The Psychometric Hepatic Encephalopathy Score for Diagnosis of Minimal Hepatic Encephalopathy in Liver Cirrhosis Patient

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ABSTRACT

Background: *The psychometric hepatic encephalopathy score (PHES) is a tool considered as a gold standard for detecting minimal hepatic encephalopathy (MHE) in liver cirrhosis patients. The PHES must be standardized based on the local healthy population before it can be used. This study aimed to standardize the PHES with Indonesian local populations and set the cutoff point of PHES so it can be used to detect MHE in liver cirrhosis patients.*

Methods: *This was a cross-sectional study. PHES were administered to all enrolled subjects, which are healthy subjects and cirrhosis without overt encephalopathy subjects. The PHES consists of 5 psychometric tests. Diagnosis of MHE was built upon the deviation from the normal range value of PHES. The influencing factors of PHES were assessed using appropriate bivariate analysis. The variables that can affect each of the test results in PHES were incorporated into the multiple linear regression analysis. The unstandardized beta coefficients were used to develop a formula.*

Results: *In total, 236 subjects participated in this research. The influencing factors of PHES of this study were age and education years. With the cutoff point of PHES less than -4, the prevalence of MHE was 37.7%, of which 7.6%, 50%, and 50% had Child-Turcotte-Pugh (CTP) grade A, B, and C respectively.*

Conclusions: *The standardized version of PHES can be used to diagnose MHE in Indonesian liver cirrhosis patients. The PHES in this study were affected by age and education years. MHE was diagnosed if the PHES was less than -4.*

Keywords: *liver cirrhosis, Minimal Hepatic Encephalopathy, Psychometric Hepatic Encephalopathy Score*

ABSTRAK

Latar Belakang: *Psychometric hepatic encephalopathy score (PHES) merupakan alat yang dapat dianggap sebagai standar emas untuk mendeteksi minimal hepatic encephalopathy (MHE) pada pasien sirosis hati. PHES harus distandardisasi berdasarkan populasi sehat lokal sebelum dapat digunakan. Tujuan dari penelitian ini adalah untuk mengstandarisasi PHES dengan populasi lokal Indonesia dan menetapkan titik potong PHES sehingga dapat digunakan untuk mendeteksi MHE pada pasien sirosis hati.*

Metode: *Studi ini merupakan studi potong lintang. PHES diberikan kepada semua subjek yang terdaftar, yaitu subjek sehat dan subjek sirosis tanpa ensefalopati terbuka. PHES terdiri dari 5 tes psikometrik. Faktor-faktor yang memengaruhi PHES dinilai, dan persamaan-persamaan dikembangkan untuk memprediksi hasil yang diharapkan dari masing-masing tes. Diagnosis MHE dibangun berdasarkan deviasi dari nilai rentang normal PHES. Variabel-variabel yang dapat memengaruhi setiap hasil uji di PHES dimasukkan ke dalam analisis regresi linear berganda. Koefisien beta yang tidak distandardisasi digunakan untuk mengembangkan sebuah rumus.*

Hasil: *Secara total, 236 subjek berpartisipasi dalam penelitian ini. Faktor-faktor yang memengaruhi PHES dalam penelitian ini adalah usia dan tahun pendidikan. Dengan titik potong PHES kurang dari -4, prevalensi MHE adalah 37,7%, di antaranya 7,6%, 50%, dan 50% memiliki Child-Turcotte-Pugh (CTP) grade A, B, dan C secara berturut-turut.*

Simpulan: *Versi standar PHES dapat digunakan untuk mendiagnosis MHE pada pasien sirosis hati Indonesia. PHES dalam penelitian ini dipengaruhi oleh usia dan tahun pendidikan. MHE didiagnosis jika PHES kurang dari -4.*

Kata Kunci: *Ensefalopati Hepatik Minimal, sirosis hati, Skor Ensefalopati Hepatik Psikometrik*

INTRODUCTION

Liver cirrhosis is one of the major causes of illness and death, which is a result of chronic liver injury that leads to progressive fibrosis and causes changes in liver architecture. This event can result in hepatic dysfunction and portal hypertension, and both or in combination can cause many complications, such as hepatic encephalopathy (HE). HE refers to a variety of cognitive, psychomotor, and psychiatric abnormalities in a patient with liver insufficiency after the exclusion of other brain diseases. The clinical manifestation of HE may vary widely, from minimal neurological changes such as a decrease of attention, concentration disturbance, to a deep coma state. HE was classified according to the severity of clinical manifestation into overt hepatic encephalopathy (OHE) and covert hepatic encephalopathy. OHE is diagnosed based on physical examination and can be graded I-IV according to the West Haven criteria. Covert HE includes OHE grade I and minimal hepatic encephalopathy (MHE). The prevalence of OHE in cirrhosis patient varies from 30% - 40%, and its percentage increase in advanced liver disease. The presence of HE in liver cirrhosis patients can indicate a poor prognosis with a negative impact on the patient's quality of life.[1,2]

MHE is characterized by mild cognitive deficits, decreased of attention and psychomotor speed, as well as impaired working memory and information processing. Patients with MHE show a failure on doing a psychometric test, but show no clinical sign of neuropsychological abnormality. MHE can affect up to 80% of liver cirrhosis patients and can impair patients' quality of life, influence driving capability, and can affect survival. The MHE patient had higher risk of developing OHE, thus MHE is important to diagnose and treat.[3-5]

The recommended tool to establish the diagnosis of MHE is the psychometric hepatic encephalopathy score (PHES). The PHES consist of 5 paper and pencil-based test, which are digit symbol test (DST), number connection test A (NTC-A), number connection test B (NTC-B), line tracing test (LTT), serial dotting test (SDT). The PHES score is a sum score of all subtests. Each subtest of the PHES can examine different neurocognitive abilities such as motor accuracy, speed, visuospatial and visual perception, concentration, and attention which are impaired in MHE patients. The PHES is objective, cheap, simple, and feasible to administer in an office setting. Nevertheless, the result of PHES can be influenced by multiple factors, such as age, sex, education, cultural background. These influencing factors may differ among the country. The recent recommendation suggests that a validated version of the psychometric test must be used to establish a diagnosis of MHE. Therefore each country should standardization of PHES using local healthy population is needed before it can be used to detect MHE.[2,5-7] The PHES had been validated and standardized in many different countries such as USA,[8] Germany,[5] Mexico,[9] India,[7] China,[10] Taiwan,[11] South Korea,[12] Turkey,[13] and the result of these study was a valid and reliable version of PHES.

Our study is performed to standardize PHES in the local healthy population to set the cutoff point of PHES so it can be used to diagnose the MHE. This study was also purposed to evaluate the prevalence of MHE among Indonesian liver cirrhosis patients.

METHODS

Study Design

This study is a cross-sectional design study that was held from April 2013 to April 2015. This study involved liver cirrhosis patients and healthy subjects. The study participant was recruited voluntarily and written informed consent was obtained from each study participant. This study's ethical approval was received from the Health Research Ethics Committee, Faculty of Medicine of Udayana University number 252/UN.14.2/Litbang/2013. The demographic characteristic of subjects was assessed. The subject occupation was classified as a blue collars worker (farmer, housewife, laborer, fisherman), as a white collars worker (secretary, a university graduate, teacher), and as an unemployed or retired. The number (in years) that was spent on attending school starting from elementary school was used to define education years.

Healthy subject

The healthy Indonesian adult (>18 years) was enrolled to establish a standard or reference value for the PHES. The healthy subject was recruited from general populations and was chosen from among those living in both rural and urban areas. The healthy person who is willing to participate were allowed to join including Hospital staff, people who did health examinations, or patients' companions. The volunteers were interviewed for screening by our researcher. All subject was required to have a normal result of anamnesis and physical examination, also have a fair knowledge of alphabetic and numbers. The exclusion criteria for this group subjects was: known cognitive impairment, known neurological disease or history of neurological disease, psychiatric disease, history of chronic liver disease, history of benzodiazepine and psychotropic drug consumption, history of alcohol abuse (> 50g/day for men and > 20g/day for women).

Liver cirrhosis subjects

The liver cirrhosis patients without OHE who attended Sanglah Hospital Denpasar Bali were enrolled. The diagnosis of liver cirrhosis was obtained from the medical record. Diagnosis of liver cirrhosis is established by the presence of biochemical liver dysfunction and portal hypertension finding on ultrasonography or endoscopy. To grade, the severity of liver disease was determined using Child-Turcotte-Pugh (CTP) classification. The exclusion criteria included: the existence of OHE, having a transhepatic portosystemic shunt (TIPS) procedure, known cognitive impairment, known psychiatric diseases, known neurological disease, visual impairment, psychoactive and benzodiazepine drug consumption, current hospitalization because of gastrointestinal hemorrhage or spontaneous bacterial peritonitis, experienced severe comorbidity including renal, respiratory, or heart failure, currently on lactulose and antibiotic treatment, and inability to read and write.

PHES testing

The PHES is consist of 5 psychometric test which are DST, NTC-A, NTC-B, LTT, and SDT. Our study used a form of PHES test that had been kindly sent to us by Professor Karin Weissenborn (Weissenborn.Karin@mh-hannover.de) with minor modifications, in which we translate the German phrase "start" and "end" to the Indonesian phrase. The PHES was administered to all enrolled subjects by our researcher who had been trained by a psychologist and were directed on one to one basis. The tests were performed in a quiet room with appropriate lighting. For the scoring system of each test as follow: DST were deliberated as a score; the NCT-A, NCT-B, and SDT were deliberated as seconds; and the LTT results was deliberated from the summation of time to complete the test (LTTtime, second) with the error score (LTTeror): LTTt × (1 + LTTe/100). A higher number of score results from DST equals better performance, but it's not applied for other tests like NTC-A, NTC-B, SDT, and LTT in which a lower result (a shorter time to finish the test) equal better performance.[6,9]

Statistical analysis

The statistical analyses were performed using a statistical package for the social science (SPSS version 18.0 Chicago: SPSS Inc) software, with a p-value <0.05 that was considered statistically significant. The continuous variable was expressed as mean ± standard deviation (SD) or median, and the categorical data were expressed as a proportion or percentages. Bivariate analyses were performed using the student's t-test, Mann-Whitney test, Chi-square test, and Pearson's correlations test as appropriate. The variables that can affect each of the test results in PHES (DST, NTC-A, NTC-B, LTT, SDT) were incorporated into the multiple linear regression analysis. The unstandardized beta coefficients resulting from these analyses were used to develop a formula that can predict the result value of

each psychometric test in liver cirrhosis patients. The expected result of each PHES test is the result value that generates from the predictive formula. We compute the Z-score as a delta between the predicted or expected result value and the observed result value of each test in PHES divided by the correlated SD of the healthy reference population to generate deviation from the "normal" value. PHES is an integer generated from the sum Z-score of 5 tests, so the Z-score of each test was adjusted, as follows: the result of DST within ± 1 SD from the mean result value of the reference population was scored as 0 points, results between -1 and -2 SD were scored as -1, results between -2 and -3 SD and worse than -3 SD were scored as -2 and -3 respectively, a result value better than mean + 1 SD was scored as +1; results value of NCT-A, NCT-B, SDT, and LTT within ± 1 SD from the mean result value of the reference population were scored as 0 points, results value between +1 and +2 SD, between +2 and +3 SD, and worse than +3 SD were scored as -1, -2 and -3 points respectively, the result value better than -1 SD were scored as +1 point. Therefore the sum score of PHES ranged from +5 to -15. To determine the cutoff PHES that is used to distinguish between normal and MHE, we set the value at the lower boundary 95% confidence interval range between mean – 2 SD and mean + 2 SD from the result value of healthy subjects.[6,7,9,11]

RESULTS

A total of 236 subjects were enrolled in this study, they were 167 healthy subjects and 69 liver cirrhosis subjects. The characteristics of the subjects' demography are shown in Table 1.

Age and education years showed a significant correlation with all 5 tests of PHES in healthy subjects. The education years showed a positive correlation with DST, and showed a negative correlation with NTC-A and B, LTT, and SDT, while age showed a positive correlation with NTC-A and B, LTT, and SDT, but have a negative correlation with DST (Table 2).

The result of each test in PHES was not correlated with gender. The occupation only affected NTC-A, NTC-B, and DST results, whereas LTT and SDT results were not affected. Therefore only age and education years were incorporated in multiple linear regression analysis to determine the beta coefficients that were used to develop the formula to generate the expected result value of each test in PHES. The predictive formulas are shown in Table 3.

The PHES was calculated from a sum of the Z-score of 5 psychometric tests. The average result values of the PHES in healthy subjects and liver cirrhosis subjects were: -0.40 ± 2.04; and -3.44 ± 3.48. The lower boundary of the 95% range between mean – 2 SD and mean + 2 SD of PHES result of the healthy subject was -4.49, thus the result lower than that value was used to distinguish the normal and MHE. Therefore the total PHES value < -4 was used to diagnose MHE in the liver cirrhosis subject. Using this cutoff, 26 (37.7%) of the liver cirrhosis subjects were diagnosed to have MHE.

The characteristics of liver cirrhosis subjects with and without MHE are shown in Table 5. The age, education years, gender, and occupations were found no difference in MHE and without MHE groups. The MHE condition was found to increase along with the increase of the Child-Turcotte-Pugh grade. Only 1 subject of MHE had CTP A criteria (7.6%).

Table 1. Subjects characteristic

Characteristic	Healthy Subject N = 167	Cirrhosis N = 69	Cirrhosis with OHE N = 65
Male/Female	78/89 (46.7%/53.3%)	57/12 (82.6%/17.4%)	50/15/(76.9%/23.0%)
Age	41 ± 13	45.14 ± 9.55	51.03±10.91
Education years	12.1 ± 3.6	9.78 ±2.79	9.14±2.9
Occupations			
Unemployed	25 (15%)	17 (24.6%)	26 (40.0%)
Blue-collar	105 (62.9%)	31 (44.9%)	30 (46.15 %)
White-collar	37 (22.2%)	21 (30.4%)	9 (13.38%)
DST	37.99 ± 11.95	25.16±8.43	10 ± 3.90
NTC-A	58.51 ± 31.9	85.78±37.73	251 ± 112.12
NTC-B	106.02 ± 53.29	167.42±78.99	537 ± 226.85
LTT	53.43 ± 23.86	73.43±28.53	212 ± 213.16
SDT	61.66 ± 21.41	90.03±36.87	196 ± 53.15
CTP			
CTP C	-	12(17.4%)	0 (0 %)
CTP B	-	44(63.8%)	24 (36.9%)
CTP A	-	13(18.8%)	41 (63.1%)

DST: Digit symbol test; NCT-A; Number connection test-A; NCT-B: Number connection test-B; SDT: Serial dotting test; LTT: Line tracing test; CTP: Child-Turcotte-pugh.

Table 2. Correlation between PHES test (DST, NTC-A, NTC-B, LTT, SDT) with age and education years

	DST	NTC-A	NTC-B	LTT	SDT
Education years	0.62*	-0.53*	-0.53*	-0.57*	-0.59*
Age	-0.61*	0.54*	0.58*	0.50*	0.59*

*p < 0,05

DST: Digit symbol test; NCT-A; Number connection test-A; NCT-B: Number connection test-B; SDT: Serial dotting test; LTT: Line tracing test

Table 3. The predictive formula to generate the expected value based on age and education years

Test	Equations
DST	= 4.215 + (education years x 0.51) - (age x 0.513)
NTC-A	= 4.192 + (0.455 x age) – (0.778 x education years)
NTC-B	= 3.388 + (0.703 x age) – (0.578 x education years)
LTT	= 4.202 + (0.231 x age) – (0.469 x education years)
SDT	= 3.681 + (0.305 x age) – (0.3 x education years)

DST: Digit symbol test; NCT-A; Number connection test-A; NCT-B: Number connection test-B; SDT: Serial dotting test; LTT: Line tracing test

Table 4. Characteristic of liver cirrhosis subjects without and with MHE

Characteristic	Cirrhosis without MHE	Cirrhosis with MHE	P
Sex (Male/Female)	36/7	21/5	0.75
Age	45.13±8.80	45.17±10.66	0.80
Education Years	10.33±2.66	9.03±2.82	0.15
Occupation			
Unemployed	9 (52.9%)	8 (47.05%)	0.46
Blue Collar	16 (51.61%)	15(48.38%)	
White Collar	15 (71.42%)	6(28.57%)	
CTP			
CTP C	6 (50%)	6 (50%)	0.03*
CTP B	22 (50%)	22 (50%)	
CTP A	12 (92%)	1 (7.6%)	
DST	28.75±7.39	20.21±7.28	0.00
NTCA	65.15±18.8	114.25±38.97	0.00
NTCB	125.58±42.24	225.14±81.97	0.00
LTT	61.85±24.61	89.41±26.05	0.00
SDT	69.18±22.24	118.8±33.7	0.00
PHES	0.85 ± 1.39	-7 ± 2	0.00

*p < 0,05

MHE: Minimal hepatic encephalopathy; DST: Digit symbol test; NCT-A; Number connection test-A; NCT-B: Number connection test-B; SDT: Serial dotting test; LTT: Line tracing test; PHES: Psychometric hepatic encephalopathy score.

A PHES calculator was made based on the statistical formula from this study to calculate the PHES after the test was administered to the patient. The components included in this calculator were: age, education years, a result of DST (raw point), NTC-A and B (in seconds), LTT (LTTt in seconds + LTTe), and SDT (in seconds). The PHES result will appear after input the mandatory component and click "calculate" (figure 1).

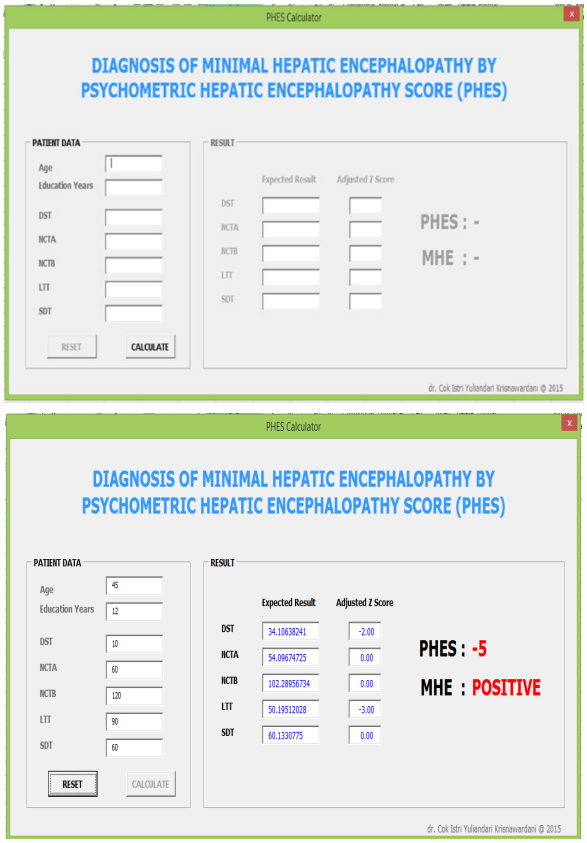

Figure 1. PHES calculator

DISCUSSION

The MHE is a neurocognitive dysfunction that can be found in patients with liver cirrhosis. The cirrhosis patient may look clinically normal but have impaired on a specific psychometric test. The activities that require fine motor skills abilities, attention, visual-spatial abilities, executive functions, and emotional behavior may be impaired, whereas the activities of daily living and verbal communication still be preserved. MHE may also be associated with a decrease in driving capability and can lead to vehicle accidents. The MHE may negatively affect the patient's quality of life, and the patient with MHE had an increased risk of developing OHE thus increasing the mortality. Because of the lack of tools, MHE remained undetected and untreated in clinic practice.[3,14]

The PHES is a low-cost, simple, bedside, valid, and one of the recommended tools for detecting MHE on liver cirrhosis patients. But, before it can be used, the PHES should be standardized with the normal population where it was intended to be used. The differences in culture, customs, and language can affect the PHES, so the PHES version that had been standardized and validated in the previous country with their standardized population can not be used in other different countries. Therefore, the diagnosis of

MHE is based on the deviation from the normal result of the PHES test from local reference populations.[6,15]

This was the first study to find out the normal value of PHES in Indonesian local populations. The demographic characteristic of healthy subjects in our study nearly represents the general population. These healthy subjects were shared the same social culture, history, and geography with general populations. An unrepresentative reference population can lead to an inaccurate diagnosis of MHE and may have adverse consequences for patients. The healthy subjects in our study were nearly representative to be used as a standard or reference population for several reasons. Our healthy subjects were from both rural and urban areas, the proportion of female and male in our healthy subject were nearly appropriate with male and female proportion based on national statistical data in 2010.

In our study, age and education years were correlated with each test of PHES in the healthy subjects. This finding was consistent with other study results.[9-12,16] The young and with higher education levels equal a better PHES performance. While gender was not associated with each psychometric test result in this study. This is supported by other studies in China[10] and Germany,[5] which found no association between gender and PHES. However, gender has been noted to be associated with the sub-test of PHES in studies that were held in South Korea[12] and Mexico.[9] In our study occupation was found associated only with DST, NTC-A, and NTC-B, and a similar finding was also found in another study in Mexico.[9] There was a tendency that white-collar occupations had better test performance compared with blue-collar and unemployed, this may be because the white-collar occupation had a more familiar with "pencil and papers" than the other occupation.

In this present study, the cutoff point less than - 4 was used to diagnose MHE in liver cirrhosis patients. This was based on the lower boundary of the 95% range between mean – 2 SD and mean + 2 SD of PHES result from the healthy subjects. The same formula was used by the majority of studies that concentring on PHES to determine the cutoff point for diagnosing MHE. The very first, this formula was used by Weissenborn et al. for diagnosing MHE and it was found to have good sensitivity and specificity.[5,6] The use of cut-off points less than -4 were in accordance with the validation study of Mexico,[9] China,[10] Taiwan,[11] and Germany.[5] The prevalence of MHE in our study using this cut-off was 37.7%. These findings were higher than the prevalence in Mexico (15%), Germany (25%), Taiwan (29%), South Korea (26.5%), but lower than found in India (48%), and China (49.1%). The difference in the prevalence of MHE in these studies may because of the varying severity of liver function in the studied population.[5,7,9-12]

We found no significant differences in education years, gender, age, and occupation between the MHE group and the non-MHE group. This result was consistent with a study by Li, et al. in China.[10] However, other studies in Italy[9] and South Korea[12] found that the MHE group had lower education levels compared with the non-MHE group. Other study in South Korea also validate paper and pencil test battery for the diagnosis of MHE.[17] The MHE incidence was found to increase along with the increase of the Child-Turcotte-Pugh grade. In our study, only 1 (7.6%) of MHE patients compared with 92% of non-MHE patients had a CTP grade A. Other studies also found a similar finding that the liver disease severity was associated with impairment of the PHES test result.[9,10,18,19] Based on the result of these studies, caution should be taken in care for cirrhosis patients whose liver disease severity was expected to deteriorate because some of these patients may progress to MHE conditions or eventually develop OHE.

The limitation of our study is that we did not do the blood test examination for the healthy subjects to exclude the possibility of "silent" chronic liver disease. We solely depend on careful history taking and physical examinations. A history of known chronic liver disease and an obvious finding on physical examination were excluded from this study.

CONCLUSION

the standardized version of PHES can be used to diagnose MHE in Indonesian liver cirrhosis patients. In this study, the PHES was affected by age and education years. The cutoff point of PHES less than -4 was used to diagnose MHE conditions. The prevalence of MHE in this study was 37.7%, and this condition was found to increase along with the increase of the liver disease severity.

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