Performance of EncephalApp Stroop Test in Cirrhotic Patients for Evaluating Covert Hepatic Encephalopathy

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ABSTRACT

Background: *Covert hepatic encephalopathy (HE) is the mildest HE spectrum that is difficult to detect, but associated with significant decrease in quality of life. Currently, there is no gold standard to detect covert HE. EncephalApp Stroop Test as a newer diagnostic tool is easier, faster and its ease of availability in various health institutions is expected to be applied in Indonesia for covert HE detection. This study aimed to validate and test the reliability and diagnostic ability of EncephalApp Stroop Test to diagnose covert HE, compared to the Psychometric Hepatic Encephalopathy Score (PHES) and critical flicker frequency (CFF).* ***Methods:*** *This study is a cross-sectional test, conducted from August to September 2018, targeted at patient with cirrhosis in Jakarta, to obtain Area Under The Curve (AUC), sensitivity, specificity, cut-off point, predictive value, likelihood ratio, and post-test probability of the EncephalApp Stroop Test, compared to PHES and CFF. The Validity and reliability tests were done before diagnostic study. Translation of the EncephalApp Stroop Test were first carried out using WHO protocol. All patients first underwent a Mini Mental State Examination and Ishihara Test to rule out color blindness.* ***Results:*** *Thirty subjects participated in validity and reliability tests, and eighty in diagnostic tests. The translated application showed excellent internal consistency (Chronbach's Alpha of 0.942) and correlation coefficient of 0.82. The diagnostic study showed OnTime + OffTime as the best parameter (AUC: 0.897 (95% CI: 82.9% - 96.5%); sensitivity: 88.6%; specificity: 80%; positive predictive value (PPV): 0.77; negative predictive value (NPV): 0.9; positive likelihood ratio (LK+): 4.4; negative likelihood ratio (LK-): 1.4; positive post-test probability: 0,775; negative post-test probability: 0,1; and cut-off point ≥ 188.8 seconds.* ***Conclusion:*** *The EncephalApp Stroop Test is valid and reliable, with good AUC value, sensitivity, specificity, PPV, NPV and likelihood ratio in diagnosing covert hepatic encephalopathy in patients with cirrhosis in Indonesia.*

Keywords: *Covert hepatic encephalopathy, liver cirrhosis, EncephalApp Stroop Test, history of HE, Critical Flicker Frequency (CFF), Psychometric Hepatic Encephalopathy Score (PHES).*

INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome in acute and chronic liver disease with various manifestations, mild to severe, without any underlying brain abnormality.[1-4] Hepatic encephalopathy categorized into three types, A, B, and C, based on its etiology, with type C is the most common (30-45%), being correlated with cirrhosis and portal hypertension.[3,5,6] West Haven Criteria divided HE into 5 stages, based on its severity, i.e. 0-4, with stage 4 is the most severe form of HE.[3,7] International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) created new categories of HE, with the mild form of HE, minimal HE and first degree of HE, into one group, i.e. covert HE.[8-10] These mild forms of HE was made into one group to the bad reliability or subjectivity that may appear in evaluating the mental status, due to its clinical manifestation that may not appear.[8] The mental status examination also tends to be unreproducible, thus may not be used for surveillance.[8]

Patient with *covert* hepatic encephalopathy showed physiological and neuropsychiatric manifestation, without any disorientation nor asterixis. Covert HE was associated with the decrease of quality of life, especially in any activities that need concentration, process of information, and psychometric function, such as planning a trip or driving a vehicle, and also progression into covert HE. Covert HE has been a single predictor for death and hospitalization. The clinical manifestation may not be detected other than using psychometric or neuropsychologic test. Study by Weins et.al. showed increase of accident incident and traffic violations in person with minimal hepatic encephalopathy.[11] Data in 2003 showed a burden of US $ 930 million borne by the United States for patients with hepatic encephalopathy.[11]

The prevalence of covert HE may not be precisely known. A number of researches showed a wide range of prevalence of HE, i.e. 20-80%, due to the difficulties of diagnosing covert HE.[11] There is no gold standard that has been made to diagnose covert HE. ISHEN has recommended the use of at least two diagnostic tests in multicenter study, i.e. psychometric hepatic encephalopathy score (PHES) and either one of any tests (neurophysiologic test ((critical flicker frequency (CFF), or electroencephalogram (EEG)).[7] PHES and CFF were chosen as gold standard in this study due to their sensitivity and specificity in diagnosing covert HE and their availability in Cipto Mangunkusumo Hospital.

In PHES study, the subject will undergo several tests, using pencil, to evaluate the cognitive and psychomotor function.[9, 12] It consists of 5 tests, i.e. number connecting test (NCT) A and B, digit symbol test (DST), line tracing test (LTT) and serial dotting test (SDT).[9] The time needed to complete all these tests is recorded and calculated, with cut-off point <-4.[10,13] The PHES may showed highest sensitivity and specificity (i.e. 96% and 100% respectively), but this diagnostic test takes a lot of time to be completed and is not randomized, so patients can memorize the answer of the test.[10, 13] On the other side, CFF may take fewer time than PHES. In CFF study, the subject uses goggle that has red light blinking from higher frequency to lower frequency (faster to slower).[10,14,15] The first frequency in which the subject catches the first blink was then captured and recorded. Cut-off point was < 39 Hz, to be diagnosed as overt HE.[12] CFF showed low sensitivity, with high specificity (61% and 79%, respectively), thus must be used as an adjuvant to PHES study.[16,17]

Mini Mental Status Examination was used widely, to exclude any cognitive abnormalities, including overt HE.[15] Cut-off point >25 was chosen, based on references stated that this cut-off point can be used as a marker for overt HE, along with disorientation and loss of consciousness.[12] The limitation of all diagnostic tools in diagnosing covert HE, encourage the invention of new diagnostic tools, such as EncephalApp Stroop Test, an application based on Android and iOS to diagnose covert HE. This tool is developed by Jasmohan Bajaj, using hashtag (#) symbol and word with different colors (red, green, and blue). The subject will need to guess the color of hashtag and words, not what the words say, i.e. the text saying "green" with blue color is answered as blue, the text "red" with green color is answered as green and

so forth.[18] The test with only colored hashtag is then called as Off, while the text is called as On. There were 5 packets of test each for On and Off, each with 10 questions.[18] If the patient answered wrong, the test will be restarted.[18] The time needed to complete all 5 On called OnTime, and the time needed to complete all 5 Off called OffTime. This test consists of eight parameters, i.e. OnTime, OffTime, OnTime + OffTime, OnTime – OffTime, OnTime x number of trials needed to complete the OnTime (TrialsOn), TrialsOn, OffTime x number of trials needed to complete the OffTime (TrialsOff), and TrialsOff.[18] It evaluates psychomotor, cognitive flexibility and accuracy.[18] Previous study showed good sensitivity and specificity, with OnTime + OffTime as the best parameter, (AUC: 0.89; sensitivity 92% and specificity 75%).[19] The cut-off value was 190 seconds.[19] Different cut off point was made in patient aged below 45 years.[19] Further study showed no significant difference between degree of cirrhosis, history of overt HE and level of education.[19]

The increasing number of smartphone usage will certainly increase the distribution of this application, and along with good sensitivity and specificity, allows rapid and widespread diagnosis of covert HE among patients with liver cirrhosis. Nevertheless, the existence of differences in understanding of technology and language makes this application first need to be translated and validated, so that it can be used in the population of patients with liver cirrhosis in Indonesia. The purpose of this study is to do validity and reliability test of applications that have been translated into Indonesian so that they can be used in Indonesia and carry out diagnostic tests, to obtain cut-off value, sensitivity, specificity, likelihood ratios, predictive values, and post-test probability for the diagnosis of covert hepatic encephalopathy.

METHODS

This study was a cross sectional study, conducted during August 2018 to September 2018, involving 30 subjects with liver cirrhosis to participate in validation study and 80 subjects with liver cirrhosis to participate in diagnostic study. The translation was done by Transmedical Institute using World Health Organization (WHO) protocol. The translation was then coded back into the application through the developer of the application. Mini-Mental Status Examination (MMSE) and Ishihara tests were first carried out to exclude any cognitive impairment and color blindness.

This study was approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia (Ref. no. 1209/UN2.F1/ETIK/PPM.00.02/2021).

In validation study, the subjects answered the questions from translated app that is transposed into paper. Wrong answers were then collected and Cronbach's Alpha was then calculated to evaluate the internal consistency. Coefficient correlation test was done in all parameters to test the validity of the application. When the test had been validated and tested for reliability, the diagnostic study was then begun. In this study, the inclusion criteria were liver cirrhosis patient. The subjects were excluded if the patients had cognitive impairment, overt HE, color blindness, or any consumption of alcohol or psychoactive drugs. Subjects with MMSE > 25 and no color blind were included in this study. All subjects fulfilling the inclusion criteria were then undergo PHES, CFF and EncephalApp Stroop Test. SPSS program was then used to calculate sensitivity, specificity, positive and negative predictive value, likelihood ratio, post-test probability, receiver operating characteristic curve (ROC curve) and area under the curve (AUC).

RESULTS

Validity and Reliability Test

All questions asked in EncephalApp Stroop Test had been translated into Indonesia before the beginning of this diagnostic study. Translation was done by Transmedical Institute, through 3 processes, i.e. forward translation, back translation, and reconciliation, involving licensed translator, consisted of two translators with medical background and two translators without medical background. After the reconciliation was done, the translation was then decoded into the application. Reliability test was done using paper with its translation, since the application will ask the question in random order, so the subject

cannot memorize the answer. Internal consistency was then used to analyze the reliability. There were 17 questions, included three hashtags symbol (#) and words (red, green, blue) with different colors, i.e. three colors for each word. The subject will then answer the questions. The Cronbach's Alpha was calculated, i.e. 0.942, which showed good internal consistency. (**Table 1**). Concurrent validity was then conducted in order to test the validity of the application. All parameters were tested with Pearson/Spearman test, to find the coefficient correlation. OffTime and OnTime + OffTime parameters were shown to have the strong correlation (> 0.7). details can be seen in **Table 2**.

Demographic Data

The median age of subjects was 53 ± 10.5 years old, with Child-Turcotte Pugh grade A, B, and C were 55%, 33.75%, and 11.25%, respectively. No subjects had undergone TIPSS procedure previously. The prevalence of covert HE was 43.75%, with subjects with Child-Turcotte Pugh B was the most common (57.25%). Chronic hepatitis B was the most common etiology of liver cirrhosis in this sudy (57.25%). Only one subjects who had not undergone any formal study. There were 17 subjects with history of overt HE (21.25%), with higher number of HE events was found in this group (70.58%). Demographic table can be seen in **Table 3**.

Table 1. Cronbach's Alpha Test

Cronbach's Alpha	Cronbach's Alpha Based on Standardized Items	N of Items
0,942	0,948	10

Table 2. Correlation Test of All EncephalApp Stroop Test Parameter

Parameter	*Kolmogorov-Smirnov Test*	*Pearson/ Spearman Test*
OffTime	0.002	0.82
OnTime*	0.081*	0.552*
TrialsOff	0.000	0.162
TrialsOn	0.00	0.140
OnTime + OffTime	0.021	0.782
OnTime – OffTime*	0.200*	0.009*
OffTime x TrialsOff	0.000	0.682
OnTime x TrialsOn	0.001	0.574

*Pearson test was used due to its normal distribution

Table 3. Demographic Data

Parameter	Total (n (%))
Sex:	
- Male	52 (65%)
- Female	28 (35%)
Child-Turcotte Pugh score:	
- A	44 (55%)
- B	27 (33.75%)
- C	9 (11.25%)
Level of education:	
- No formal education	1 (1.25%)
- Elementary School (SD)	12 (15%)
- Junior High School (SMP)	8 (10%)
- Senior High School (SMA)	28 (35%)
- Undergraduate – postgraduate	31 (38.75%)
Etiology of liver cirrhosis:	
- Hepatitis B	46 (57.5%)
- Hepatitis C	23 (28.75%)
- Hepatitis Non B and Non C	9 (11.25%)
- Hepatitis B and C	2 (2.5%)
Previous history of overt hepatic encephalopathy	17 (21.25%)
- Yes	63 (78.75%)
- No	

Diagnostic Study of EncephalApp Stroop Test

Area under Receiver Operating Characteristic (AUROC) analysis was done to find AUC (Area under the Curve) value, cut-off point, sensitivity, specificity, likelihood ratio, negative predictive value (NPV), positive predictive value (PPV) and post-test probability (**Figure 1**). Every AUC value from the parameters can be seen in **Table 4**. OffTime and OffTime + OnTime parameters showed the best AUC (AUC: 0.895, 95% CI: 0.829-0.961, p: 0.000; and AUC: 0.897, 95% CI: 0.829-0.965, p: 0.000, respectively). Optimal cut-off for OffTime and OffTime + OnTime were 89.58 second and 188.8 second, respectively. The sensitivity for OffTime + OnTime parameter was 88. 6% and specificity 80% The positive predictive value and positive likelihood ratio were 0.77 and 4.4 for OffTime + OnTime parameter, respectively. Negative likelihood ratio was 1.4, thus an ideal tools for screening modality. All diagnostic value can be seen in **Table 5**.

Factors Affecting EncephalApp Stroop Test

This study tried to evaluate several factors that may contribute to this diagnostic study. No difference was found in AUC between subjects with history of overt HE and none for the best three parameters of EncephalApp Stroop Test

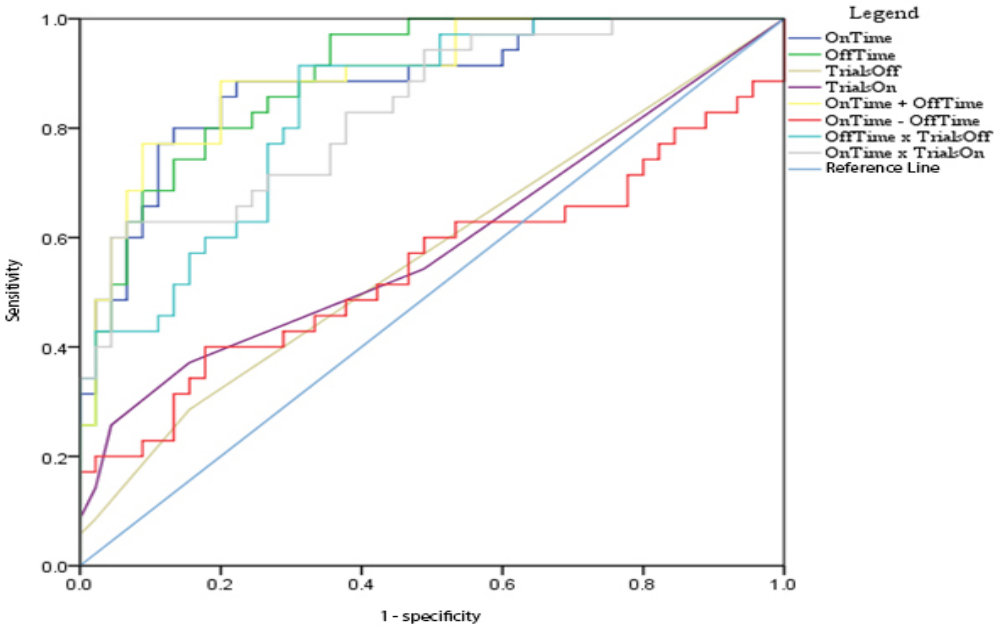

Figure 1. Area under the curve (AUC) curve of EncephalApp Stroop Test Parameter

Table 4. Area Under the Curve for Parameters in EncephalApp Stroop Test

Parameter	Area	p value	95% Confidence Interval	
			Lower Limit	Upper Limit
OffTime	0.895	0.000	0.829	0.961
OnTime	0.883	0.000	0.807	0.958
TrialsOff	0.570	0.282	0.442	0.699
TrialsOn	0.589	0.176	0.458	0.719
OnTime + OffTime	**0.897**	**0.000**	**0.829**	**0.965**
OnTime - OffTime	0.546	0.482	0.411	0.681
OffTime x TrialsOff	0.837	0.000	0.753	0.922
OnTime x TrialsOn	0.834	0.000	0.746	0.921

Table 5. Cut-off Point, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Post-Test Probability and Likelihood Ratio for every Parameters in EncephalApp Stroop Test

Parameter	Cut-Off Point (second)	Sensitivity	Specificity	PPV	NPV	LK+	LK-	Positive Post-Test Probability	Negative Post-Test Probability
OffTime	89,58	80%	80%	0.75	0.83	4	0.25	0,756	0,16
OnTime	99,72	85,7%	80%	0,76	0,87	4,2	0,17	0,76	0,12
TrialsOff	5,50	51,4%	57,8%	0,48	0,60	1,2	0,85	0,48	0,39
TrialsOn	5,50	54,3%	51,1%	0,46	0,58	1,1	0,8	0,46	0,41
OnTime + OffTime	**188,82**	**88,6%**	**80%**	**0,77**	**0,9**	**4,4**	**0,14**	**0,775**	**0,1**
OnTime - OffTime	7,75	60%	51,1%	0,48	0,62	1,2	0,78	0,48	0,37
OffTime x TrialsOff	508,029	80%	71%	0,68	0,82	2,7	0,28	0,68	0,17
OnTime x TrialsOn	578,73	71,4%	73,3%	0,67	0,76	2,67	0,3	0,67	0,23

Abbreviation: PPV=positive predictive value; NPV=negative predictive value; LK+=positive likelihood ratio; LK-=negative likelihood ratio

from the overall diagnostic study (OffTime, OnTime, and OffTime + OnTime) ($p > 0.05$), and the AUC was within 10-20% of total AUC (**Table 6**). There was also no difference in AUC between degree of Child-Turcotte Pugh score (**Table 7**). The age of the subjects was categorized into two groups, i.e. the subjects below 45 years old and 45 years old and above, based on previous study. This study, on the contrary from previous study, showed no significant difference in AUC of EncephalApp Stroop Test between two groups (**Table 8**).

Length of education was also proven to be statistically insignificant in affecting the EncephalApp Stroop Test diagnostic study. However, only one subject with no formal education, thus making it unable to analyzed. The comparison of AUC in each degree can be seen in **Table 9**. The etiology of liver cirrhosis (hepatitis B, hepatitis C, hepatitis non-B non-C, hepatitis B and C) was also analyzed, but only hepatitis B versus hepatitis C can be analyzed, to due to the low incident of coinfection hepatitis B and C and also hepatitis non-B non-C. The difference of AUC between these two groups was also not significant ($p>0.05$) (**Table 10**). Hence, no factors statistically significant affecting the diagnostic ability of EncephalApp Stroop Test.

Table 6. The Role of History of Overt HE in Diagnostic Study of EncephalApp Stroop Test

Parameter	AUC of EncephalApp Stroop Test based on History of Overt HE		P value of Comparison of AUC between groups	**Range of AUC that is considered not significant (from total AUC)**
	Yes	No		
OffTime	0.897	0.917	0.829	0.716 – 1
OnTime	0.888	0.883	0.9565	0.706 – 1
TrialsOff	0.586	0.483		0.456 – 0.684
TrialsOn	0.596	0.650		0.47 – 0.70
OnTime + OffTime	0.905	0.900	0.9545	0.716 – 1
OnTime - OffTime	0.518	0.583		0.43 – 0.65
OffTime x TrialsOff	0.840	0.817		0.66 – 1
OnTime x TrialsOn	0.814	0.917		0.667 – 1

Abbreviation: HE=hepatic encephalopathy; AUC=area under the curve

Table 7. The Role of Child-Turcotte Pugh Score in Diagnostic Study of EncephalApp Stroop Test

Parameter	**AUC of EncephalApp Stroop Test Based on Child-Turcotte Pugh**			**P value of Comparison of AUC Between Groups**			**Range of AUC That is Considered Not Significant (from total AUC)**
	A	**B**	**C**	**A vs B**	**A vs C**	**B vs C**	
OffTime	0.958	0.824	0.778	0.1442	0.3718	0.83	0.716 – 1
OnTime	0.927	0.841	0.889	0.3459	0.77	0.745	0.706 – 1
TrialsOff	0.517	0.662	0.611				0.456 – 0.684
TrialsOn	0.645	0.576	0.611				0.47 – 0.70
OnTime + OffTime	0.956	0.847	0.889	0.2156	0.77	0.77	0.716 – 1
OnTime - OffTime	0.508	0.571	0.556				0.43 – 0.65
OffTime x TrialsOff	0.875	0.794	0.778				0.66 – 1
OnTime x TrialsOn	0.867	0.794	0.778				0.667 – 1

Abbreviation: HE=hepatic encephalopathy; AUC=area under the curve

Table 8. The Role of Age in Diagnostic Study of EncephalApp Stroop Test

Parameter	AUC of EncephalApp Stroop Test Based on Age		P value of Comparison of AUC Between Groups	Range of AUC that is considered not significant (from total AUC)
	<45	≥ 45		
OffTime	0.960	0.863	0.12	0.716 – 1
OnTime	0.920	0.854	0.477	0.706 – 1
TrialsOff	0.540	0.576		0.456 – 0.684
TrialsOn	0.640	0.582		0.47 – 0.70
OnTime + OffTime	0.933	0.868	0.422	0.716 – 1
OnTime - OffTime	0.493	0.548		0.43 – 0.65
OffTime x TrialsOff	0.880	0.818		0.66 – 1
OnTime x TrialsOn	0.853	0.801		0.667 – 1

Abbreviation: HE=hepatic encephalopathy; AUC=area under the curve;

Table 9. The Role of Degree of Education in Diagnostic Study of EncephalApp Stroop Test

Parameter	AUC of EncephalApp Stroop Test based on Degree of Education				P value of Comparison of AUC Between Groups						Range of AUC that is considered not significant (from total AUC)
	Elementary School	Junior High School	Senior High School	Under-graduate	Elementary vs Junior High School	Elementary vs Senior High School	Elementary vs Under-graduate	Junior vs Senior High School	Junior vs Under-graduate	Senior vs Under-graduate	
OffTime	0.700	0.933	0.900	0.881	0.352	0.405	0.45	0.79	0.66	0.8285	0.716 – 1
OnTime	0.650	0.867	0.922	0.829	0.466	0.31	0.50	0.67	0.85	0.3727	0.706 – 1
TrialsOff	0.575	0.367	0.856	0.319							0.456 – 0.684
TrialsOn	0.525	0.467	0.514	0.740							0.47 – 0.70
OnTime + OffTime	0.750	0.867	0.956	0.867	0.634	0.31	0.58	0.5	0.96	0.2847	0.716 – 1
OnTime - OffTime	0.500	0.400	0.644	0.671							0.43 – 0.65
OffTime x TrialsOff	0.800	0.867	0.928	0.690							0.66 – 1
OnTime x TrialsOn	0.850	0.933	0.817	0.833							0.667 – 1

Abbreviation: HE=hepatic encephalopathy; AUC=area under the curve;

Table 10. The Role of Etiology of Liver Cirrhosis in Diagnostic Study of EncephalApp Stroop Test

Parameter	AUC of EncephalApp Stroop Test based on Etiology of Liver Cirrhosis				P value of Comparison of AUC Between Groups	*Range of AUC that is considered not significant (from total AUC)*
	Hepatitis B	Hepatitis C	Hepatitis Non B Non C	Hepatitis B and C	Hepatitis B vs Hepatitis C	
OffTime	0.903	0.955	0.350	1.000	0.378	0.716 – 1
OnTime	0.889	0.886	0.750	1.000	0.9163	0.706 – 1
TrialsOff	0.523	0.652	0.450	1.000		0.456 – 0.684
TrialsOn	0.591	0.598	0.625	0.500		0.47 – 0.70
OnTime + OffTime	0.911	0.924	0.650	1.000	0.8533	0.716 – 1
OnTime - OffTime	0.548	0.485	0.900	0.000		0.43 – 0.65
OffTime x TrialsOff	0.827	0.939	0.300	1.000		0.66 – 1
OnTime x TrialsOn	0.827	0.886	0.700	1.000		0.667 – 1

Abbreviation: HE=hepatic encephalopathy; AUC=area under the curve;

Factors Affecting Prevalence of Covert Hepatic Encephalopathy

Sub-analysis was done in this study to evaluate factors that may be contributed in the prevalence of covert hepatic encephalopathy. From this study, subject with Child-Turcotte Pugh B and C have prevalence ratio of having covert hepatic encephalopathy 2.3 and 2.44 times higher, respectively, than Child-Turcotte Pugh A ($p < 0.05$). No significant difference in prevalence of covert HE between Child-Turcotte Pugh B and C (**Table 11**). History of overt HE was also showed relationship with prevalence of covert HE, i.e. 1.934 times higher than without history of overt HE previously (PR: 1.934; 95% CI: 1.236-3.025). Pearson Chi-Square test was p: 0.012.

Liver cirrhosis etiology was shown to have no significant correlation with prevalence of covert HE ($p>0.05$) (**Table 12**). The age of the subject was distributed normally (Kolmogorov-Smirnov Z Asymp. Sig (2-tailed): 0.821), thus independent T-test was done to evaluate the relationship between age and prevalence of covert HE (**Table 13**). Age was shown to have no significant correlation with covert HE as well (p value >0.05).

Table 11. Prevalence Ratio of Covert HE Between Degree of Liver Cirrhosis

	P value	Prevalence Ratio Covert HE (95% CI)
Child-Turcotte Pugh B vs A	0.003	2.309 (1.315 – 4.052)
Child-Turcotte Pugh C vs A	0.048*	2.44 (1.253 – 4.768)
Child-Turcotte Pugh C vs B	1*	1.059 (0.614 – 1.826)
Child-Turcotte Pugh B + C vs A	0.001	2.343 (1.363 – 4.026)

*Fischer Exact Test was done due to one of the cells count was below 5
Abbreviation: HE=hepatic encephalopathy; CI=confidence interval

Table 12. Prevalence Ratio of Covert HE Between Liver Cirrhosis Etiology

	P value	Prevalence Ratio Covert HE (95% CI)
Hepatitis B vs Hepatitis C	0.490	0.818 (0.468 – 1.43)
Hepatitis B vs Hepatitis B and C	1*	0.783 (0.187 – 3.277)
Hepatitis B vs Hepatitis Non B Non C	0.467*	0.704 (0.355 – 1.399)
Hepatitis C vs Hepatitis B and C	1*	0.957 (0.224 – 4.078)
Hepatitis C vs Hepatitis Non B Non C	1*	0.861 (0.418 – 1.775)
Hepatitis Non B Non C vs Hepatitis B and C	1*	1.11 (0.247 – 5.0)
Viral Hepatitis vs Hepatitis Non-B Non-C	0.494*	1.315 (0.69 – 2.505)

*Fischer Exact Test was done due to one of the cells count was below 5
Abbreviation: HE=hepatic encephalopathy; CI=confidence interval

Table 13. Independent T-Test Between Age and Prevalence of Covert HE

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% CI	
		F	P value	t	df	P value	Mean Difference	Std. Error Difference	Lower Limit	Upper Limit
Age	Equal variances assumed	2.077	0.154	1.923	78	0.058	4.498	2.339	0.159	9.155
	Equal variances not assumed			1.953	76.691	0.054	4.498	2.303	0.088	9.084

DISCUSSION

Covert hepatic encephalopathy (CHE) is part of hepatic encephalopathy with neuropsychometric or neurophysiology abnormalities in liver cirrhosis patient without any disorientation nor asterixis.[8] This group of HE was made by ISHEN in 2010 due to its poor reliability and subjectivity that may come up in evaluating the mental status, considering that the clinical manifestation in minimal HE may not be appeared.[8, 10] The prevalence itself may range from 20-80%, due to the difficulty in diagnosing covert HE.[7, 10, 11] The prevalence of minimal HE in RSCM in 2009 was 63.2%, while data in 1999 showed the prevalence of overt HE (stage 2-4 HE) was 14.9%.[20, 21] In this study, we found a prevalence of 43.75%, using PHES and CFF as the gold standard.

Hepatitis B has been the most etiology of liver cirrhosis found in this study (57.5%), in accordance to other studies. This data was higher than South East Asia data in 2010 (54%). Child-Turcotte Pugh A was the most common stage found in liver cirrhosis population (55%). However, prevalence of covert HE in Child-Turcotte Pugh B and C was found higher than Child-Turcotte Pugh A. This study tried to analyze prevalence risk of covert hepatic encephalopathy in different Child-Turcotte Pugh and found that Child Pugh B and C have prevalence ratio of 2.3 and 2.44, compared to Child-Turcotte Pugh A. Although previous study showed no correlation between Child-Turcotte Pugh score and minimal HE, another study by Wang, et.al. showed the opposite.[22, 23]

History of previous overt HE was also found to be correlated with prevalence of covert HE. This study found subjects with previous overt HE (PR: 1.934; 95% CI: 1.236 – 3.025; $p < 0.05$). Another study by Wang, et.al. also found similar outcome, with history of overt HE showed odd ratio of 7.18 (95% CI: 3.45-14.92, $p<0.05$) of having covert HE, compared to without previous history of overt HE.[24] No other factors found in this study (age and etiology of liver cirrhosis) to be correlated with the prevalence of overt HE, also in accordance to same study stated previously.[24]

It is very important to be able to diagnose covert HE, due to its correlation with the decrease of quality of life, especially in activities requiring concentration, information process and psychomotor ability, such as driving a vehicle or planning a trip, even though basic ability was still intact, i.e. shopping, getting dressed, and maintain personal hygiene.[11, 25, 26] Risk of fall was also increasing by 28% in minimal HE patient, correlated with the decrease of attention, time of reaction, visuomotor coordination and psychomotor speed.[26] A study by Bajaj et. al. found that cognitive, response inhibition, visuomotor coordination, set shifting, psychomotor speed and accuracy were all impaired in covert HE.[18] A number of studies found the increase of accident and traffic violation in patient with minimal HE.[11]

Validity and Reliability Test of EncephalApp Stroop Test

All questions asked in the application were translated previously into Indonesia. Translation was done by Transmedical Institute, through 3 processes, i.e. forward translation, back translation, and reconciliation, involving licensed translator, consisted of two medical-based translators and two non-medical-based translators. Reconciliation was done and the translation was inputted into the application. Reliability test was then done, i.e. the internal consistency test. Thirty subjects were given the questions and answered all 17 questions. Cronbach's Alpha was then calculated. The value was 0.942, which show excellent internal consistency. Validation of the test was then carried out, by using diagnostic study of EncephalApp Stroop Test.

Concurrent validity was done to test the validity of this study. All parameters were tested with Pearson or Spearman test, depending on the normality of these parameters, to find the correlation coefficient of each parameters. OffTime + OnTime were shown to have strong correlation with the diagnosis of covert HE, with coefficient correlation > 0.7. This was also in accordance to the result of diagnostic study, which showed OffTime+OnTime as the best parameter to diagnostic covert HE. The other parameters were shown moderate to correlation (OnTime, OffTime x TrialsOff, and OnTime x

TrialsOn), with the correlation coefficient ranged from 0.3-0.7. The weakest correlation, but still positive were shown by TrialsOff, TrialsOn, and OnTime – OffTime parameter. This was also reflected in the result of diagnostic study.

Diagnostic Study of EncephalApp Stroop Test

The study showed good AUC value with OnTime + OffTime as the best parameter (AUC 0.897; 95% CI: 0.829-0.965; p:0.000), rather than the errors committed (number of runs required) and cognitive flexibility (OnTime-OffTime).[19] This was also in accordance with the previous study, showed that psychomotor function is more predictive than cognitive flexibility.[19] Psychomotor speed, captured by OnTime + OffTime was associated with poor connectivity between anterior cingulate cortex, dorsolateral prefrontal cortex, and posterior parietal lobes.[18]

The optimal cut-off value for this AUC was 188.8 second. The sensitivity was 88.6%, while specificity was 80%. The PPV and NPV were 0.77 and 0.9, respectively, with positive likelihood ratio (LK+) was 4.4. As a diagnostic tool, EncephalApp Stroop Test was only moderate, with LK+ less than 10. However, the negative likelihood ratio was 1.4 an also NPV was 0.9, which shown EncephalApp Stroop Test as an ideal screening test (LK- < 2).

This was similar with previous study of EncephalApp Stroop Test (cut-off point for OnTime + OffTime parameter: > 190 seconds, sensitivity 80%, specificity 80%, AUC 0.91).[19] The first study conducted by Bajaj, et.al. found that poorer result was found in subjects with previous overt HE.[18] We found higher prevalence of covert HE in subject with previous overt HE PR: 1.934; 95% CI: 1.236 – 3.025; p < 0.05). However, no significant difference of AUC between groups with history of overt HE and without it, as well as previous study.[18]

Validation study conducted by Bajaj, et.al. found that age play role in EncephalApp Stroop Test, thus defining two different cut-offs for OnTime+OffTime parameters, i.e. > 190 seconds for age 45 years and above, and >145 seconds for age below 45 years old.[19] However, this study showed that age has no significant effect in AUC, meaning that the cut-off of 191.4 seconds for OnTime+OffTime in this study can be used for all ages in Indonesian population. Level of education, history of covert hepatic encephalopathy, etiology of liver cirrhosis, Child-Turcotte Pugh score were similarly insignificant to the AUC of EncephalApp Stroop Test.[19] There were three parameters that showed poor AUC, i.e. TrialsOff, TrialsOn, and OnTime-OffTime (0.57, 0,58, and 0,546, respectively). This was also similar to the same study by Bajaj, et.al, even though the number was slightly higher (0.65, 0,68, and 0.73, respectively).[19]

CONCLUSION

The translated EncephalApp Stroop Test was found to be reliable and valid test for Indonesian population. It showed good sensitivity, specificity, AUC, and PPV as a diagnostic tool for detecting covert hepatic encephalopathy in Indonesian population. It showed moderate positive predictive value, but it has an excellent negative predictive value, thus making it as an ideal screening tool for covert HE. The study is very important, as Indonesia is currently lacking diagnostic tool to diagnose covert hepatic encephalopathy, while it plays major impact in patient's quality of life and be a sole predictor of death and progression into overt HE.[10] This study may also open the opportunity to conduct studies, to see whether EncephalApp Stroop Test could be used as a surveillance tool for covert HE subjects who are on treatment, as well as evaluating the effectiveness of the HE management.

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