, infection, and constipation in four (16%), three (12%), and three patients (12%), respectively. In 10 (40%) patients, no HE triggers were identified (Table S2).

Table 2. Spearman rho correlation of the mHE tests at baseline before TIPS insertion.

		PHES	CFF	ANT
PHES	Correlation coefficient	1.000	0.176	0.521
	p value		0.120	**<0.001**
	Number of patients	80	79	79
CFF	Correlation coefficient	0.176	1.000	0.260
	p value	0.120		**0.021**
	Number of patients	79	81	79
ANT	Correlation coefficient	0.521	0.260	1.000
	p value	**<0.001**	**0.021**	
	Number of patients	79	79	84

Values of p <0.05 are highlighted in bold font.
ANT, animal naming test; CFF, critical flicker frequency; mHE, minimal hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; TIPS, transjugular intrahepatic portosystemic shunt.

Predictive value of PHES, ANT, and CFF results for overt HE development after TIPS insertion

Incidence of overt HE after TIPS was 22.2%, 28.6%, 45.5%, and 55.6% in those with no, one, two, and three pathological tests at baseline, respectively (Fig. 2).

In the univariable competing risk model, all three tests were numerically associated with overt HE development after TIPS insertion during the 180 days of follow-up. In addition, the number of pathological mHE tests in each patient at baseline showed a numerical association with HE development but missed the level of statistical significance. PHES and ANT reached higher levels of sensitivity (PHES 75.0% and ANT 72.0%) for predicting post-TIPS HE compared with CFF (37.5%). In contrast, CFF had a higher specificity (75.4%) than PHES and ANT (PHES 37.5% and ANT 38.6%). Positive and negative predictive values were comparably low for all tests (positive predictive value: PHES 34.0%, CFF 39.1%, and ANT 34.0%; negative predictive value: PHES 77.8%, CFF 74.1%, and ANT 75.9%) (Table S3). However, the link to overt HE development was not statistically significant for any of the three analysed tests irrespective of the consideration of either quantitative or qualitative (normal/pathological) test results in neither the univariable model nor the two multivariable models (Fig. 3A–D). The only investigated parameter that was found to be statistically significantly associated with HE in univariable analysis was age (hazard ratio 1.051, 95% CI 1.005–1.099; p = 0.028) (Table 3).

Changes in test performance before and after TIPS insertion

During the follow-up appointments, we could reproduce similar correlation coefficients between the three tests, showing a strong correlation between PHES and ANT, a weak correlation

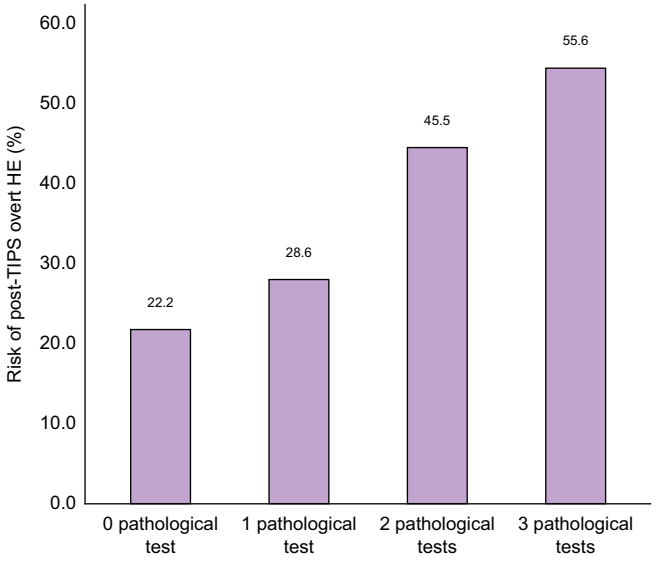

Fig. 2. Risk of post-TIPS overt HE in the first 180 days after TIPS insertion depending on the number of pathological tests at baseline. Bars represent percentages. HE, hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt.

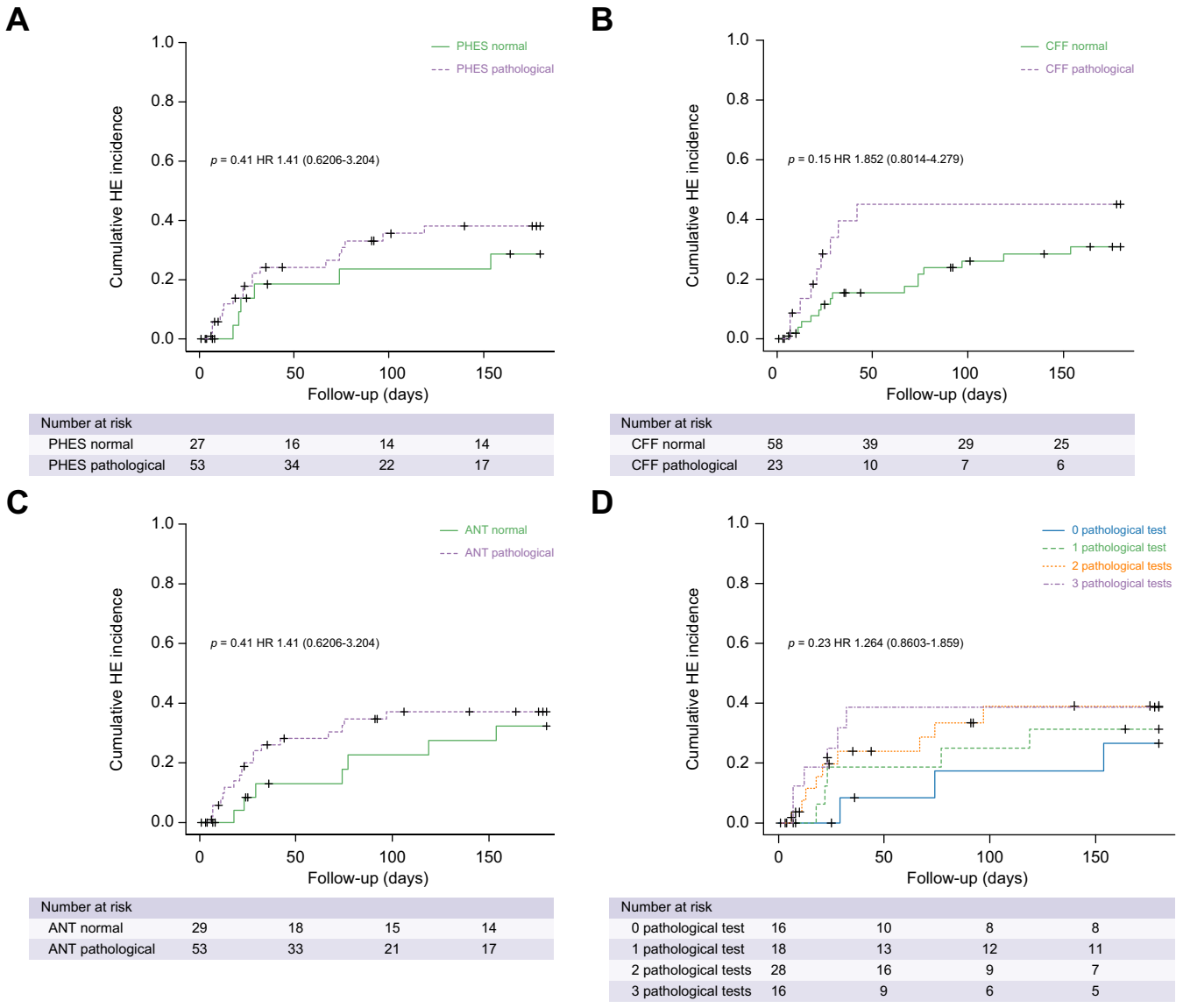

Fig. 3. Univariable competing risk analysis of the mHE tests for overt HE development post-TIPS. (A) PHES normal/pathological test results, (B) CFF normal/pathological test results, (C) ANT normal/pathological results, and (D) the number of pathological mHE tests at baseline for overt HE in the first 180 days after TIPS insertion. Time-dependent Fine–Gray model for competing risk analysis treating death or liver transplantation as competitor.
ANT, animal naming test; CFF, critical flicker frequency; HE, hepatic encephalopathy; HR, hazard ratio; mHE, minimal hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; TIPS, transjugular intrahepatic portosystemic shunt.

between ANT and CFF, and no significant correlation between PHES and CFF (Tables S4A–C). In a subgroup of 25 patients, PHES, ANT, and CFF results were available at baseline and at all three time points after TIPS insertion. Of note, there was no statistically significant evidence of a deterioration in the test results. Regarding PHES, even a statistically significant increase in the score during the time was detected (Friedman test for multiple testing, $p = 0.018$). Using the Bonferroni correction for multiple testing, there was a significant amelioration in PHES ($p = 0.044$) between Month 1 and Month 3 after TIPS insertion with a weak effect strength of r = 0.196. Concerning CFF and ANT, no statistically significant changes before and after TIPS insertion were found (in repeated measures ANOVA, CFF $p = 0.543$ and ANT $p = 0.729$). However, ANT and CFF results numerically improved also over time (Table 4 and Fig. 4A–C).

Discussion

The development of overt HE is a frequent and clinically relevant complication after TIPS insertion. Therefore, a careful selection of patients before the procedure is crucial. So far, no established predictors for the development of overt HE after TIPS insertion have been established. In this study, we analysed three tests, which are usually used to diagnose mHE, for their predictive value and the evolution of their results in patients over time after TIPS insertion.

The comparability of the three diagnostic tools to measure mHE is low as shown by the limited correlation between the three tests at baseline. This finding could be reproduced during the follow-up measurements. The value of all three tests for predicting overt HE after TIPS insertion is quite limited. Although we documented a numerical increase in the risk of post-TIPS HE

Table 3. Univariable and multivariable competing risk analysis for the development of overt HE in the first 180 days after TIPS insertion.

Evaluated factors	Hazard ratio	Lower 95% CI	Upper 95% CI	*p* value
Univariable competing risk analysis (n = 84)				
Age	1.051	1.005	1.099	**0.028**
Sex male	0.5408	0.2488	1.175	0.12
Stent diameter 6 mm	0.7026	0.304	1.624	0.41
Aetiology of cirrhosis				
Alcohol related	0.4878	0.2221	1.071	0.074
NASH	0.8384	0.227	1.795	0.39
Viral	0.5939	0.08178	4.313	0.61
TIPS indication (multiple selection possible)				
Refractory ascites	1.212	0.4414	3.326	0.71
Bleeding	1.023	0.438	2.39	0.96
PSG before TIPS (mmHg)	1.005	0.9156	1.103	0.91
PSG after TIPS (mmHg)	0.9805	0.8482	1.133	0.79
Diabetes at baseline	2.151	0.9971	4.639	0.051
History of HE	1.879	0.8208	4.303	0.14
PHES	0.9866	0.8952	1.087	0.79
PHES pathological	1.458	0.5936	3.581	0.41
CFF (Hz)	0.9406	0.8812	1.004	0.066
CFF pathological	1.852	0.8014	4.279	0.15
ANT (animals per minute)	0.9871	0.9402	1.036	0.6
ANT pathological	1.41	0.6206	3.204	0.41
Number of pathological mHE tests at baseline	1.264	0.8603	1.859	0.23
Sodium (mmol/L)	1.016	0.9447	1.093	0.67
Creatinine (μmol/L)	1.004	0.9964	1.013	0.28
CHE (kU/L)	1.097	0.8512	1.415	0.47
Bilirubin (μmol/L)	0.9907	0.9667	1.015	0.46
Albumin (g/L)	0.9549	0.8999	1.013	0.13
Haemoglobin (g/dl)	1.044	0.8793	1.239	0.62
Platelets (tsd/μl)	0.9979	0.9933	1.002	0.35
INR	0.08604	0.0038	1.944	0.12
Ammonia (μmol/L)	1.007	0.9782	1.037	0.63
MELD	0.9682	0.8503	1.102	0.63
FIPS score	1.362	0.8291	2.237	0.22
Child–Pugh score	1.149	0.8478	1.558	0.37
HE prophylaxis at discharge				
Lactulose*	0.4251	0.162	1.116	0.082
Rifaximin†	0.6838	0.3155	1.482	0.34
L-Ornithine L-aspartate‡	0.3	0.0778	1.157	0.08
Multivariable competing risk analysis				
Model 1§				
PHES	0.9982	0.9006	1.106	0.970
CFF	0.9536	0.8918	1.020	0.160
ANT	1.00	0.9506	1.052	0.99
PHES	0.9982	0.9006	1.106	0.970
Model 2¶				
PHES	0.9914	0.8887	1.106	0.88
CFF	0.9420	0.8782	1.010	0.095
ANT	0.9836	0.9265	1.044	0.59
PHES	0.9914	0.8887	1.106	0.88

Time-dependent Fine–Gray model for competing risk analysis treating death or liver transplantation as competitor. Values of p <0.05 are highlighted in bold font.
ANT, animal naming test; CFF, critical flicker frequency; CHE, cholinesterase; FIPS, Freiburg index of post-TIPS survival; HE, hepatic encephalopathy; INR, international normalised ratio; MELD, model for end-stage liver disease; mHE, minimal hepatic encephalopathy; NASH, non-alcoholic steatohepatitis; PHES, psychometric hepatic encephalopathy score; PSG, portosystemic gradient; TIPS, transjugular intrahepatic portosystemic shunt.
* Dose: up-titrating dose until two to three bowel movements per day.
† Dose: 1,100 mg/day.
‡ Dose: 9–18 g/day.
§ With all factors with p <0.05 in univariable analysis: age.
¶ With preselected factors: rifaximin, FIPS, stent diameter.

with every additional pathological test result in the patients, none of the tests was significantly associated with overt HE development in the univariable and multivariable models. Of note, the only parameter that was significantly associated with post-TIPS HE was age. That is in line with the findings of previous studies that highlighted advanced age as a risk factor for HE development in patients with cirrhosis.[10,20] In our cohort, the percentage of HE development after TIPS insertion was 30.4%. This is comparable with other current studies using covered stent grafts.[13,42,43] However, in contrast to the study of Berlioux *et al.*,[19] which included 54 patients, we could not confirm the significant relationship between pathological CFF results and the development of overt HE after TIPS insertion. That could be related to the fact that we used another model for HE prediction with the Fine–Gray model for competing events. Contrary to the study of Nardelli *et al.*,[20] which included 82 patients, pathological PHES results were not significantly associated with HE development after TIPS in our cohort. However, the studies are not well comparable

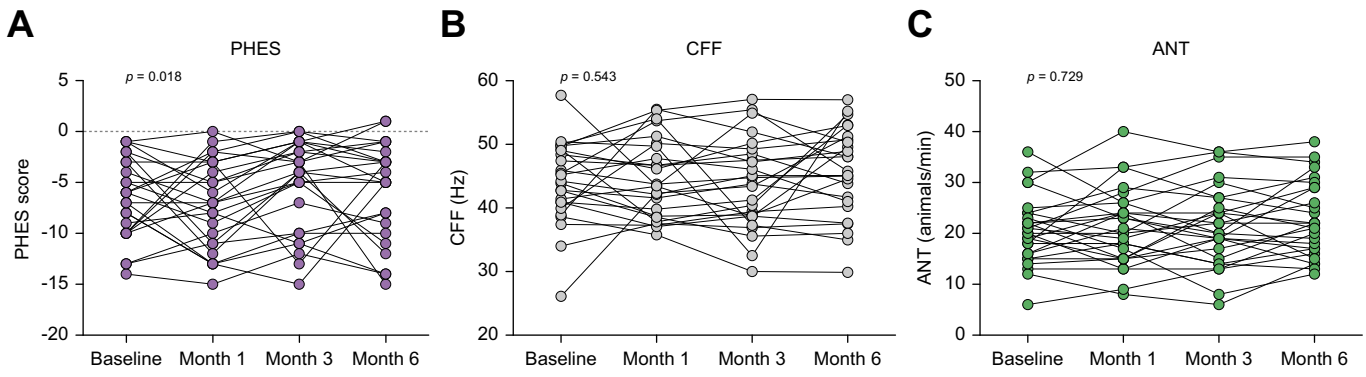

Fig. 4. Results of the mHE tests during follow-up (between baseline before TIPS and 6 months after TIPS insertion). (A) PHES (Friedman-test for not normally distributed values); (B) CFF (repeated measures ANOVA for normally distributed values); and (C) ANT (repeated measures ANOVA for normally distributed values). ANT, animal naming test; CFF, critical flicker frequency; PHES, psychometric hepatic encephalopathy score; TIPS, transjugular intrahepatic portosystemic shunt.

Table 4. Changes in test performances of the subgroup of patients tested at all time points before and after TIPS insertion.

	Baseline before TIPS insertion	Follow-up Month 1 after TIPS insertion	Follow-up Month 3 after TIPS insertion	Follow-up Month 6 after TIPS insertion
PHES	-6 (-10 to -3)	-7 (-11 to -4)	-4 (-10 to -2)	-5 (-9 to -3)
CFF (Hz)	42.8 (38.8–48.7)	43.6 (38.7–49.8)	43.8 (38.0–48.9)	45.5 (38.3–51.1)
ANT (animals per minute)	21 (17–26)	22 (15–26)	22 (18–28)	23 (17–31)

Median and IQR for all continuous variables.
ANT, animal naming test; CFF, critical flicker frequency; PHES, psychometric hepatic encephalopathy score; TIPS, transjugular intrahepatic portosystemic shunt.

regarding the aetiology of cirrhosis with a majority of alcohol-related aetiology associated with thiamine deficiency and the neurotoxicity of alcohol itself in our cohort and a majority of virus-related aetiology in the cohort of Nardelli *et al.*[20]

As the ANT is a very simple and easily applicable test, we present data for it for predicting post-TIPS overt HE development, suggesting that also the ANT has only a limited predictive value for HE after TIPS insertion.

Considering data from studies that explored risk factors for overt HE development in patients with cirrhosis without TIPS, it can be assumed that the underlying pathomechanisms of HE after TIPS insertion might be different. The diagnostic tests are validated for diagnosing and predicting HE type C, but it would be conceivable that HE after TIPS insertion is predominantly induced through iatrogenic portosystemic shunting and therefore could include aspects of the so-called HE type B.[8] This is supported by the fact that the median time to HE onset after TIPS insertion was less than 1 month, highlighting the increased portosystemic shunting as an influence.

We analysed changes in the different test results in patients undergoing TIPS insertion from before to after the procedure. It is widely suspected that TIPS insertion increases the HE risk, but there is only limited data on the evolution of mHE before and after TIPS insertion. We found no evidence of a significant deterioration in the psychometric performance after TIPS insertion, nor did we observe a significant change in CFF results. Our results are in line with two other studies[44,45] from 1998 and 2011 where also no significant psychometric deterioration was observed in the long-term follow-up after TIPS insertion. It is conceivable that the positive effects of TIPS, such as the reduced risk for variceal bleeding[5] and improved sarcopaenia,[22] compensate for the negative effects of the portosystemic blood shunting on the psychometric performance as well as CFF. Moreover, it has to be acknowledged that studies reporting an increased risk of overt HE as a result of TIPS insertion were performed with uncovered stents,[46,47] which were frequently linked to TIPS dysfunction and the need for consequent interventions. The latest randomised trial using only covered stents compared with large volume paracentesis in patients with ascites did not find a higher HE frequency among patients who underwent TIPS.[6] Thus, the often-assumed general negative impact of TIPS on HE and cognitive function needs to be questioned and deserves further research.

The strengths of this study include the prospective design, the structured follow-up, and the large sample size. In addition, we compared three different assessment tools for the diagnosis of mHE in the same patients. As an easily applicable tool, the ANT was evaluated for its predictive value for post-TIPS HE.

However, some limitations need to be considered. Although this is so far the largest study investigating three diagnostic tools in comparison for this topic, the sample size remains relatively small. This might have led to the fact that no statistically significant results were achieved regarding the predictive value of the tests. Moreover, some of the patients did not reach the follow-up of 180 days. Nevertheless, this was considered by using a time-dependent model for the predictive value of HE. As we included only patients who were considered suitable for TIPS independent of the mHE test results, we are not able to assume whether mHE tests are able to rule in TIPS therapy in patients in whom the risk for HE is assumed to be too high according to current standards.[3,8]

Although PHES, ANT, and CFF results did not reach the level of statistical significance as risk markers for the development of post-TIPS HE, but only showed a trend, these tests are still an important and useful tool in clinical practice to estimate the neurological performance of patients.[8] It was shown that pathological results in these measures are associated with a reduced quality of life,[14,15,48,49] impaired driving performance,[50,51] and increased hospitalisation and mortality.[14,15,52] This is another

reason to regularly screen patients with cirrhosis for signs of mHE, especially after TIPS insertion. Further studies regarding the pathomechanisms underlying HE development after TIPS are necessary, and other recently used psychometric tests should be assessed for their predictive value concerning the development of HE after TIPS insertion.

In conclusion, this study shows that PHES, ANT or CFF test results should not be used as the sole factor to weigh the risk for post-TIPS HE. In a subgroup analysis, we found no general negative effect of TIPS on mHE test performances. The impact of TIPS insertion on long-term cognitive function remains unclear and requires further research.

Abbreviations

ANT, animal naming test; CFF, critical flicker frequency; CHE, cholinesterase; FIPS, Freiburg index of post-TIPS survival; HE, hepatic encephalopathy; HR, hazard ratio; INR, international normalised ratio; ISHEN, International Society on Hepatic Encephalopathy and Nitrogen Metabolism; MELD, model for end-stage liver disease; mHE, minimal hepatic encephalopathy; NASH, non-alcoholic steatohepatitis; PHES, psychometric hepatic encephalopathy score; PSE, portosystemic encephalopathy; PSG, portosystemic gradient; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflicts of interest

KW has taken part in the development of the Psychometric Hepatic Encephalopathy Score (PHES), and the copyright of this test is held by Hannover Medical School. BM received lecture fees from Norgine. HW received fees from Falk, Intercept, Norgine, and Pfizer.

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

Authors' contributions

Conceptualisation: BM, KW, AFE. Formal analysis: AFE. Investigation: AFE, HS, LS, AT, CL, JBH. Methodology: BM, KW, MMG, MD AFE. Project Administration: BM, HS, LS, AT, JW. Resources: BM, KW, HW, HS, LS, AT, JBH. Supervision: BM, KW, MMG, MD. Visualisation: AFE. Writing – original draft: AFE. Writing – review and editing: AFE, BM, KW.

Data availability statement

Anonymised data that support the findings of this study are available from the corresponding author on request.

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Supplementary data

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