Original Article

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Internal Medicine Section

Psychometric Hepatic Encephalopathy Score in the Diagnosis of Minimal Hepatic Encephalopathy in Cirrhosis of Liver: A Cross-sectional Study

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ABSTRACT

Introduction: Minimal Hepatic Encephalopathy (MHE) is a subclinical condition in patients with liver cirrhosis, often preceding Overt Hepatic Encephalopathy (OHE). MHE impairs driving ability and Quality of Life (QoL) but requires specialised neuropsychological tests such as the Psychometric Hepatic Encephalopathy Score (PHES) for diagnosis, as routine exams are insufficient.

Aim: To establish normal values for the PHES and assess its diagnostic efficacy for MHE in patients with liver cirrhosis.

Materials and Methods: A cross-sectional study was conducted at BLDE (DU) Medical College, Vijayapura, Karnataka, India, from May 2023 to December 2024, with a sample of 166 participants (cases and controls). Patients with OHE were excluded. The PHES was administered and biochemical tests including Alanine Transaminase (ALT), Aspartate Transaminase (AST), International Normalised Ratio (INR) and albumin, among others, were performed. Imaging {Ultrasound (USG) abdomen/pelvis} was also conducted. MHE was diagnosed if the PHES score was < –4 based on healthy nomograms. Statistical analysis was performed using the t-test, Mann-Whitney U test and Chi-square test, with a p-value <0.05 considered statistically significant.

Results: Of the 166 participants, 83 had cirrhosis and 83 unmatched participants without cirrhosis were included for comparison. Cases were predominantly male (92.77% vs. 67.47%, p-value <0.001). Higher proportion of controls had primary education while secondary and higher secondary education levels were slightly more prevalent among cases (p-value=0.330). Cases showed significant impairment in all PHES subtests (p-value <0.001) and a lower mean PHES score (–4.40 vs. 2.28, p-value <0.001). A total of 37.35% of cases had MHE, while none in the control group had MHE (p-value <0.001). No correlation between ammonia levels and MHE status was observed.

Conclusion: PHES is a reliable, non invasive tool for the early detection of MHE in cirrhosis patients, aiding timely intervention. While it should complement clinical evaluation, its cost-effectiveness and accessibility enhance patient management and outcomes.

Keywords: Cirrhosis, Neuropsychological tests, Psychometrics, Quality of life

INTRODUCTION

Hepatic Encephalopathy (HE) is a neurological complication of advanced liver disease, with MHE representing its mildest form. MHE affects 20-80% of patients with cirrhosis, impairing cognitive functions such as memory, attention and psychomotor skills. Despite its subtle presentation, MHE significantly reduces QoL, leading to sleep disturbances, impaired daily functioning, an increased risk of motor vehicle accidents and higher healthcare utilisation [1-3].

MHE and Covert HE (CHE), which includes grade I HE, often progress to OHE at a rate of 5-25% within five years, particularly in patients with complications such as infections, variceal bleeding, ascites, or metabolic disorders [4-6]. MHE is frequently underdiagnosed due to a lack of routine psychometric screening. It negatively impacts QoL domains such as mobility, emotional health and social interaction, as measured by tools like the Sickness Impact Profile [6,7]. Early detection is crucial because MHE is reversible with treatments targeting ammonia reduction, including lactulose (a non absorbable disaccharide), rifaximin (an antibiotic) and probiotics/prebiotics (shown to be as effective as lactulose in trials) [8-12].

Psychometric testing has evolved from unstandardised assessments to validated batteries like the PHES, introduced in 2001 [4]. PHES originated from the PSE-Syndrome-Test (1980s) and evaluates attention (Number Connection Tests: NCT-A, NCT-B), visuospatial coordination (Line Tracing Test: LTT) and psychomotor speed (Digit Symbol Test: DST, Serial Dotting Test). PHES is now considered the gold standard for MHE diagnosis, with normative data from over 400 individuals confirming its reliability [13,14]. MHE was first recognised in the 1970s when cirrhotic patients with normal neurological exams exhibited abnormal neuropsychological test results [15,16]. Beyond PHES, other diagnostic methods include the Critical Flicker Frequency test (CFF), Inhibitory Control Test (ICT), Electroencephalogram (EEG) and imaging tests [17,18]. Therefore, this study aimed to address this gap by establishing the diagnostic efficacy of the PHES in patients with cirrhosis from a tertiary care centre, as prior studies have highlighted the need for population-specific validation of PHES, including in Indian and South Asian settings [1,9,13].

MATERIALS AND METHODS

A cross-sectional study was conducted at Shri BM Patil Medical College, Hospital and Research Centre (Deemed-to-be University), Vijayapura, Karnataka, India, from May 2023 to December 2024. This study was carried out in the Inpatient and Outpatient Departments (IPD/OPD) of the Medicine wards. The study was approved by the Institutional Ethics Committee (IEC) with approval number BLDE(DU)/IEC/880/2022-2023. Written informed consent was obtained from all participants before enrollment.

Inclusion criteria: Based on clinical, laboratory and radiological evidence confirmed cases of cirrhosis were included in the study.

Exclusion criteria: Patients with recent OHE, gastrointestinal bleeding, or infections within the past two weeks; had used lactulose, antibiotics, or psychoactive drugs within the past two weeks; had

neurological or psychiatric disorders (Mini-Mental State Examination score < 25); had heart, respiratory, or renal failure; had hepatocellular carcinoma or other malignancies; had undergone Transjugular Intrahepatic Portosystemic Shunt/shunt surgery; or were illiterate, as this affected their ability to provide consent or complete the PHES administration were excluded from the study.

Sample size calculation: To achieve a power of 80% for detecting a difference in means, a total sample size of 166 (for each group, assuming equal sizes) was calculated using G*Power version 3.1.9.4 software. A t-test was used to compare the means between two independent groups with a 5% level of significance.

Study Procedure

Based on clinical and radiological evaluations, 83 participants with cirrhosis were identified, while 83 without cirrhosis were included for comparison. The groups were not matched for age or gender. Face-to-face interviews were conducted to collect socio-demographic details. Parameters assessed included albumin, ALT, AST, serum ammonia, aPTT, BUN, creatinine, glucose, haemoglobin, haematocrit, INR, platelet count and USG of the abdomen and pelvis.

The Child-Pugh classification was calculated for all cirrhotic patients at baseline using standard parameters such as serum bilirubin, albumin, prothrombin time, ascites and HE. Patients were graded into Child-Pugh A [5-6], B [7-9], or C [10-15]. This score was used to assess the severity of liver disease and its correlation with PHES.

All participants, including both cases and controls, were administered a comprehensive battery of neurocognitive tests, including Number Connection Test-A (NCT-A), Number Connection Test-B (NCT-B), Simple Dot Test (SDT), Line Tracing Test (LTT), and Digit Symbol Test (DST) in a quiet room. Each test evaluates different domains such as attention, visual-motor coordination, processing speed and executive function. NCT-A and NCT-B measure psychomotor speed and cognitive flexibility. The outcomes are recorded in seconds, with lower scores indicating better performance. The normal range is 20-180 seconds. LTT assesses visuomotor coordination, with scoring based on the time taken and deviation from the path; higher values indicate worse performance. SDT tests motor speed by asking the subject to mark dots within a time limit, with a maximum possible score of 200; the normal range is 80-180 dots. DST evaluates attention and visual memory, with a maximum score of 90; higher scores reflect better function [19].

The PHES battery is validated and widely used for the diagnosis of MHE, with reported sensitivity between 85-95% and specificity between 80-90% [4,5,14,15]. Test normalisation was performed using regional reference values to reduce cultural bias [1,5,6,9,13]. These tests are non invasive, cost-effective and recommended in clinical guidelines for MHE diagnosis due to their strong predictive value in assessing driving fitness, QoL and the risk of progression to OHE [7,10].

STATISTICAL ANALYSIS

The collected data was entered into a Microsoft Excel sheet and statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) (Version 20.0). The results were displayed as means, standard deviations (SD), counts, percentages and diagrams. The Independent sample t-test was used to compare normally distributed continuous variables between the two groups, the Mann-Whitney U test was employed for non normally distributed variables, and the Chi-square test/Fisher's exact test was utilised to compare categorical variables between the two groups. Linear regression analysis was used to derive equations for each psychometric test score based on age and years of education and standard deviations of the predicted scores were reported. Diagnostic performance metrics, including sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), accuracy, Area Under the Curve (AUC), and Cohen's kappa, were calculated for different combinations of psychometric subtests (NCT-A, NCT-B and DST) in identifying minimal hepatic encephalopathy (MHE). A p-value <0.05 was considered statistically significant.

RESULTS

The total number of study participants was 166. A higher proportion of individuals aged 40-49 years was found in the case group (36 participants, 43.37%) compared to the control group (17 participants, 20.48%). A higher proportion of males were in the case group (77 participants, 92.77%) compared to the control group (56 participants, 67.47%). The comparison of education categories between the groups indicates that a higher proportion of controls had primary education (57 participants, 68.67%) compared to cases (48 participants, 57.83%), while secondary and higher secondary education levels were slightly more prevalent among cases [Table/Fig-1]. However, the difference was not statistically significant (p-value=0.330).

Variables	Cases (N=80) n (%)	Controls (N=80) n (%)
Age in years		
≤29	4 (4.82)	14 (16.87)
30-39	16 (19.28)	23 (27.71)
40-49	36 (43.37)	17 (20.48)
≥50	27 (32.53)	29 (34.94)
Gender		
Female	6 (7.23)	27 (32.53)
Male	77 (92.77)	56 (67.47)
Education		
Primary	48 (57.83)	57 (68.67)
Secondary	20 (24.10)	16 (19.28)
Higher secondary and above	15 (18.07)	10 (12.05)

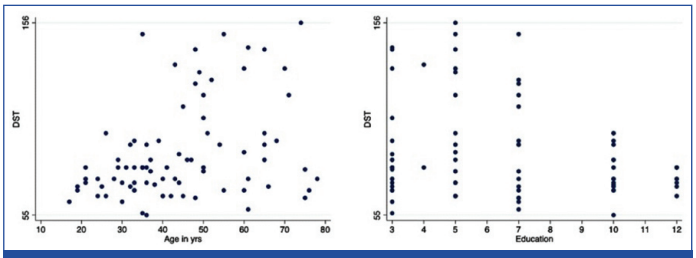
[Table/Fig-1]: Socio-demographic characteristics of the study participants.

All subtests-NCT-A, NCT-B, SDT, LTT and DST-showed significantly higher mean scores in the cirrhosis group, indicating poorer performance. The overall PHES score was lower in the cirrhosis group (-4.40±3.89) compared to the non cirrhosis group (2.28±1.21). All differences were statistically significant, with p-values <0.001 [Table/Fig-2].

Test	Controls (Mean±SD)	Cases (Mean±SD)	t-value	p-value
NCT-A	54.48±16.48	127.31±54.33	-11.69	<0.001
NCT-B	95.7±23.86	162.82±51.3	-10.76	<0.001
SDT	27.29±9.76	80.23±41.75	-11.25	<0.001
LTT	50.12±19.06	172.68±93.44	-11.71	<0.001
DST	87.0±24.96	222.59±73.78	-15.84	<0.001
PHES	2.28±1.21	-4.4±3.89	14.92	<0.001

[Table/Fig-2]: Comparison of PHES subtest scores between participants with and without cirrhosis.

DST scores show greater variability with age but tend to increase with higher years of education among healthy individuals [Table/Fig-3].



[Table/Fig-3]: Distribution of Digit Symbol Test (DST) in healthy individuals based on age and education years.
(The X-axis represents years of education; a value of 0 indicates no formal education, 1 corresponds to the completion of class 1, and so on. Individuals who completed graduation are coded as 13, and those with education beyond graduation are coded as 14.)

MHE was identified in 31 participants (37.35%) with cirrhosis, while none of the participants without cirrhosis had MHE (p-value <0.001). Additionally, 3 participants (3.61%) with cirrhosis could not complete the assessment [Table/Fig-4].

MHE status	Cases n (%)	Controls n (%)	p-value
MHE	31 (37.35)	0	<0.001
No MHE	49 (59.04)	83 (100.00)	
Not completed	3 (3.61)	0	

[Table/Fig-4]: Comparison of MHE status between the groups.

Participants with MHE had significantly lower serum ammonia levels (33.52±11.08 vs. 40.00±11.22, p-value=0.013) and higher Child-Turcotte-Pugh (CTP) scores (9.52±1.53 vs. 8.47±1.42, p-value=0.002).

All PHES subtests (NCT-A, NCT-B, SDT and DST) showed significantly poorer performance in the MHE group (p-value <0.001). Differences in age, education and sex were not statistically significant [Table/Fig-5]. The regression equations demonstrate the relationship between cognitive test scores and two predictors: age and years of education. All five tests-NCT-A, NCT-B, SDT, LTT and DST-showed positive coefficients for both variables, indicating that scores tend to increase with increasing age and educational attainment. Among them, DST showed the strongest influence of education with a coefficient of 3.883. The SD values provided reflect the variability in predicted scores for each test. These findings are detailed in [Table/Fig-6].

Variable	No MHE Mean±SD	MHE Mean±SD	t-value/U/χ^2	p-value
Age (years)	46.90±9.89	42.39±10.64	1.93	0.057
Education	7.59±3.63	8.48±3.13	-1.13	0.263
Sex n (%)				
Female	3 (6.12)	0	χ^2=1.97	0.160
Male	46 (93.88)	31 (100)		
Serum ammonia (µmol/L)	40.00±11.22	33.52±11.08	2.53	0.013
CTP score	8.47±1.42	9.52±1.53	-3.13	0.002
NCT-A	95.37±36.53	173.35±42.67	-8.71	<0.001
NCT-B	135.85±29.12	204.58±50.49	-7.67	<0.001
SDT	55.80±22.34	116.52±36.60	-9.23	<0.001
DST	177.52±51.46	286.42±48.34	-9.40	<0.001

[Table/Fig-5]: Clinical characteristics of patients with liver cirrhosis.

Test	Equation	SD
NCT-A	36.153+0.749×Age+2.892×Education	53.667
NCT-B	77.946+0.749×Age+2.334×Education	51.510
SDT	21.837+0.443×Age+1.644×Education	40.089
LTT	52.123+0.751×Age+3.465×Education	90.903
DST	72.089+1.193×Age+3.883×Education	86.587

[Table/Fig-6]: Regression results for cognitive tests.

The combination of NCT-A and NCT-B demonstrated the highest sensitivity (93.55%), with an overall diagnostic accuracy of 85.79%. The highest specificity (90.15%) was observed with the combinations NCT-A+DST and all three tests abnormal. Using at least one abnormal result from any of the three tests yielded 100% sensitivity but lower specificity (54.55%) and accuracy (77.28%). The lowest accuracy (51.25%) was noted when at least two tests were abnormal. PPV were generally lower across combinations, while NPV remained high, indicating strong rule-out potential for normal results [Table/Fig-7].

DISCUSSION

MHE is a common and clinically significant complication of cirrhosis, known to impair QoL and driving ability [3]. In the present study, MHE was detected in 37.35% of cirrhotic patients using the PHES. This prevalence was consistent with previous reports from China (49.1%) [1] and India (35-39%) [9], supporting the reliability of PHES across diverse geographic and ethnic populations. Here, NCT-A shows a significant delay in completion time among MHE cases (127.31 seconds vs. 54.48 seconds, p-value <0.001). This supports previous studies in Germany and Korea where NCT-A was found to be particularly sensitive in detecting cognitive slowing in MHE [4,15].

DST performance was strongly influenced by educational background, consistent with findings from Bangladesh, Cameroon, and India. In Bangladesh, Podder MK et al., established normative PHES values showing significant variation by education level [13]. Djomatcho LP et al., normalised PHES for the Cameroonian population and emphasised educational adjustment due to its impact on test performance [6]. Similarly, Pawar VB et al., reported that PHES and DST scores in Indian patients were significantly associated with years of schooling, reinforcing the need for region-specific normative data [9]. Despite this, the PHES battery demonstrated overall reliability when demographic variables were appropriately adjusted.

In present study control group, PHES scores remained consistent across age and sex, validating the standardised cut-off of PHES < -4 for diagnosing MHE, as proposed by Weissenborn K [4] and supported by multicentre efforts [14,15]. Contrary to findings from Spanish cohorts that reported gender-based differences [16], present study observed no significant sex-based influence, highlighting that the severity of liver disease was the principal determinant of PHES performance.

A key observation was that MHE patients had significantly lower serum ammonia levels than non-MHE patients (33.52 vs. 40.00 µmol/L, p-value=0.013). This contradicts the conventional paradigm of increased ammonia levels being the central mechanism of HE [2,7,8], suggesting the involvement of alternative mechanisms such as systemic inflammation, neuroinflammation and gut dysbiosis

Diagnostic test	Sensitivity	Specificity	PPV	NPV	AUC	Kappa	Accuracy
NCT-A+NCT-B abnormal	93.55%	78.03%	50.00%	98.10%	0.858	0.537	85.79%
NCT-A+DST abnormal	77.42%	90.15%	64.86%	94.44%	0.838	0.560	83.79%
NCT-B+DST abnormal	77.42%	88.64%	61.54%	94.35%	0.830	0.545	83.03%
All of the three tests were abnormal	77.42%	90.15%	64.86%	94.44%	0.838	0.560	83.79%
At least one of NCT-A/NCT-B abnormal	100.00%	54.55%	34.07%	100.00%	0.773	0.401	77.28%
At least one of NCT-A/DST abnormal	100.00%	62.12%	38.27%	100.00%	0.811	0.449	81.06%
At least one of NCT-B/DST abnormal	93.55%	68.94%	41.43%	97.85%	0.812	0.471	81.25%
At least one of NCT-A/NCT-B/DST abnormal	100.00%	54.55%	34.07%	100.00%	0.773	0.401	77.28%
At least two of NCT-A/NCT-B/DST abnormal	16.13%	86.36%	21.74%	81.43%	0.512	0.220	51.25%

[Table/Fig-7]: Comparisons between Psychometric Hepatic Encephalopathy Score (MHE status) and Number Connection Test-A (NCT-A), Number Connection Test-B (NCT-B), and Digit Symbol Test.

[10,12]. This study suggests that ammonia alone is not sufficient for diagnosing MHE [2,10].

This study states the efficiency of NCT-A and DST, particularly in resource-limited environments. These tests could serve as first-line screening tools, with full PHES reserved for confirmatory diagnosis. Early detection of MHE using PHES helps in managing cases with rifaximin or lactulose, which have been shown to reverse MHE and improve patient outcomes [9]. In resource-limited settings, NCT-A can act as a reliable screening tool for diagnosing MHE. This study also emphasises that a single measurement of ammonia alone is insufficient for diagnosing MHE. As a single-centre study, it requires larger multicentre validation studies. Alternative biomarkers, such as IL-6 and TNF-α, could assist in better understanding and diagnosis [2,10,12].

The use of PHES through app-based tools or AI-assisted scoring aids in screening and monitoring, especially in outpatient or domiciliary settings [11]. Finally, since 3.61% of present study patients were unable to complete the PHES, this indicates a need for adjunctive modalities like the CFF test or ICT to expand diagnostic coverage [10].

Limitation(s)

This study was conducted at a single centre, which limits the generalisability of the findings. The participant groups were not matched for age, sex, or education level, which may introduce confounding variables. Additionally, variations in serum ammonia levels over time were not assessed; serial measurements or inclusion of alternative biomarkers such as inflammatory cytokines could provide deeper insight into the underlying mechanisms of MHE. Furthermore, 3.61% of participants with cirrhosis were unable to complete the PHES battery, underscoring the need for supplementary diagnostic tools such as the CFF test in advanced cases.

CONCLUSION(S)

The PHES is a reliable tool for diagnosing MHE to assess attention, psychomotor skills and visuospatial function, facilitating the early detection of cognitive decline. While its use is limited by population-specific normative data, it remains central to MHE diagnosis. Routine screening with NCT-A and DST aids in quick diagnosis. The study reinforces PHES as the diagnostic gold standard and emphasises the need for ancillary tools to improve early detection.

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