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RESEARCH ARTICLE

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Animal naming test is a simple and valid tool for detecting covert hepatic encephalopathy and predicting outcomes in Chinese-speaking regions: a preliminary study

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ABSTRACT

Background and aims: Hepatic encephalopathy (HE) implies high morbidity and mortality. The assessment of covert HE (CHE) [i.e. minimal HE (MHE) plus grade 1 HE] is often neglected in Taiwan. Therefore, the aim was to investigate the potential of the animal naming test (ANT_1 and simplified ANT_1 (S-ANT_1)) for assessing CHE in Chinese-speaking regions, specifically Taiwan.

Methods: A prospective cohort study was conducted, comprising 65 cirrhotic patients and 29 healthy controls (relatives of the patients). Patients were followed up every three months and censored after two years or until death. Hospitalization for overt HE (OHE) and mortality were considered. All subjects underwent ANT_1, psychometric HE score (PHES), and mini-mental state examination (MMSE). The patients underwent an electroencephalogram (EEG) to detect slowing indicative of MHE. Cut-off values for ANT_1 and S-ANT_1 were assessed by ROC analysis and Youden's index, considering CHE as a reference. The prognostic values for OHE and OHE-free survival were assessed.

Results: Preliminary analysis confirmed that PHES ≤-4 is a good discriminant point for abnormal results. CHE was found in 29 patients: 9 had MHE (PHES ≤-4 or altered EEG) and 20 had grade 1 HE. ANT_1 and S-ANT_1 were found to have diagnostic values for CHE: AUC = 0.807, 0.786; cut off: 18 and 19, respectively. ANT_1 and S-ANT_1 were found to have prognostic value for OHE, number of hospitalization episodes for OHE, and OHE recurrence-free survival.

Conclusions: ANT_1 shows promise as a tool for CHE detection, quantification, and follow-up in Taiwan and other Chinese-speaking regions.

KEY MESSAGES

- The animal naming test (ANT_1) is a simple and valid semantic fluency test that can be easily performed in outpatient or bedside settings in one minute and can also be used as a tool for covert hepatic encephalopathy (CHE) detection, quantification, and follow-up in Taiwan, other Chinese-speaking regions, and many other countries.
- The diagnostic value of ANT_1 and S-ANT_1 for CHE were found to be significant, with area under the receiver operating characteristic curve (AUROC) values of 0.807 and 0.786 respectively, and cut-off scores of 18 and 19.
- ANT_1 and S-ANT_1 have prognostic value for the first breakthrough of overt hepatic encephalopathy (OHE), number of hospitalization episodes for OHE, and OHE recurrence-free survival, independent of the MELD score.

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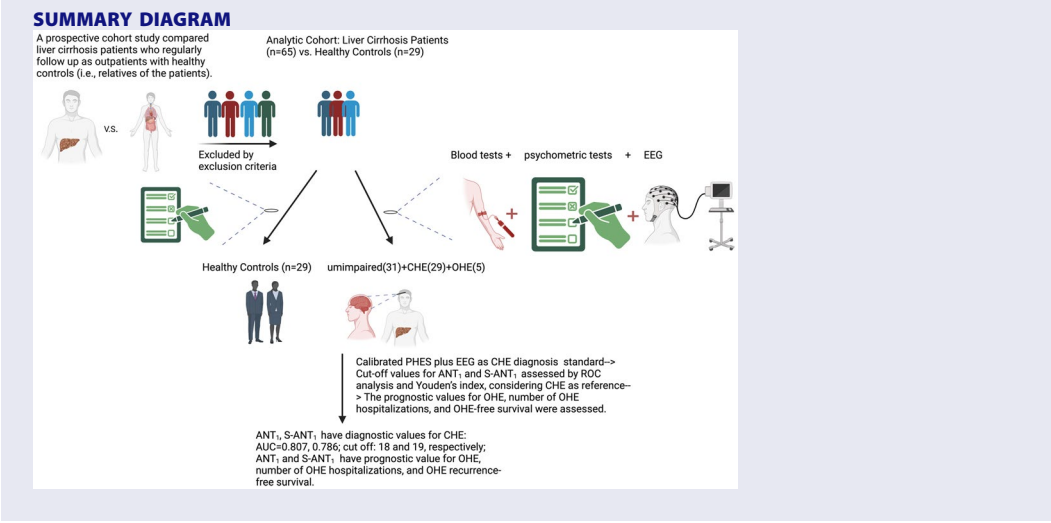

Introduction

Hepatic encephalopathy (HE) is a serious neurological-psychiatric condition caused by liver failure and/or portosystemic shunt; it manifests as a broad spectrum of changes from coma to subclinical cognitive or neurophysiological alterations [1].

The detection and quantification of covert HE (CHE) (i.e. when there are minimal cognitive/neurophysiologic alterations or slight and equivocal clinical findings without clear disorientation or asterixis [1])is relevant [2], since it is associated with increased risk for (i) overt HE (OHE) [3], (ii) poor health-related quality of life [4], (iii) increased caregiver burden [5], (iv) poor driven ability [6], (vi) falls [7], and (vii) poor income [8]. Furthermore, detecting CHE before the occurrence of OHE [1] may enable precocious treatments in a wider number of patients to reduce the burden of HE on patients, caregivers, and the health system.

However, the search and quantification for CHE are impractical in normal hepatological consultations because (i) it is based on paper and pencil psychometric tests [6] that require specific forms to be filled in, (ii) is time-consuming and (iii) cannot be easily performed at bedside. In addition, alternative procedures based on smartphone application [9] or computerized tests are not universally standardized and cannot be not easily performed by people who are not familiar with smartphones or computers.

Recently a verbal psychometric test based on semantic fluency, the animal naming test (ANT_1), which can be performed in a few minutes was suggested as a first-line tool to screen subjects for covert HE and a tool useful to follow up the cognitive performance of the patients [10]. Its routine use in clinical practice was supported by the Italian Guidelines for HE [11] and it was found a reasonable tool in Germany [12] and India [13], so recently the European Association for the Study of the Liver (EASL) considered its use in clinical practice [14].

In Taiwan, there is a need for an easy tool to detect and monitor CHE, because this condition is widely neglected in clinical practice. Thus, this preliminary study aimed to assess if the use of ANT_1, and its simplified age/education adjusted version (the S-ANT_1), and with which cut-off, for Chinese people, deserves to be investigated.

Thus, we planned a single-center prospective cohort study (i) to detect the preferable cut-off for the ANT_1 and S-ANT_1 in Taiwan and (ii) to assess if it has prognostic value comparable to the Porto-Systemic Encephalopathy (PSE) Battery that produces the Porto Hepatic Encephalopathy Score (PHES), which is conventionally considered a valuable/reference tool to detect minimal HE. In addition, also the value of the mini-mental state examination (MMSE), which is a widely-used tool to assess cognition in clinical practice, was tested.

Methods

Study design and patient enrollment

We planned a single-center prospective cohort study in a Taiwan tertiary referral center to assess the cut-off for the diagnosis of CHE of the ANT_1 and its predictive value concerning the occurrence of overt HE (requiring hospitalization) in consecutive outpatients with liver cirrhosis diagnosed based on clinical, biochemical and abdominal ultrasound findings. The S-ANT_1 [10] (an age and education-adjusted score of ANT_1 which was standardized in Italy) was also considered. On the

same day on which the subjects underwent the ANT_1, they underwent the PHES and the MMSE. Healthy controls that were recruited from patients' relatives were considered.

The exclusion criteria were: age < 20 years old, neurological or psychiatric comorbidities (dementia or minimal cognitive impairment due to Alzheimer's disease, Parkinson's disease, cerebrovascular disease), alcoholic dementia (Wernicke encephalopathy, Korsakoff syndrome), active alcohol misuse, substance abuse within the previous 6 months, liver transplantation within one-year, advanced hepatocellular carcinoma (HCC) [Barcelona clinic liver cancer classification (BCLC) ≥ stage B], active extra-hepatic malignancy, unstable vital signs, hospitalization because of acute decompensation, cardiac failure, respiratory insufficiency.

Definition/diagnosis of symptomatic HE, MHE, CHE, and OHE

In the patients with cirrhosis, symptomatic HE(grade I~IV) was assessed according to the operative criteria reported in the EASL/American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (West Haven Criteria) [1]. In addition to routine evaluation of cirrhosis and psychometric testing, the patients underwent an eye-closed digitalized electroencephalogram (EEG) that was examined by an expert electroencephalographer for signs of slowing compatible with HE [15–17].

Cirrhotic patients without symptomatic HE, but with abnormal PHES (≤-4) or EEG slowing (a rhythm below 8 Hz (or the presence of significant theta or delta activity) [17] were considered to have MHE [18]. CHE includes minimal HE (MHE) and grade 1 HE [14,18]. OHE is defined as grade ≥ 2 HE [14].

Calculations of psychometric test scores

The ANT_1 is a semantic fluency test that involves recalling as many animal names as possible within 1 min. The $S\text{-}ANT_1$ score was derived by adding three animals for individuals with less than 8 years of education and six animals for those over 80 years of age to adjust for age and education [10]. MMSE was performed according to the study done by Folstein et al. [19]. PHES can be calculated through Hannover Medical School [20].

Patient follow-up

The patients were followed-up with planned visits to the outpatient department every 3 months for at least two years or until death. The number of hospitalizations for OHE within two years was recorded and analyzed. The patients were censored at liver transplants.

Statistical analysis

Continuous variables are expressed as mean ± SD or median [interquartile range (IQR)] as appropriate. A non-parametric Kruskal Wallis test or Mann–Whitney U test was used to compare continuous variables among three or more groups, or between two groups respectively. Categorical variables were described as frequencies and percentages with the Chi-square test for comparison. When it came to a situation where more than 20% of data cells presented an expected frequency of <5, Fisher's exact test was substituted for the Chi-square test.

Receiver operating characteristic (ROC) analysis was used to compare the prediction performance of the psychometric tests. The DeLong test was used to conduct inter-measure comparisons. The optimal cutoff values were determined by Youden's index. Cox and Kaplan Meier survival analyses were performed to assess the predictive value of the tests in terms of recurrence-free days and OHE occurrence days. Multiple linear regression was employed to assess the prediction ability of ANT1 and other clinical parameters for the number of hospitalization episodes for OHE.

Statistics were performed using SPSS software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism, version 5.0 (GraphPad Software, Inc.). A p-value of <0.05 was considered statistically significant.

Ethical clearance

The study protocol was reviewed and approved (n. 201701810B0) by the Institutional Review Board of Linkou Chang Gung Memorial Hospital; informed consent was obtained from all patients and the study was conducted according to the declaration of Helsinki of the World Medical Association [21].

Results

Calibration of PHES and Baseline characteristics

Eighty patients with liver cirrhosis and 30 healthy controls were considered for the study from May 2018 to April 2020. 15 cirrhotic patients and one healthy control, who met the exclusion criteria, were excluded. Thus, 65 cirrhotic patients and 29 healthy controls entered the study (Figure 1). The median follow-up

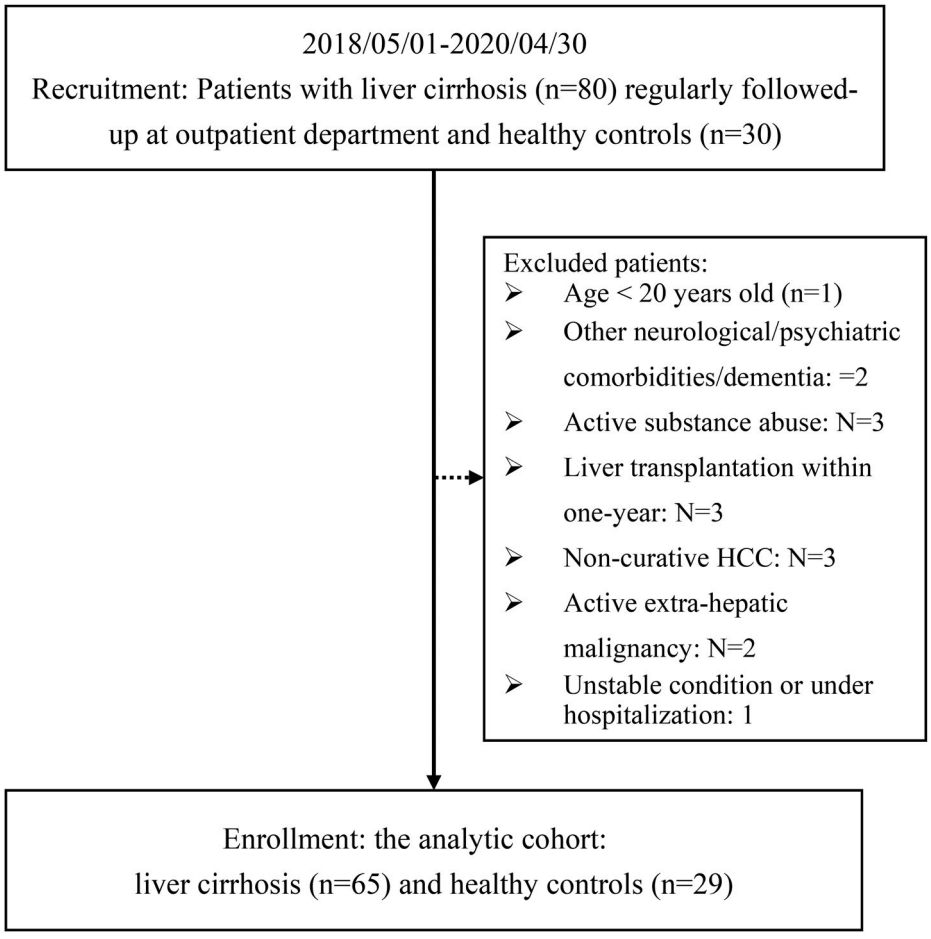

Figure 1. Flowchart of the study.

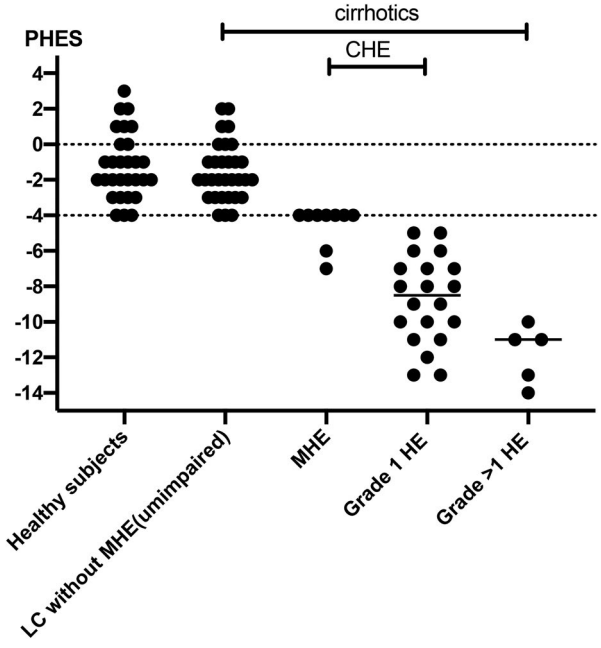

Figure 2. The distribution of Porto hepatic encephalopathy score (PHES) in the five groups (healthy subjects vs. liver cirrhosis (LC) without minimal hepatic encephalopathy (MHE) (unimpaired) vs. MHE vs. grade 1 HE vs. grade > 1 HE). PHES ≤ −4 was set as the definition for MHE.

period was 730 days. Following the specific criteria outlined in the Method section, twenty-five patients were identified as having symptomatic HE: 20 with grade 1 HE and 5 with subcontinuous grade ≥ 2 HE (i.e. OHE) as revealed in Figure 2. Consistency with the PHES German norms was observed [22], as all healthy subjects were found to have PHES ≥−4. Furthermore, patients with cirrhosis and a PHES score >−4, along with the absence of EEG slowing, were considered to be unimpaired. Nine patients who were asymptomatic but had a PHES score of ≤−4 and/or exhibited EEG slowing were classified as having MHE (Figure 2). It is noteworthy that all nine of these patients also displayed EEG slowing as an additional indicator of impaired cognitive function. Together, 9 patients with MHE plus those 20 patients with grade 1 HE were considered to have CHE.

The baseline demographic and clinical parameters are reported in Table 1. Age, education years, serum ammonia, international normalized ratio (INR), hemoglobin, alanine transaminase (ALT), albumin levels, and Child-Turcotte-Pugh (CTP) score were significantly different depending on HE severity. On closer inspection, the patients with OHE were older and had more severe

Table 1. Demographics and baseline clinical data.

		Patients with cirrhosis (65)				
			Covert HE		Overt HE	
	Healthy subjects (29)	Unimpaired (31)	MHE (9)	Grade 1 (20)	Grade ≥2 (5)	*p*-value
Clinical parameters						
Age, mean ± SD	44.2±13.6	56.0±11.6	58.8±6.8	65.6±10.1	69.4±7.2	<0.001
Sex male (%)	11 (37.9)	21 (67.7)	6 (66.7)	13 (65.0)	2 (40.0)	0.123
Etiology, n (%)						0.292
Alcohol	NA	4	3	4	2	
HBV	NA	19	3	6	2	
HCV	NA	6	2	9	1	
Others	NA	2	1	1	0	
Education years	16 (12–16)	12 (9–12)	9 (9–12.5)	6 (6–12.0)	6 (6–9)	<0.001
Ascites, n (%)						0.346
Nil	29 (100)	28 (90.3)	7 (77.8)	17 (85.0)	5 (100)	
Mild /moderate / severe	0/0/0	2(6.5)/0/1 (3.2)	2(22.2)/0/0	0/1(5.0)/2 (10.0)	0/0/0	
Laboratory parameters: median (IQR)						
Ammonia (μg/dL)	NA	52.0 (38.1–96.6)	83.5 (56.5–129.8)	67.5 (53.3–145.5)	155.5 (69.5–257)	0.045
INR	NA	1.1 (1.1–1.20	1.3 (1.2–1.5)	1.3 (1.2–1.6)	1.3 (1.3–1.7)	0.001
WBC (10^3/uL)	NA	5.6 (4.1–6.7)	5.7 (4.1–7.8)	4.4 (2.7–6.2)	5.5 (2.5–6.1)	0.365
Hemoglobin (g/dL)	NA	13.8 (11.7–15.3)	14.4 (11.9–15.5)	11.2 (9.3–13.6)	10.3 (9.4–11.5)	0.006
PLT (10^3/uL)	NA	147.0 (95.5–178.5)	131.0 (67.5–182.5)	91.0 (62–204)	102.0 (55.0–121.5)	0.283
Creatinine (mg/dL)	NA	0.8 (0.6–1.1)	0.8 (0.7–0.9)	0.9 (0.7–1.1)	1.1 (0.9–4.1)	0.225
Bilirubin Total (mg/dL)	NA	0.8 (0.7–1.1)	1.9 (1.0–2.0)	0.9 (0.5–1.8)	1.8 (1.0–3.1)	0.064
AST (U/L)	NA	34.0 (29–52)	49.0 (33.5–57.5)	30.0 (26.3–47.5)	38.0 (29–62)	0.526
ALT (U/L)	NA	36.5 (23.5–44.3)	29.0 (22–39.5)	20.5 (16–31)	21.0 (18–34)	0.009
Na (mmol/L)	NA	140.0 (138.0–141.5)	139.5 (138.8–140.3)	139.0 (137.0–142.0)	136.0 (134.5–143.0)	0.466
Albumin (g/dL)	NA	4.3 (3.7–4.5)	3.7 (2.7–4.0)	3.5 (3.3–4.1)	3.1 (3.0–3.2)	0.001
MELD score	NA	7.0 (6.0–10.8)	12.0 (8–13)	7.0 (6–16)	14.0 (11–19)	0.080
CTP score	NA	5.0 (5–5)	5.5 (5–7)	6.0 (5–8.5)	7.0 (7–8.5)	0.003

NA: Not applicable.
* HE grades: EASL/AASLD practice guidelines.
MELD: Model for End Stage Liver Disease.
CTP: Child-Turcotte-Pugh (CTP) score.

liver disease as well as higher ammonia than the others. In addition, education was lower in symptomatic than in asymptomatic patients. The healthy controls were younger than the patients with cirrhosis.

The predictive power of ANT_1, S-ANT_1, and MMSE in detecting CHE

First, a significant decline in the average scores of ANT_1 and S-ANT_1 was observed in patients with CHE when compared to the majority of healthy subjects and unimpaired patients. This decline further progressed from MHE to grade 1 HE and eventually to OHE, as demonstrated by the data presented in Table 2 and Figure 3A, B. In contrast, the decline in MMSE scores was more pronounced only in patients with OHE compared to those with CHE or unimpaired (Figure 3C). Of note, abnormal MMSE results (i.e. <25) were detectable also in some unimpaired patients (LC without MHE).

The power of ANT_1, S-ANT_1, and MMSE in detecting CHE is shown in Table 3 and Figure 4. ANT_1 had the highest AUROC value of 0.807. Applying the Youden index, the best cut-off value to detect CHE was ≤ 18 for ANT_1 and ≤19 for S-ANT_1, respectively (see Supplementary Table 1). In contrast, it was ≤ 27

Table 2. Baseline psychometric test scores.

		Patients with cirrhosis (65)			
			CHE		OHE	
	Healthy subjects (29)	Unimpaired (31)	MHE (9)	Grade 1 (20)	Grade ≥2 (5)	*p*-value
Psychometric tests						
PHES, median (IQR)	−2 (−3–0)	−2 (−3–−1)	−4 (−5–−4)	−9 (−11–−7)	−11 (−14–−11)	<0.001
ANT_1, median (IQR)	25 (21–31.5)	20 (16–23)	15 (14.5–19.5)	12.5 (9.3–16)	8 (4.5–11.5)	<0.001
S-ANT_1, median (IQR)	25 (21–31.5)	20 (17–23)	16 (15–19.5)	15.5 (10.3–18)	8 (7.5–14.5)	<0.001
MMSE, median (IQR)	29 (27.5–29)	29 (28–30)	27 (25.5–29.5)	26.5 (23.3–29)	23 (22.5–24)	<0.001

CHE: Covert HE.
OHE: Overt HE.
IQR: interquartile range (Q1-Q3).

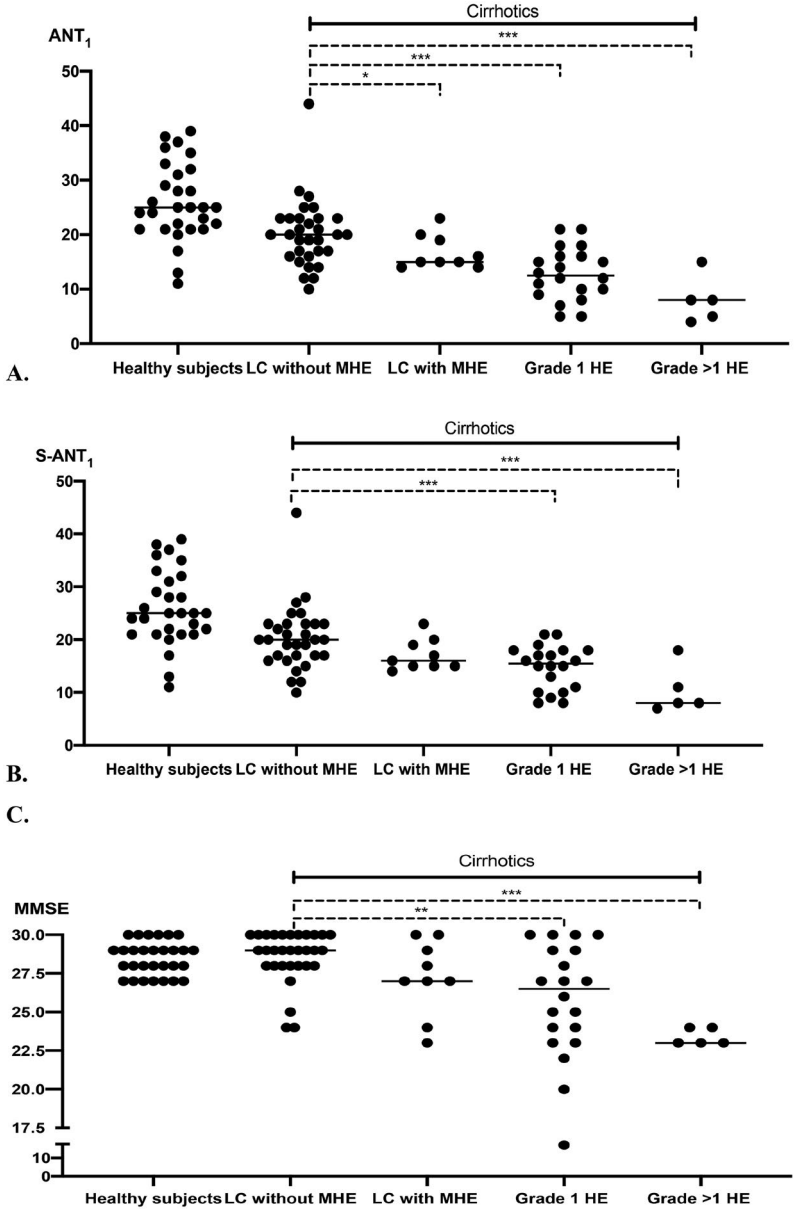

Figure 3. The average psychometric score in the three groups [normal vs. liver cirrhosis (LC) without hepatic encephalopathy (HE) vs LC with HE]: A. ANT1. B. S-ANT1. C. MMSE. *Indicates $p < 0.05$, ** < 0.01, *** < 0.001.

for the MMSE, thus within the range of normality for this test.

The predictive power of ANT_1, S-ANT_1, and MMSE in predicting first OHE, the number of hospitalization episodes for OHE, and OHE recurrence-free days

The ANT_1 and the S-ANT_1 had predictive values for the first breakthrough of OHE (β = −0.110, $p = 0.002$ and β = −0.111, $p = 0.006$, respectively). There were 50 future OHE events observed among 14 patients. The median number of OHE events per patient was 3(IQR: 1–6). The median time to OHE occurrence was 170.0 days, ranging from 29 to 730 days. ANT_1 could also predict the number of hospitalization episodes for OHE independent to MELD score in the two-year follow-up (Supplementary Table 2). Furthermore, both ANT_1 and the MELD score were identified as independent predictors of OHE recurrence-free days in the multivariable Cox regression analysis (Table 4). The Kaplan-Meier survival curves revealed that patients with an ANT_1 score and S-ANT_1 score > 14, as well as a PHES score > −8, had a recurrence-free period greater than two years in approximately 90% of cases (Figure 5).

Table 3. The AUROC and the pairwise comparison of ANT_1, S-ANT_1, and MMSE in detecting CHE.

		Pair-wise comparison for AUROC (*p*-value)		
	AUROC (95%CI)	ANT_1	S-ANT_1	MMSE
ANT_1	0.807 (0.721–0.894)			
S-ANT_1	0.786 (0.696–0.877)	0.114		
MMSE	0.672 (0.542–0.802)	0.029	0.083	

AUROC: area under the receiver operating characteristic curve.

The risks for OHE in patients with CHE (MHE/Gr.1HE) compared to those with unimpaired, using death as a competing risk

Since the occurrence of OHE is a crucial outcome, an analysis has been conducted to assess the risks of developing OHE in patients with CHE (MHE/Grade1HE) compared to those with unimpaired, while considering death as a competing risk. Our analysis revealed that patients

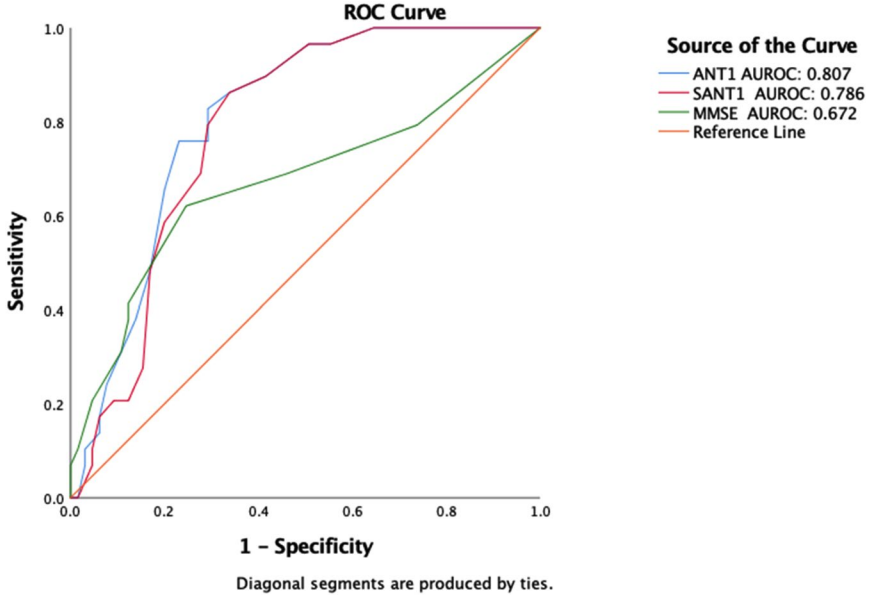

Figure 4. The predictive abilities of ANT_1, S-ANT_1, and MMSE in detecting CHE as demonstrated by AUROC. The pairwise comparisons were revealed in Table 3.

Table 4. Correlation and prediction of ANT_1 and clinical parameters with recurrence-free days in all participants.

	Correlation		Multivariate Cox regression		
Variables	Pearson	*p*-value	Standardized coefficients	95% CI	*p*-value
ANT_1	0.312	0.011	0.256	1.359 ~ 17.194	0.022
S-ANT_1*	0.290	0.019			
Age	−0.117	0.355			
Sex	0.128	0.311			
MELD score	−0.506	<0.001	−0.477	−32.194~−11.988	<0.001

*S-ANT_1 is not included in the multiple linear regression analysis due to collinearity with ANT_1.

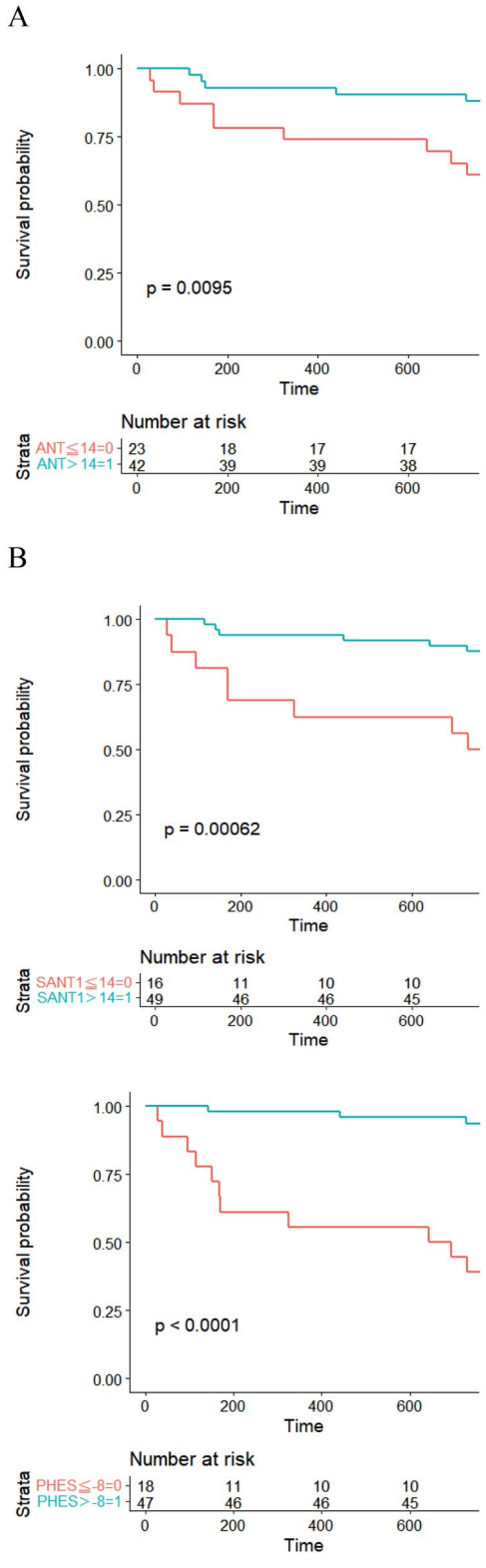

Figure 5. Kaplan-Meier OHE recurrence-free survival curves showed that patients (A) ANT_1 >14 (B) S-ANT_1 > 14 (C) PHES > -8 had a survival rate of about 90% free of OHE for two years.

with CHE had a significantly higher risk of developing OHE within two years, in comparison to those who were unimpaired (p=0.007), as depicted in Figure 6.

Discussion

The study confirmed that cognition is related to the severity of liver disease in patients with cirrhosis, as well as to ammonia levels and some demographic indexes, such as age and education, even using age-education-adjusted tests. Further, cognition was proved to have prognostic value concerning the risk for OHE/hospitalization and recurrence-free survivals, even among patients with CHE. These findings suggest that cognitive assessments, especially the simple, rapid, and valid ANT_1, which can be easily conducted in one minute at an outpatient or bedside setting, should be considered a crucial aspect of clinical care for patients with HE. Such evaluations may facilitate earlier detection of cognitive impairment and inform tailored interventions aimed at reducing the incidence of OHE and improving patient outcomes (also see the summary plot and key messages).

The finding that all our patients with MHE had PHES equal to or less than −4 and EEG slowing showed that PHES German norms [22] can be used in Taiwan to detect the asymptomatic individuals who have the cognitive features of MHE. This supports the consensus that defined MHE as the existence of cognitive or neurophysiological alterations related to liver insufficiency and/or shunt in patients with cirrhosis [1,14], on the basis of a well-documented tradition [23,24].

The finding that the ANT_1 and S-ANT_1 in healthy individuals were slightly higher in Taiwan than in Italy is in agreement with the different semantic fluency in various languages, depending on the speech speed and the length of words [25]. This supports the need for a proper standardization in Taiwan, also to correctly adjust for the effect of education and aging, which influence semantic fluency [25]. Indeed, the Italian adjustment, which was used to produce the S-ANT_1 [10], might be tuned more precisely for the Taiwan population. In fact, the lower diagnostic value of S-ANT1 than ANT_1 can be easily explained by the need for a specific age/education adjustment for Taiwan where the Italian ones could not function perfectly. For this reason, the optimal cut-off for the ANT_1 or the S-ANT_1 should be tuned in various cultural contexts, considering also if the clinical use aims at favoring sensitivity or specificity [12]. On the basis of the published papers, the values produced in Taiwan were closer to the ones of Germany [12] than those of Italy [10] or India [13].

The finding that ANT_1 and S-ANT_1 were confirmed to be different in patients with MHE and grade 1 HE, with lower values in the latter, is of great relevance since it emphasizes that this tool can provide a

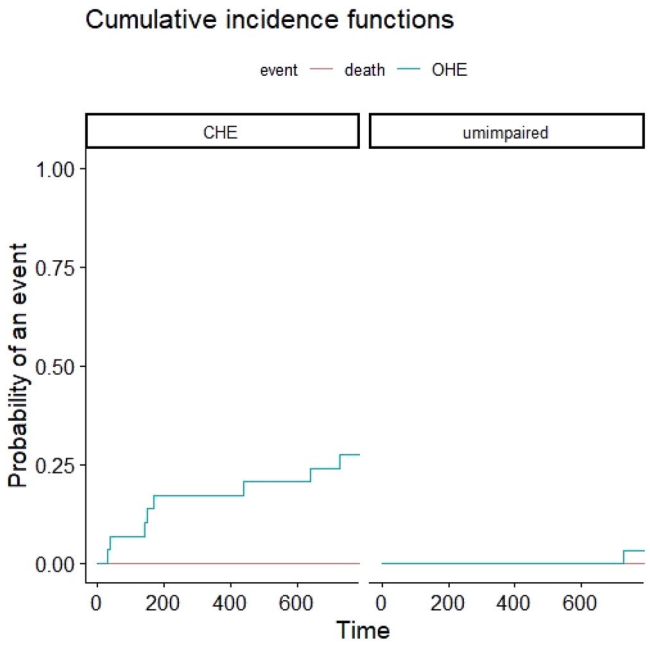

Figure 6. The Kaplan-Meier cumulative OHE incidence curves, with green curves representing the incidence of OHE and red curves as the incidence of death as a competing risk. The analysis demonstrated that patients with CHE had a significantly higher risk of developing OHE within two years compared to those who were unimpaired ($p = 0.007$).

quantification of CHE. In fact, the concept of CHE was introduced with the recommendation that this rather heterogeneous condition requires testing to be quantified [1]. While grade 1 HE can be clinically detectable by experienced physicians familiar with the patients, the semi-quantitative nature of its features, such as distractibility, disinhibition, or a change in behavior from polite to rude, without asterixis or disorientation, can pose a challenge [26]. In contrast, MHE refers to patients who appear normal on clinical evaluation but show abnormalities on neuropsychological testing or exhibit electrophysiological alterations on EEG. Therefore, clinicians commonly use the term CHE to describe an entity that requires a quantified test [17]. From a clinical perspective, it is crucial to differentiate between asymptomatic patients with MHE and those with grade 1 HE because a previous study has demonstrated that CHE is a heterogeneous entity, with significantly higher rates of hospitalizations and mortality observed in patients with grade 1 HE compared to those with MHE [27]. The use of ANT_1 and S-ANT_1 holds promise in distinguishing these two entities here; however, further validation through a larger prospective study is necessary to confirm our preliminary findings.

Furthermore, our study demonstrated a strong correlation between ANT_1 and S-ANT_1 scores and the number of hospitalization episodes for OHE within two years. These scores also had predictive value for OHE recurrence-free survival. These findings align with the result reported by Bajaj et al. which showed a correlation between the number of OHE hospitalizations and the severity of residual impairment as indicated by the digit symbol test ($r = -0.387$, $p = 0.02$) and number connection test-B ($r = 0.353$, $p = 0.047$) [28]. Indeed, the risks and costs associated with rehospitalization for OHE have been studied to be substantial [29]. An American study revealed that the mean hospital cost in 2003 for patients admitted with a primary diagnosis of HE was US$23,192 [30]. Early detection of this high-risk OHE recurrence group is of utmost importance for prompt intervention, saving costs and lives as well as for clinical trials.

Our study has limits, the principal one is that age and education were not well-balanced across groups and the subjects involved were only few. At any rate, the finding that the follow-up was able to find a predictive value supports the conviction that a large study about ANT_1 standardization and use in Taiwan will be useful to introduce a practical and easy-usable tool for CHE monitoring.

Conclusion

The early detection of covert hepatic encephalopathy (CHE) is crucial for timely intervention, costs, and life-saving, as well as for facilitating clinical trials. Our preliminary study provided evidence that

ANT_1(either in its rough or in a properly age/education-adjusted modality) is a simple and valid semantic fluency test that can be easily performed in outpatient or bedside settings in one minute and has the potential to be used as a tool for CHE detection, quantification, and follow-up in Taiwan, other Chinese-speaking regions, and many other countries. A large prospective study to standardize the optimal cut-off values of ANT_1 and S-ANT_1 and utilize them to detect and follow up HE in Taiwan and other countries is warranted.

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Authors' contributions

CHH and PA designed the study, analyzed the results, and drafted the manuscript. TYY, WEHT, SHC, SYH, and RNC executed clinical portions of the study including data collection and literature review. CHH, PA, and YTH designed and executed the data analysis plan.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Data are not publicly available but may be accessed upon reasonable request, IRB approval, and data policy.

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