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Minimal hepatic encephalopathy is associated with a higher risk of overt hepatic encephalopathy and poorer survival

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Abstract. Gairing SJ, Mangini C, Zarantonello L, Gioia S, Nielsen EJ, Danneberg S, et al. Minimal hepatic encephalopathy is associated with a higher risk of overt hepatic encephalopathy and poorer survival. *J Intern Med.* 2023;**00**:1–15.

Background and aims. Minimal hepatic encephalopathy (MHE) is a frequent complication in patients with liver cirrhosis. Its impact on predicting the development of overt hepatic encephalopathy (OHE) and survival has not been studied in large multicenter studies.

Methods. Data from patients recruited at eight centers across Europe and the United States were analyzed. MHE was detected using the psychometric hepatic encephalopathy score (PHES). A subset was also tested with the simplified animal naming test (S-ANT1). Patients were followed for OHE development and death/liver transplantation (LTx).

Results. A total of 1462 patients with a median model of end-stage liver disease of 11 were included (Child-Pugh (CP) stages: A 47%/B 41%/C 12%). Median follow-up time was 19 months, during which 336 (23%) patients developed an OHE episode and 464 (32%) reached the composite end point of death/LTx (369 deaths, 95 LTx). In multivariable analyses, MHE (defined by PHES) was associated with the development of OHE (subdistribution hazard ratio 1.74, $p < 0.001$) and poorer LTx-free survival (hazard ratio 1.53, $p < 0.001$) in the total cohort as well as in the subgroup of patients without a history of OHE. In subgroup analyses, MHE (defined by PHES) was associated with OHE development in patients with CP B, whereas there was no association in patients with CP A or C. In the subgroup of patients with available S-ANT1, MHE (defined by S-ANT1) was independently associated with OHE development. Combined testing (PHES+S-ANT1) was superior to single testing for predicting OHE and poorer LTx-free survival.

Conclusions. This large multicenter study demonstrates that screening for MHE is a useful tool for predicting OHE and poorer survival.

Keywords: animal naming test, covert hepatic encephalopathy, decompensated cirrhosis, psychometric hepatic encephalopathy score

Abbreviations: ALBI, albumin–bilirubin; ANT, animal naming test; CHE, covert hepatic encephalopathy; CI, confidence interval; CP, Child-Pugh; HE, hepatic encephalopathy; HR, hazard ratio; INR, international normalized ratio; IQR, interquartile range; ISHEN, International Society of hepatic encephalopathy and nitrogen metabolism; LTx, liver transplantation; MELD, model of end-stage liver disease; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; S-ANT1, simplified animal naming test; SD, standard deviation; sHR, subdistribution hazard ratio

Introduction

Liver cirrhosis is widely prevalent worldwide and the main cause of about 1.32 million deaths yearly [1]. The prognosis of cirrhosis is mainly determined by the occurrence of decompensation events. Hepatic encephalopathy (HE)—a neurophysiological complication with detrimental impact on patients' quality of life and huge burden for caregivers [2, 3]—is a common complication in patients with cirrhosis. According to the current guidelines, HE can be divided into covert (CHE) and overt HE (OHE) [4]. CHE is an umbrella term combining the two lowest grades—minimal HE (MHE) and HE grade 1 according to the West-Haven-Criteria, whereas OHE covers grades 2–4. The prevalence of MHE is heavily dependent on the liver disease stage and ranges from <25% in patients with Child-Pugh (CP) A cirrhosis to >50% in patients with CP C [5]. The incidence rates of OHE are less well studied and have been reported to be approximately 10% and 25% per year in patients with CP A and B cirrhosis, respectively [6]. One of the most important predictors for OHE development is the presence of MHE. However, the accuracy of prediction is variable and MHE is not a prerequisite for and may not be detected prior to diagnosis of OHE given the lack of systematic screening for MHE among patients with cirrhosis [6–11]. Most currently available studies on the influence of MHE on OHE development are limited by either small to mediocre sample sizes with heterogeneous cohorts precluding subgroup analyses and different testing strategies used for the detection of MHE. Additionally, it is still a matter of debate on which test should be used to define MHE. Thus, definitive conclusions on the predictive ability of MHE, for example, defined by the psychometric hepatic encephalopathy score (PHES) or the simplified animal naming test (S-ANT1), for OHE development cannot be drawn. The aims of this study were to investigate the association between MHE defined by PHES or the S-ANT1 and OHE development as well as mortality in a large multinational cohort of patients with cirrhosis.

Patient and methods

This retrospective study analyzed data of 1462 patients, who underwent MHE testing with PHES at the following centers with expertise in diagnosing MHE: Mainz, Siegen, Lübeck (all Germany), Paris (France), Padua, Rome (both Italy), Esbjerg (Denmark), and Ann Arbor (Michigan, US). The details of this study are also described elsewhere [5]. At each center, the primary etiology of the underlying liver disease was determined according to clinical, serological, and histological findings. Diagnosis of cirrhosis was established by histology, conclusive appearance on ultrasound, elastography or radiological imaging, endoscopic features of portal hypertension, or medical history. The severity of liver disease was determined by calculating the model for end-stage liver disease (MELD), CP scores, and the albumin–bilirubin (ALBI) scores [12–14]. MELD scores were calculated centrally using the original MELD formula of Kamath et al. The three ALBI grades were defined by cut-offs of ≤ -2.60 (grade 1), > -2.60 to ≤ -1.39 (grade 2), and > -1.39 (grade 3).

Patients were not included in this study if they had a history of any other disease leading to mental alterations (e.g., dementia or a history of stroke). At some centers, patients with self-reported ongoing (mild) alcohol consumption were included provided that they were not under the effects of alcohol during testing with PHES or animal naming test (ANT). Other exclusion criteria varied between centers and are detailed for each center in Table S1.

Diagnosis of minimal hepatic encephalopathy

All patients were examined at the respective hospitals by an experienced hepatologist to rule out clinical signs of HE. For each patient, PHES was performed to diagnose MHE. PHES is a paper-and-pencil testing battery including five subtests (number connection test A and B, serial dotting test, digit symbol test, and line tracing test). PHES was scored at each center using the validated country-specific norms (Germany [15], US [16], Italy [17], and France [18]). The Danish center used the German norms. A score < -4 was considered diagnostic of MHE for centers from Germany, France, and Denmark, whereas the centers from Italy and the US used a score ≤ -4.

In addition, a subgroup of 651 patients (from Germany and Italy) was tested with the ANT. The detailed procedure of ANT is described elsewhere [19]. In brief, patients were asked to name as many animals as possible in 1 min and the number of named animals was defined as the ANT score. Repeats and errors were excluded from the calculations. To adjust for the influence of age and education, we calculated the S-ANT1 which has been proposed by Campagna et al. [19]. For centers from Italy, a score <15 animals was considered

diagnostic of MHE [19], whereas a score <20 animals was used in centers from Germany and Denmark [20].

Follow-up evaluation

Patients were followed during regular clinic visits or via electronic chart review at the respective centers for the occurrence of OHE. The presence of OHE was diagnosed after detailed neurological examination according to the West-Haven-Criteria by an experienced hepatologist. Moreover, patients were followed for the occurrence of either death or liver transplantation (LTx). Patients who did not reach the end point of death/LTx were censored at the date of last contact.

Ethics

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (7th revision, 2013). This study used anonymized electronic medical records without directly identifiable data. According to German regulations and the recommendations of the Ethics Committee of the Landesärztekammer Rheinland-Pfalz, no ethical approval is required for this type of study. Anonymized data were analyzed as aggregates with no protected health information available. For the subset of patients with data recorded in a prospective setting (Mainz, Siegen, Lübeck), the respective study protocols were approved by the Ethics Committees of the respective centers, and all patients provided informed consent for participation.

Statistical analysis

R 4.1.3 (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and RStudio version 2022.12.0.353 (Posit Team (2022). RStudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA. URL http://www.posit.co/.) were used for data analysis and graphic design. The {table1} R package (v1.4.3; Benjamin Rich 2023) was used for calculating demographics and clinical characteristics. Quantitative data are expressed as median with range. Pairwise comparisons for continuous variables were performed using the Mann–Whitney *U* Test. Categorical variables are displayed as frequencies and percentages. For the comparison of two or more patient groups, a chi-squared test was applied.

Missing data were excluded from the respective analysis (complete-case analysis). Median follow-up time was calculated using the reverse Kaplan–Meier method and the {prodlim} R package (v2019.11.13, Thomas A. Gerds 2019).

Cumulative incidence functions for competing risk analyses and Fine and Gray competing risk regression analyses were conducted using the {tidycmprsk} R package (v0.2.0, Daniel D. Sjoberg and Teng Fei 2022).

To identify the impact of MHE on OHE development, multistate models with three states were used to calculate OHE incidences and to fit Fine and Gray regression models (coding: 0: alive without LTx and no OHE event at the end of follow-up, 1: OHE event during follow-up, 2: death or LTx during follow-up). Gray's test was used to assess differences between groups in cumulative incidence function. Follow-up time was defined as time from study inclusion to censoring, OHE, death, or transplantation, respectively.

To analyze the impact of MHE on overall survival, analyses were conducted using cumulative incidence functions with a three-state model (0: alive and not transplanted at the end of follow-up; 1: death, 2: LTx). Gray's test was used to evaluate differences between groups. To identify independent variables associated with poorer overall survival, we conducted multivariable regression analyses using the method of Fine and Gray.

To analyze the impact of MHE on transplantation-free survival, Kaplan–Meier curves and Cox proportional hazards regression models were fitted using the {survminer} R package (v0.4.9; Alboukadel Kassambara, Marcin Kosinski, and Przemyslaw Biecek 2021) and the {survival} R package (v3.5-3, Therneau T 2023). Differences between groups were assessed with the log-rank test. For these survival analyses, a two-state model with death and LTx as a composite end point was applied (0: alive, not transplanted; 1: death or LTx).

Regarding multivariable Fine and Gray as well as Cox regression analyses, models were adjusted for age, bilirubin, international normalized ratio, creatinine, albumin, and history of OHE. These variables were selected because they have been found

to be relevant risk factors for developing OHE in previous studies. Continuous variables were kept continuous without categorization, dichotomization, or transformation and were modeled as linear.

For all tests, a 0.05 level was used to define statistically significant deviations from the respective null hypothesis.

Results

In total, data from 1462 patients with cirrhosis were available for analyses (Fig. S1). The cohort was predominantly male (66.4%) with a median age of 61 years (range 23–87). A history of OHE was noted in 419 patients (29.1%) and MHE according to PHES was present in 503 patients (34.4%). Additional demographics and clinical characteristics are displayed in Table 1. In addition, demographics and clinical characteristics of patients without a history of OHE and the subgroup of patients with available testing with S-ANT1 are shown in Tables S2 and S3, respectively. The patient characteristics differed between centers. The detailed characteristics of the cohorts of each center are displayed in Table S4.

Association between MHE and development of OHE during follow-up

All included patients were followed for the development of the first OHE episode after enrollment or death/LTx. Median follow-up time was 18.8 months (interquartile range 10.3; 29.9). In total, 336 (23%) patients experienced at least one OHE episode. Additionally, 274 (19%) patients died or received a LTx before an episode of OHE.

In the total cohort, the cumulative OHE-incidences differed significantly between patients with MHE defined by PHES compared to patients without MHE ($p < 0.001$, Fig. 1). The cumulative OHE-incidences for patients with MHE at 6, 12, and 24 months for patients with MHE were 19%, 28%, and 38%, respectively, whereas they were 7%, 12%, and 20% for patients without MHE (Table 2). Sensitivity, specificity, positive predictive value, and negative predictive value of MHE defined by PHES for the prediction of an OHE event during one year is displayed in Table S5. To further analyze the association between MHE and OHE development, we stratified the cohort according to CP stages. Here, cumulative OHE-incidences differed significantly between patients with and without MHE in the subgroup of patients with CP B cirrhosis ($p < 0.001$), whereas there was no significant difference in patients with CP A ($p = 0.09$) or CP C ($p = 0.7$) (Fig. 1, Table 2). The same was also done for different MELD groups (Fig. S5). Next, we analyzed the association between MHE defined by PHES and OHE development in the subgroup of patients with alcoholic, viral, or other/mixed cirrhosis. Here, patients with MHE had a significantly higher risk of OHE development in all subgroups (1-year cumulative incidence (MHE− vs. MHE+) for alcohol: 10% vs. 26% ($p < 0.001$), viral: 15% vs. 41% ($p < 0.001$), and others/mixed: 12% vs. 21% ($p = 0.029$)). To identify variables independently associated with the development of OHE, we fitted multivariable regression models using the method of Fine and Gray under consideration of the competing events of death or LTx (Table 3). MHE defined by PHES was independently associated with the development of OHE (subdistribution hazard ratio [sHR] 1.74, 95% CI 1.34–2.27, $p < 0.001$). In subgroup analyses, the association between MHE and OHE development only remained significant in patients with CP B (sHR 2.23, 95% CI 1.57–3.18, $p < 0.001$), whereas there was no significant association in patients with CP A (sHR 1.40, 95% CI 0.75–2.61, $p = 0.3$) or CP C (sHR 1.10, 95% CI 0.68–1.78, $p = 0.7$) (Table 3).

Given that patients with a history of OHE are at higher risk for recurrent OHE, we repeated our analyses in the subgroup of patients without a history of OHE ($n = 1021$). Again, the cumulative OHE-incidences differed significantly between patients with and without MHE ($p < 0.001$, Fig. 2). This was also true in a subgroup analysis after excluding patients with a prescription of rifaximin and/or lactulose or in those with a prescription of lactulose and/or rifaximin (Fig. S2). The cumulative OHE-incidences for patients with MHE at 6, 12, and 24 months were 16%, 25%, and 37%, respectively, whereas they were 5%, 9%, and 16% for patients without MHE (Table 2). In subgroup analyses stratified by CP stage, cumulative OHE-incidences differed significantly between patients with and without MHE in the subgroup of patients with CP A ($p = 0.01$) or CP B cirrhosis ($p < 0.001$), whereas there was no significant difference in patients with CP C ($p = 0.5$) (Fig. 2). In multivariable analysis, MHE remained significantly associated with the development of OHE (sHR 2.23, 95% CI 1.57–3.17, $p < 0.001$, Table S6). In subgroup multivariable analyses, the association between MHE and OHE development remained

Table 1. Demographics and clinical characteristics of the study cohort.

	Total cohort ($n = 1462$)	MHE− ($n = 959$)	MHE+ ($n = 503$)	p-Value
Age (years)				
Median [min, max]	61.0 [23.0, 87.0]	60.0 [23.0, 87.0]	62.0 [27.0, 87.0]	0.03
Missing	1 (0.1%)	1 (0.1%)	0 (0%)	
Gender				
Male	971 (66.4%)	618 (64.4%)	353 (70.2%)	0.03
Female	491 (33.6%)	341 (35.6%)	150 (29.8%)	
Etiology				
Alcohol	637 (43.8%)	388 (40.8%)	249 (49.6%)	0.005
Viral	356 (24.5%)	242 (25.4%)	114 (22.7%)	
Others/Mixed	460 (31.7%)	321 (33.8%)	139 (27.7%)	
Missing	9 (0.6%)	8 (0.8%)	1 (0.2%)	
MELD score				
Median [min, max]	11.0 [6.00, 34.0]	10.0 [6.00, 29.0]	12.0 [6.00, 34.0]	<0.001
Missing	67 (4.6%)	50 (5.2%)	17 (3.4%)	
ALBI score				
Median [min, max]	−2.06 [−3.75, 0.272]	−2.19 [−3.75, 0.272]	−1.79 [−3.40, 0.143]	<0.001
Missing	328 (22.4%)	224 (23.4%)	104 (20.7%)	
Child Pugh				
A	648 (46.6%)	497 (54.7%)	151 (31.3%)	<0.001
B	574 (41.2%)	333 (36.6%)	241 (49.9%)	
C	170 (12.2%)	79 (8.7%)	91 (18.8%)	
Missing	70 (4.8%)	50 (5.2%)	20 (4.0%)	
ALBI grade				
1	260 (22.9%)	205 (27.9%)	55 (13.8%)	<0.001
2	659 (58.1%)	425 (57.8%)	234 (58.6%)	
3	215 (19.0%)	105 (14.3%)	110 (27.6%)	
Missing	328 (22.4%)	224 (23.4%)	104 (20.7%)	
MHE (S-ANT1)				
No	336 (51.6%)	283 (66.1%)	53 (23.8%)	<0.001
Yes	315 (48.4%)	145 (33.9%)	170 (76.2%)	
Missing	811 (55.5%)	531 (55.4%)	280 (55.7%)	
History of ascites				
No	660 (45.7%)	494 (52.1%)	166 (33.5%)	<0.001
Yes	784 (54.3%)	454 (47.9%)	330 (66.5%)	
Missing	18 (1.2%)	11 (1.1%)	7 (1.4%)	
History of OHE				
No	1021 (70.9%)	730 (77.0%)	291 (59.1%)	<0.001
Yes	419 (29.1%)	218 (23.0%)	201 (40.9%)	
Missing	22 (1.5%)	11 (1.1%)	11 (2.2%)	
Sodium (mmol/L)				
Median [min, max]	138 [112, 149]	139 [118, 149]	137 [112, 147]	<0.001
Missing	215 (14.7%)	156 (16.3%)	59 (11.7%)	
Creatinine (mg/dL)				
Median [min, max]	0.840 [0.100, 7.51]	0.814 [0.100, 7.51]	0.900 [0.300, 6.73]	<0.001
Missing	85 (5.8%)	67 (7.0%)	18 (3.6%)	

(*Continued*)

Table 1. *(Continued)*

	Total cohort ($n = 1462$)	MHE− ($n = 959$)	MHE+ ($n = 503$)	p-Value
Bilirubin (mg/dL)				
Median [min, max]	1.28 [0.100, 46.5]	1.17 [0.175, 33.3]	1.50 [0.100, 46.5]	<0.001
Missing	87 (6.0%)	70 (7.3%)	17 (3.4%)	
Albumin (g/L)				
Median [min, max]	35.0 [14.0, 54.0]	36.0 [15.0, 54.0]	32.0 [14.0, 51.1]	<0.001
Missing	238 (16.3%)	167 (17.4%)	71 (14.1%)	
INR				
Median [min, max]	1.24 [0.800, 3.30]	1.21 [0.800, 3.30]	1.30 [0.900, 3.23]	<0.001
Missing	122 (8.3%)	96 (10.0%)	26 (5.2%)	
Platelets (per nL)				
Median [min, max]	115 [12.0, 1150]	120 [19.0, 1150]	107 [12.0, 644]	0.1
Missing	475 (32.5%)	344 (35.9%)	131 (26.0%)	
Lactulose[a]				
No	962 (65.9%)	699 (73.0%)	263 (52.5%)	<0.001
Yes	497 (34.1%)	259 (27.0%)	238 (47.5%)	
Missing	3 (0.2%)	1 (0.1%)	2 (0.4%)	
Rifaximin[a]				
No	877 (74.8%)	634 (80.6%)	243 (63.1%)	<0.001
Yes	295 (25.2%)	153 (19.4%)	142 (36.9%)	
Missing	290 (19.8%)	172 (17.9%)	118 (23.5%)	

Abbreviations: ALBI, albumin–bilirubin; INR, international normalized ratio; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; S-ANT1, simplified animal naming test; SD, standard deviation.
[a]Intake at study inclusion. Percentages refer to the patients with available data.

significant in patients with CP A cirrhosis (sHR 2.14, 95% CI 1.02–4.49, $p = 0.043$) as well as CP B (sHR 2.92, 95% CI 1.76–4.82, $p < 0.001$), whereas there was no significant association in patients with CP C (sHR 1.16, 95% CI 0.60–2.21, $p = 0.7$) (Table S6).

We also investigated cumulative OHE-incidences in patients with a history of OHE. No significant difference was detected in patients with or without MHE (Fig. S6).

A subgroup of 651 patients was also tested with S-ANT1 at baseline and MHE according to S-ANT1 was present in $n = 315$ (48%). In this subgroup, 20.7% developed an episode of OHE during follow-up, whereas 25.8% of the cohort without available S-ANT1 developed an OHE episode (Table S7). In the total cohort as well as in the subgroup of patients without a history of OHE, the cumulative OHE-incidences differed significantly between patients with MHE defined by S-ANT1 compared to patients without MHE ($p = 0.002$ and $p = 0.006$, Fig. 3). In multivariable analysis, MHE according to S-ANT1 remained significantly associated with OHE development (sHR 1.56, 95% CI 1.11–2.21, $p = 0.011$) (Table S8). We also compared the cumulative OHE incidences of patients with abnormal results in both PHES and S-ANT1 ($n = 170$) to patients with abnormal results in only one test ($n = 198$) and patients with no abnormal results ($n = 283$). The cumulative OHE incidences differed significantly between the groups (Fig. 3, $p < 0.001$). This finding also remained true after excluding patients with a history of OHE (Fig. 3, $p < 0.001$). In multivariable analysis, abnormal results in both PHES and S-ANT1 had a stronger association with the development of OHE (sHR 2.44, 95% CI 1.59–3.74, $p < 0.001$) compared to abnormal results in only one test (sHR 1.47, 95% CI 0.95–2.27, $p = 0.082$) (Table S8).

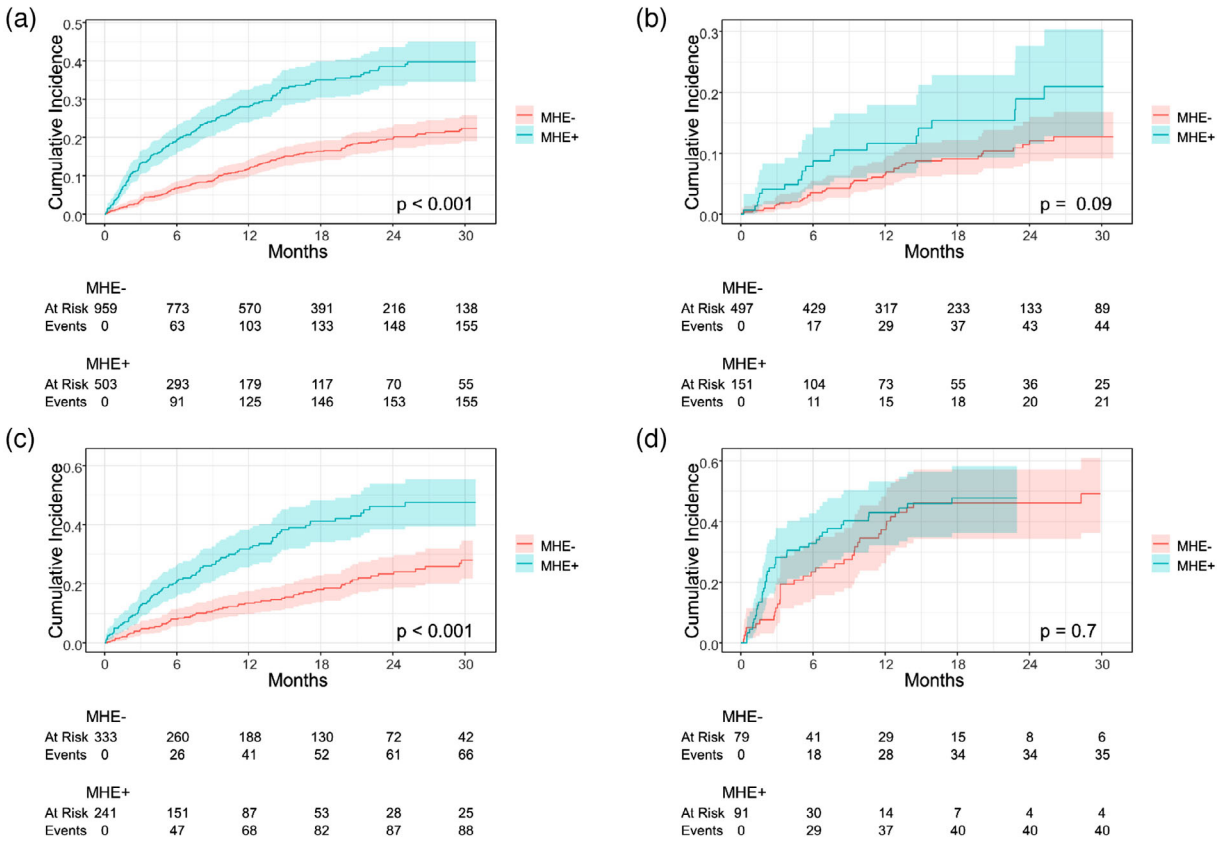

Fig. 1 *Cumulative incidence of overt HE (OHE). A three-state model was fitted with death and liver transplantation as competing events. Differences between groups were calculated with Gray's test. Cumulative OHE incidence in patients with versus without MHE defined by PHES in (A) all patients, (B) patients with Child-Pugh A, (C) patients with Child-Pugh B, and (D) patients with Child-Pugh C. MHE, minimal hepatic encephalopathy (defined by PHES); PHES, psychometric hepatic encephalopathy score.*

Association between MHE and death/liver transplantation during follow-up

In total, 464 (32%) patients died ($n = 369$) or underwent LTx ($n = 95$) during follow-up. Patients with MHE according to PHES had significantly poorer overall survival and transplantation-free survival compared to patients without MHE ($p < 0.001$ each, Fig. 4). When stratifying the cohort according to CP stage, MHE according to PHES remained significantly associated with poorer transplantation-free survival across all CP stages ($p < 0.01$ each, Fig. S3). In multivariable Cox regression analysis, MHE was independently associated with poorer transplantation-free survival (hazard ratio [HR] 1.53, 95% CI 1.22–1.92, $p < 0.001$, Table 4). In competing risk regression analysis using the method of Fine and Gray, MHE remained independently associated with poorer overall survival even when LTx was defined as a competing event (sHR 1.66, 95% CI 1.27–2.18, $p < 0.001$, Table S9).

In the subgroup of patients with available S-ANT1 results, MHE defined by S-ANT1 was not significantly associated with poorer transplantation-free survival (HR 1.27, 95% CI 0.94–1.72, $p = 0.12$, Table S10) in multivariable Cox regression analysis. Additionally, in multivariable competing risk regression analysis, MHE defined by S-ANT1 was not significantly associated with overall survival when treating LTx as a competing risk (sHR 1.30, 95% CI 0.91–1.84, $p = 0.2$) (Table S9).

We also investigated the association between combined testing with PHES and S-ANT1 and transplantation-free as well as overall survival. In Cox regression analysis, pathologic results in both

Table 2. Cumulative OHE incidences at 6, 12, and 24 months in different subgroups stratified by MHE status.

Time	MHE (PHES)	No MHE (PHES)	
	Cumulative OHE incidence (95% CI)	Cumulative OHE incidence (95% CI)	*p*-Value[a]
Total cohort (*n* = 1462)			
6 months	19% (16%, 23%)	6.8% (5.3%, 8.5%)	<0.001
12 months	28% (24%, 32%)	12% (9.8%, 14%)	
24 months	38% (33%, 44%)	20% (17%, 23%)	
Child-Pugh A (*n* = 648)			
6 months	7.9% (4.2%, 13%)	3.6% (2.1%, 5.5%)	0.09
12 months	12% (6.7%, 18%)	6.6% (4.5%, 9.3%)	
24 months	19% (12%, 28%)	12% (8.7%, 16%)	
Child-Pugh B (*n* = 574)			
6 months	21% (16%, 26%)	8.1% (5.4%, 11%)	<0.001
12 months	32% (26%, 38%)	13% (9.9%, 18%)	
24 months	46% (38%, 54%)	23% (18%, 29%)	
Child-Pugh C (*n* = 170)			
6 months	33% (23%, 43%)	23% (15%, 33%)	0.7
12 months	43% (32%, 53%)	37% (26%, 48%)	
Patients without a history of OHE (*n* = 1021)			
6 months	16% (12%, 21%)	5.4% (3.9%, 7.2%)	<0.001
12 months	25% (20%, 31%)	8.8% (6.8%, 11%)	
24 months	37% (30%, 44%)	16% (13%, 19%)	
Child-Pugh A without a history of OHE (*n* = 530)			
6 months	5.3% (1.9%, 11%)	2.7% (1.4%, 4.6%)	0.01
12 months	10% (5.0%, 18%)	4.9% (3.0%, 7.5%)	
24 months	20% (11%, 31%)	8.9% (6.0%, 12%)	
Child-Pugh B without a history of OHE (*n* = 357)			
6 months	19% (13%, 27%)	5.9% (3.3%, 9.6%)	<0.001
12 months	31% (22%, 40%)	9.7% (6.1%, 14%)	
24 months	48% (36%, 59%)	18% (13%, 25%)	
Child-Pugh C without a history of OHE (*n* = 105)			
6 months	32% (20%, 46%)	25% (14%, 38%)	0.5
12 months	45% (30%, 59%)	33% (21%, 47%)	

Abbreviations: CI, confidence interval; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score.
[a]Gray's test.

PHES and S-ANT1 had a stronger association with poorer transplantation-free survival (HR 1.97, 95% CI 1.36–2.85, $p < 0.001$) compared to pathologic results in only one test (HR 1.51, 95% CI 1.04–2.20, $p = 0.032$) (Table S10). In multivariable competing risk regression analysis, pathologic results in both PHES and S-ANT1 were associated with poorer overall survival when LTx was defined as a competing event (sHR 2.03, 95% CI 1.33–3.09, $p < 0.001$), whereas pathologic results in only one test were not (sHR 1.26, 95% CI 0.81–1.95, p = 0.3) (Table S9).

To adjust for within-center dependence, we fitted a Fine and Gray regression model including seven centers as dummy variables with Mainz as the largest center in the reference group, respectively (Table S11). Here, MHE remained independently associated with OHE development with a sHR of 1.61 (95% CI 1.23–2.09, $p < 0.001$).

Table 3. Multivariable competing risk regression analysis for the development of overt HE in the total cohort and stratified by Child-Pugh (CP) stage.

	Total cohort				CP A				CP B				CP C			
Variables	N	sHR	95% CI	*p*	N	sHR	95% CI	*p*	N	sHR	95% CI	*p*	N	sHR	95% CI	*p*
MHE (PHES)																
No	746				404				275				67			
Yes	417	1.74	1.34, 2.27	**<0.001**	125	1.40	0.75, 2.61	0.3	212	2.23	1.57, 3.18	**<0.001**	79	1.10	0.68, 1.78	0.7
Albumin (g/L)	1,163	0.94	0.92, 0.96	**<0.001**	529	0.91	0.85, 0.98	**0.009**	487	0.98	0.95, 1.01	0.2	146	0.95	0.89, 1.01	0.11
Creatinine (mg/dL)	1,163	1.22	1.03, 1.46	**0.023**	529	1.17	0.52, 2.64	0.7	487	1.28	1.07, 1.54	**0.009**	146	0.82	0.49, 1.37	0.5
History of OHE																
No	845				445				308				92			
Yes	318	1.72	1.32, 2.23	**<0.001**	84	2.95	1.71, 5.09	**<0.001**	179	1.34	0.95, 1.91	0.10	54	1.35	0.81, 2.23	0.3
Bilirubin (mg/dL)	1,163	1.01	0.98, 1.05	0.4	529	0.77	0.29, 2.08	0.6	487	1.04	1.01, 1.07	**0.011**	146	0.96	0.89, 1.03	0.3
INR	1,163	1.57	1.07, 2.32	**0.022**	529	2.78	0.55, 14.0	0.2	487	0.77	0.44, 1.34	0.4	146	1.50	0.71, 3.18	0.3
Age (years)	1,163	1.01	1.00, 1.03	**0.025**	529	1.03	0.99, 1.06	0.11	487	1.02	1.00, 1.03	0.063	146	1.01	0.98, 1.05	0.4

Note: Patients with missing data were excluded from analysis (complete-case analysis). *p*-Values in bold show significant values.
Abbreviations: CI, confidence interval; CP, Child-Pugh; INR, international normalized ratio; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; sHR, subdistribution hazard ratio.

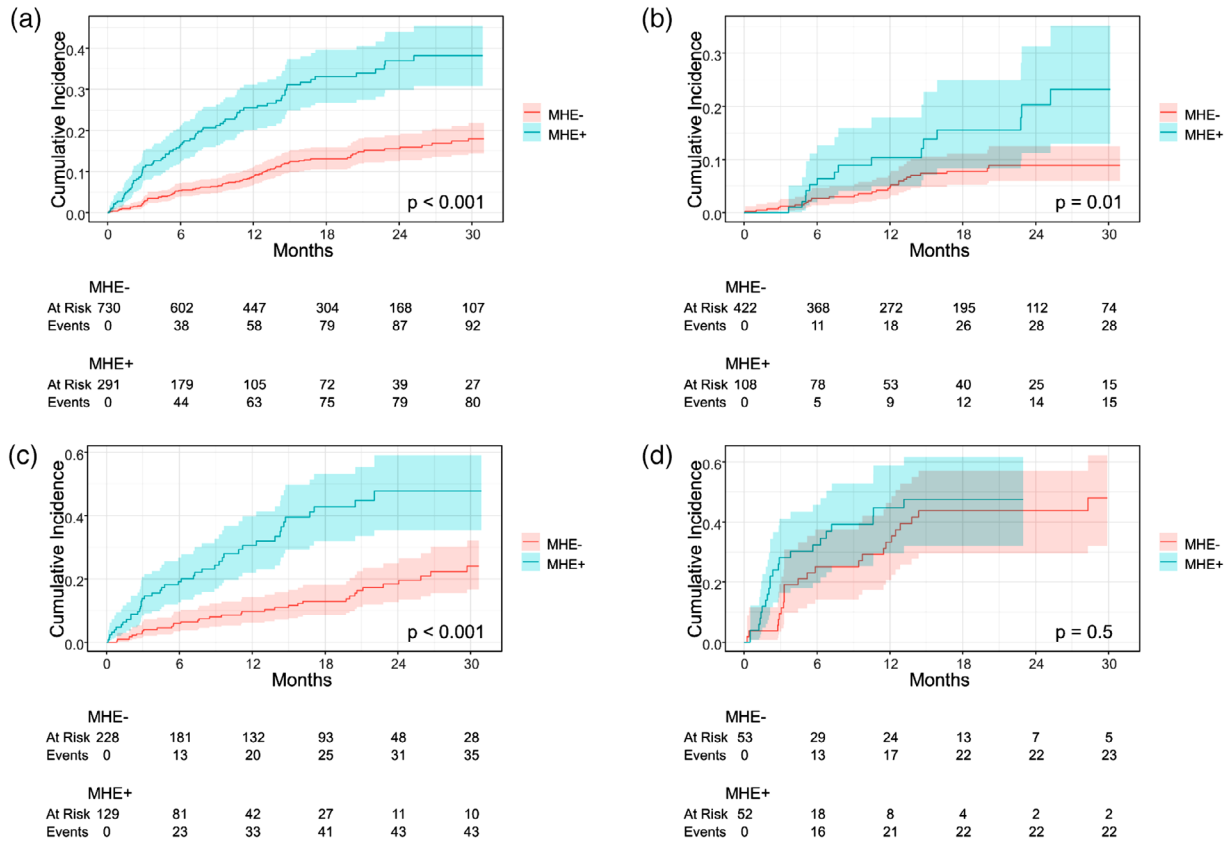

Fig. 2 *Cumulative incidence of overt HE (OHE) in patients without a history of OHE. A three-state model was fitted with death and liver transplantation as competing events. Differences between groups were calculated with Gray's test. Cumulative OHE incidence in patients with versus without MHE defined by PHES in (A) all patients without a history of OHE, (B) patients with Child-Pugh A without a history of OHE, (C) patients with Child-Pugh B without a history of OHE, and (D) patients with Child-Pugh C without a history of OHE. MHE, minimal hepatic encephalopathy (defined by PHES); PHES, psychometric hepatic encephalopathy score.*

Discussion

In this study, we provide detailed data on the predictive value of MHE regarding hard clinical end points in patients with cirrhosis in a large multinational cohort. We were able to demonstrate that MHE according to PHES is associated with a higher risk for OHE development; however, this association was restricted to patients with CP B cirrhosis in the total cohort. Moreover, we found a robust association between MHE defined by PHES and poorer (transplantation-free) survival. The findings regarding OHE prediction were also consistent in a subgroup of patients with available S-ANT1. Additionally, we were able to demonstrate that when using combined testing, abnormal results in both PHES and S-ANT1 are superior to abnormal results in only one test in identifying a group at greater risk of OHE in the subgroup with both tests available.

MHE> is a common complication in patients with cirrhosis and its prevalence strongly depends on the grade of decompensation of cirrhosis and the respective test used to define the disease [5]. Consequently, testing strategies for MHE are highly debated and studies demonstrated only poor correlation between different tests, such as PHES, critical flicker frequency, or Stroop EncephalApp [21, 22]. This is most likely explained by the fact that in patients with MHE not every sign or symptom may be present at any given time. That's why the international guidelines and the International Society of Hepatic Encephalopathy and Nitrogen Metabolism recommended the use of two

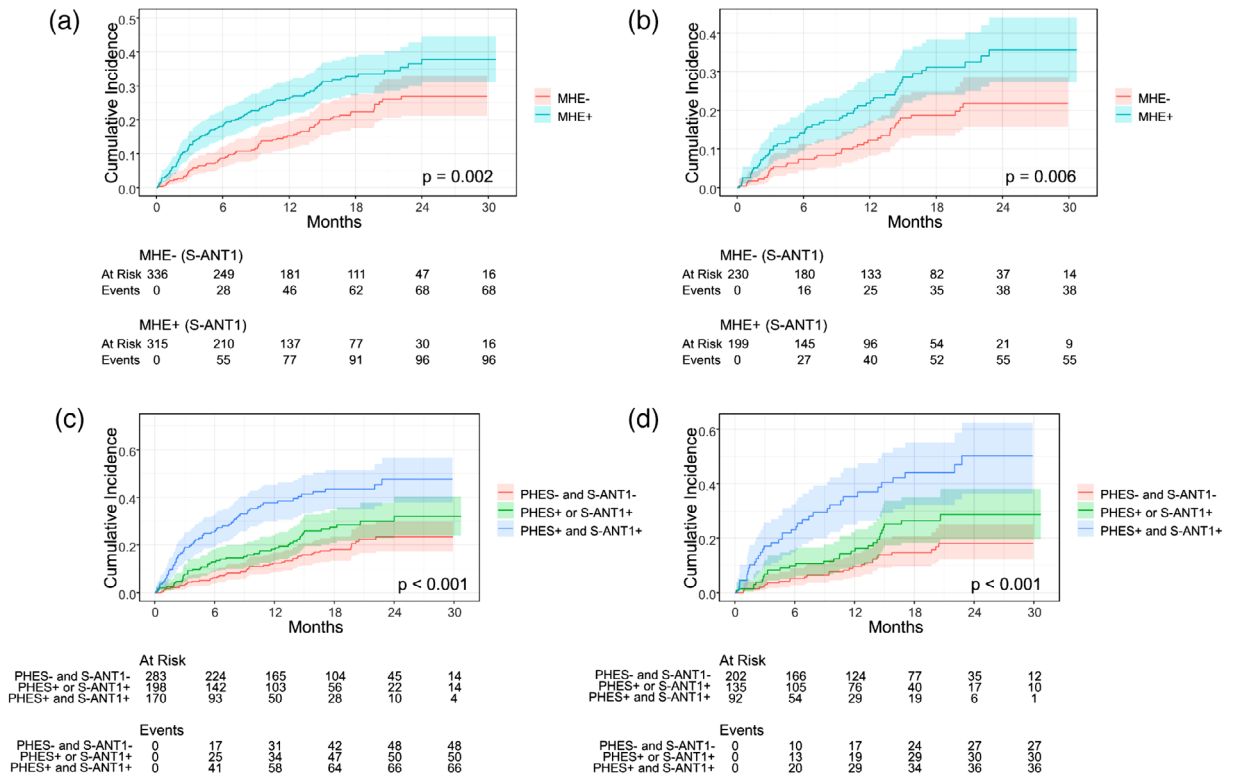

Fig. 3 *Cumulative incidence of overt HE (OHE). Cumulative OHE incidence stratified by MHE status defined by S-ANT1 in (A) total cohort and (B) subgroup of patients without a history of OHE. Cumulative OHE incidence stratified according to their results in PHES and S-ANT1 (group 1: no MHE according to PHES and S-ANT1; group 2: MHE according to PHES or S-ANT1; group 3: MHE according to both PHES and S-ANT1) in (C) total cohort and (D) subgroup of patients without a history of overt HE. Differences between groups were calculated with Gray's test. MHE–, MHE negative defined by S-ANT1; MHE+, MHE positive defined by S-ANT1; PHES, Psychometric Hepatic Encephalopathy Score; S-ANT1, simplified animal naming test.*

Table 4. Multivariable Cox regression analysis for transplantation-free survival.

Variables	*N*	HR	95% CI	*p*
MHE (PHES)				
No	746			
Yes	417	1.53	1.22, 1.92	<0.001
Albumin (g/L)	1163	0.94	0.92, 0.96	<0.001
Creatinine (mg/dL)	1163	1.46	1.29, 1.67	<0.001
History of OHE				
No	845			
Yes	318	1.16	0.92, 1.47	0.2
Bilirubin (mg/dL)	1163	1.07	1.05, 1.09	<0.001
INR	1163	2.17	1.59, 2.97	<0.001
Age (years)	1163	1.02	1.01, 1.04	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; INR, International Normalized Ratio; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score.

independent testing strategies for the detection of MHE in multicenter studies in the past [23]. However, this approach has not been extensively validated and a recent study by Duarte-Rojo et al. challenged this concept regarding outcome prediction [11]. When focusing on PHES, the existing literature is quite heterogeneous indicating a potential association between MHE defined by PHES and development of OHE, whereas studies regarding a potential association with overall survival are conflicting [7–10]. This may most likely be explained by only mediocre sample sizes with a lack of power or single/bicentric study settings. Our current study solidifies the association between PHES and hard clinical outcome events, such as OHE and death/LTx, in a large multinational setting. Due to the large sample size, we were also able to perform robust subgroup analyses in different CP stages for the first time. The by far strongest association between MHE and OHE development was found

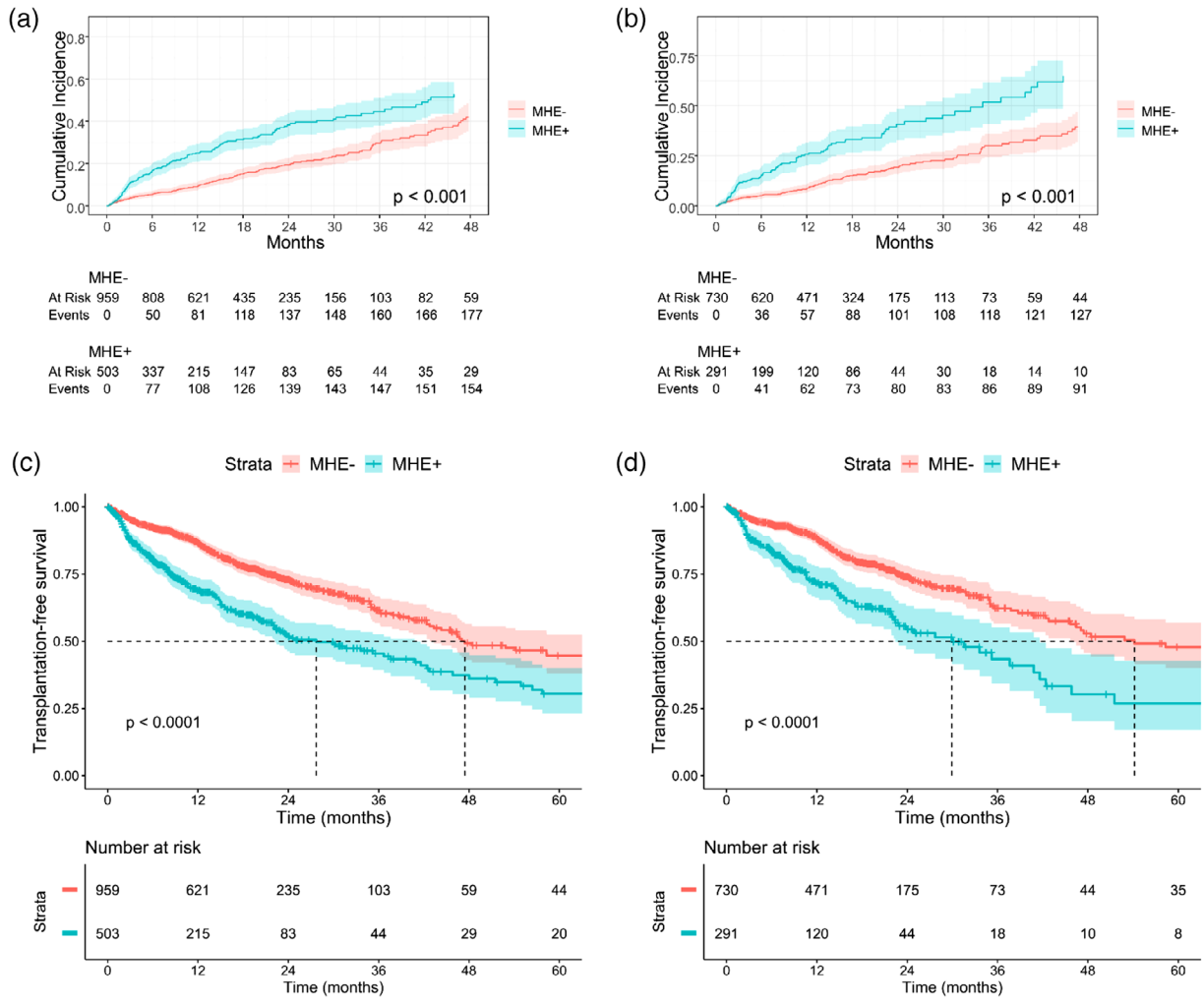

Fig. 4 *Survival of patients stratified by MHE status. Cumulative incidence of death in patients with versus without MHE defined by PHES, with liver transplantation as a competing event in (A) total cohort and (B) subgroup of patients without a history of overt HE. Differences between groups were calculated with Gray's test. (C) Kaplan–Meier curves showing transplantation-free survival stratified according to MHE status defined by PHES in (C) total cohort and (D) subgroup of patients without a history of overt HE. Differences between groups were calculated with the log-rank test. MHE−, MHE negative defined by PHES; MHE+, MHE positive defined by PHES; PHES, psychometric hepatic encephalopathy score.*

in patients with CP B cirrhosis. This finding is of great clinical importance given that most clinicians are aware of MHE. However testing is frequently neglected given the effort needed for cognitive testing in the busy daily routine [24]. In this setting, our study robustly indicates that testing for MHE with PHES for predicting OHE development is especially useful in patients with CP B cirrhosis and should be implemented into routine care for risk stratification. Evidence already suggests that prevention of a first OHE episode may be achievable, and our data may also serve as a blueprint for designing future trials on primary prophylaxis [25–27]. In this context, it seems mandatory that future studies on primary prophylaxis of OHE in patients with CP B cirrhosis need stratification for the presence of MHE, because OHE frequency differs markedly between patients with and without MHE. Another important finding of our study is that primary prophylaxis does not appear to be justified in patients with CP A cirrhosis without a history of OHE irrespective of MHE status given the

low 1-year cumulative incidence of OHE of <10% even in patients with MHE. This is also in line with a single center study published by Tapper et al. (10% 1-year OHE incidence in patients with CP A and portal hypertension) [6]. On the other side, our data suggest that primary prophylaxis trials in patients with CP C cirrhosis independent of MHE status should be strongly encouraged given the high probability for OHE during the subsequent year (>33%).

Despite the availability of various tools for detecting MHE, screening is often neglected in clinical practice [24, 28]. An important explanation is the often busy daily schedules and limited time for patient contact. In this context, the implementation of testing with S-ANT1 may enhance cognitive testing in patients with cirrhosis. Our study indicates in a multicenter setting that MHE defined by S-ANT1 is robustly associated with OHE development. Nevertheless, it has to be kept in mind that S-ANT1 has its weaknesses and the results must be interpreted in the context of a wide variety of influencing factors [29].

There is an ongoing debate on whether testing for MHE should be conducted using one or more testing strategies in routine care as well as study settings [23, 30]. The rationale behind this recommendation is that although the requirement of abnormal results in a combination of tests decreases the prevalence of MHE, pathologic results in two tests could identify patients at the highest risk of OHE. However, a US-based multicenter study by Duarte-Rojo et al. found that a combination of PHES, inhibitory control test, or Stroop EncephalApp was not superior for predicting OHE compared to PHES or Stroop EncephalApp alone [11]. By contrast, our study showed that patients with pathologic results in both PHES and S-ANT1 had a significantly higher risk of OHE and lower probability of transplant-free survival compared to abnormal results in only one test. The study by Duarte-Rojo et al. and ours are not easily comparable given that except for PHES different testing strategies were used to define MHE. Moreover, our current study cannot answer whether the predictive ability of a combination of PHES and S-ANT1 is better for predicting OHE episodes than a combination of PHES and, for example, an oral glutamine challenge or even genetic risk scores [31, 32]. Additionally, we acknowledge that results in S-ANT1 were only available for a subset of the cohort; therefore, our findings need validation in future prospective studies. In this context, our results lead to the hypothesis that the assessment of different cognitive domains may improve the prediction of OHE. Here, the combination of PHES and S-ANT1 could be potentially beneficial as they investigate partly different cognitive domains.

One of the most important strengths of our study is the large multicenter patient cohort and sufficient follow-up time allowing robust subgroup analyses. However, there are also limitations. First, this was a retrospective analysis. Therefore, patients were not specifically recruited for this study following a dedicated protocol and no monitoring of the quality of testing was possible. Moreover, information on neurotoxic drugs, narcotic analgesia, precipitating events of the OHE episodes or ammonia levels at diagnosis of OHE are not available in this study. Second, patients were only included if testing with PHES was available. This may introduce relevant selection bias as in some parts of the cohort testing with PHES might have only been performed in case of suspicion of MHE. This may lay a focus on sicker patients and therefore our findings might not be generalizable to every patient with cirrhosis. However, we are unable to speculate on the direction of this selection bias. Third, we are unable to provide ideal cut-offs for PHES or S-ANT1 for predicting clinical outcomes in this study. This is explained by the fact that we used country-specific norms for scoring PHES and S-ANT1; therefore, raw results are not completely comparable between centers. Fourth, there is missing data on some laboratory characteristics in some patients. However, these values were missing at random and are not expected to have a major impact on our results. Fifth, data on S-ANT1 were only available in a subgroup of patients; therefore, these analyses lack statistical power. Therefore, these results have to be interpreted with more caution. Sixth, detailed information on the underlying etiology of cirrhosis in the "mixed/other" group was unavailable and consequently precluded additional analyses. Last, we performed a lot of statistical tests in this study and did not adjust for multiple testing. This might cause type I error and *p*-values should be interpreted with caution.

In conclusion, we provide detailed data on the predictive utility of MHE regarding hard clinical end points in patients with cirrhosis in a large multinational cohort. We were able to demonstrate that MHE according to PHES is associated with a higher risk for OHE development, with the strongest asso-

ciation in patients with CP B cirrhosis. Additionally, we were able to demonstrate the superiority of combined testing with PHES and S-ANT1 compared to single testing for OHE prediction. These data need to be validated in prospective, large cohorts to be adopted into routine clinical practice.

Author contributions

Performed research: Simon Johannes Gairing, Chiara Mangini, Lisa Zarantonello, Stefania Gioia, Elise Jonasson Nielsen, Sven Danneberg, Patricia P. Bloom, Philippe Sultanik, Peter Robert Galle, Joachim Labenz, Dominique Thabut, Anna S. Lok, Jens Uwe Marquardt, Mette Munk Lauridsen, Silvia Nardelli, Sara Montagnese, and Christian Labenz. *Contributed to acquisition of data*: Simon Johannes Gairing, Chiara Mangini, Lisa Zarantonello, Stefania Gioia, Elise Jonasson Nielsen, Sven Danneberg, Patricia P. Bloom, Philippe Sultanik, Peter Robert Galle, Joachim Labenz, Dominique Thabut, Anna S. Lok, Jens Uwe Marquardt, Mette Munk Lauridsen, Silvia Nardelli, Sara Montagnese, and Christian Labenz. *Designed the experiments and analyzed the data*: Simon Johannes Gairing and Christian Labenz. *Contributed reagents/materials/analysis tools*: Simon Johannes Gairing and Christian Labenz. *Wrote the paper*: Simon Johannes Gairing and Christian Labenz. *Statistical analysis*: Simon Johannes Gairing and Christian Labenz.

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Conflict of interest statement

Simon Johannes Gairing: Travel expenses: Ipsen and Gilead. Joachim Labenz: Consulting: Alphasigma, Norgine. Lecture fees: Norgine. Peter R. Galle: Lecture fees and consulting: Merz Pharmaceuticals Patricia P. Bloom: Research grant from Vedanta Biosciences. Consultant for Nexilico. Dominique Thabut: Lecture fees: Alfasigma, Abbvie, Gilead. Christian Labenz: Travel expenses and consulting: Norgine, Merz Pharmaceuticals. Lecture fees: Norgine, Merz Pharmaceuticals. Research grants: Norgine, Merz Pharmaceuticals. All other authors disclose no potential financial or nonfinancial conflicts of interest regarding this study.

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Ethics statement

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (7th revision, 2013). This study used anonymized electronic medical records without directly identifiable data. According to German regulations and the recommendations of the Ethics Committee of the Landesärztekammer Rheinland-Pfalz, no ethical approval is required for this type of study. Anonymized data were analyzed as aggregates with no protected health information available. Regarding a subset of patient data that were recorded in a prospective setting, the respective study protocols were approved by the Ethics Committees of the respective centers and patients provided written informed consent.

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Supporting Information

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Supporting Information ■