International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Research Article

THE CLINICAL CHARACTERISTICS OF LIVER CIRRHOSIS PATIENTS WITH MINIMAL HEPATIC ENCEPHALOPATHY

*Dr. Shyam Sundar Yadav, Prof. Dr. Shaoqi Yang, Jia-Li Yang, Fang Wang and Ming-Hai Shan

Department of Gastroenterology, General Hospital of Ningxia Medical University, Yinchuan, 750004, Ningxia, China

ABSTRACT

Objective: This study aimed to evaluate the clinically stable liver cirrhosis patients who underwent a combination of psychometric tests (NCT-A and DST) for the diagnosis of MHE.

Methods: A total of 200 clinically stable liver cirrhosis patients were evaluated by psychometric tests (NCT-A and DST), standard biochemistry and venous ammonia. MHE was diagnosed if there were two or more abnormal psychometric tests (±2SD). The statistics methodology was analyzed by the T-test, chi-square test, and multivariate logistics analysis.

Results: in total, 200 patients with liver cirrhosis; age, and education years were confirmed to be prognosticator of both (NCT-A and DST) of the patients with liver cirrhosis; age (50.22±10.53) years; M: F ratio: 147:53, Child-Pugh A: B: C (67:85:48) who met the inclusion criteria. 128 (64%) patients had MHE (Child A=32 (25%), Child B= 65 (50.8%) and Child C= 31 (24.2%). There was no significant difference between ALT, ALB, TBIL, NA, PT, PTA, and INR, but the AST (85.24±121.55vs.62.94±87.71, P=0.028), Ammonia (49.02±33.41vs.22.06±14.67, P=0.001), Child-Pugh score (P=0.004) and MELD score (7.60±4.58vs.6.10±3.77, P=0.040) ware significantly higher in MHE as compared to Non- MHE patients. NCT-A and DST were used to diagnosing MHE with a showed excellent correlation with age and education (P=<0.05). On multivariate analysis, CTP, MELD, and venous ammonia were predictive of MHE.

Conclusion: The combination of psychometric tests including NCT-A and DST can be used for the diagnosis of MHE**.** The psychometric tests including NCT-A and DST showed excellent correlation with age and education. The prevalence of MHE in this study was 64%. Ammonia>26.5μmol/L, Child- Pugh score>7.5, and MELD score>5.31 were predictive of MHE.

Keywords: Minimal Hepatic Encephalopathy, Liver Cirrhosis, Number Connection Test-A, Digit Symbol test.

INTRODUCTION

Hepatic Encephalopathy (HE) is significant clinical issue cirrhosis of the liver and portal hypertension that is characterized by neuropsychiatric and neurologic abnormalities. It is manifested as personality changes, cognitive dysfunction, and altered level of consciousness [1]. MHE is characterized by subtle cognitive and psychomotor deficiencies and the absence of recognizable clinical signs and symptoms of HE and is documented by neuropsychological (NP) tests and neurophysiological tests, but HE grade 1 is characterized by the presence of mild clinical alterations such as euphoria, anxiety, or a shortened attention span [2]. Minimal hepatic encephalopathy cases vary worldwide between 30 to 84% in cirrhotic patients [3]. MHE is associated with impaired quality of life and driving ability and is a predictor of the development of overt hepatic encephalopathy (OHE) [3]. Complications of Liver cirrhosis such as Ascites, Variceal Bleeding, infection and HE are predictors of an unfavorable prognosis in patients with cirrhosis [4]. MHE has also been associated with a higher incidence in the development of overt hepatic encephalopathy (HE) and higher mortality in patients with cirrhosis [5]. The Model for End-stage Liver Disease (MELD)and Child-Turcotte-Pugh (CTP) scores were seen as predictors of long-term survival and complications in patients with cirrhosis [6]. Gut-derived nitrogenous substances are universally acknowledged to play a major role in the pathogenesis of HE, and MHE is similar to that of overt HE. Ammonia is thought to be a major factor in the pathogenesis of HE [7]. The Working Group on HE should be validated by at least two of the following neuropsychological tests and is used for the diagnosis of MHE: The Number Connection Test-A (NCT-A), NCT-B, Digit-Symbol Test (DST) and the Block-Design Test (BDT) [8], and PHES can be used to measure motor speed, motor accuracy, attention, concentration, visual perception, visual-spatial orientation, visual construction and memory [9], which are seen in most neuropsychological impairments in MHE. PHES has been standardized in Germany, Italy, Spain, India, Korea, and Mexico. This study aimed to build and for the psychometric tests (Number Connection Test and Digit Symbol Test), to evaluate the diagnosis of MHE patients with liver cirrhosis.

MATERIALS AND METHODS

Patient population:

The Prospective of this study was executed between December 2018 to December 2019 at General Hospital of Ningxia Medical University, 200 clinically stable liver cirrhosis patients without MHE were screened prospectively for MHE.

Subjects and study plan:

Patients were included if they were ages >18 to <64 years of age. Liver cirrhosis was diagnosed on a clinical basis involving laboratory tests, sonographic findings, endoscopic evidence, abdomen CT and liver histology, if available. The following were the etiologies of cirrhosis: Chronic Hepatitis B (116), Chronic Hepatitis C (21) and Primary Biliary Cirrhosis (23), Alcoholic Cirrhosis (n=18), Autoimmune Hepatitis (11)

and Cryptogenic Cirrhosis (11). The exclusion criteria used were history of taking lactulose or any alcohol intake, antibiotics, gastrointestinal hemorrhage or spontaneous bacterial peritonitis during the past 6 weeks, previous TIPS or shunt surgery, significant comorbid illness such as heart, respiratory or renal failure; and history of any neurologic disease such as Alzheimer's Disease, Parkinson's Disease or Non-Hepatic Metabolic Encephalopathy's. Patients on psychoactive drugs, such as antidepressants or sedatives, were excluded. History of alcohol intake was assessed by either asking the patient or his/ her relatives. Liver function tests and venous ammonia were measured at inclusion. All patients who were enrolled in the study were evaluated using Psychometric Tests (Number connection tests and Digit symbol tests).

Psychometric testing:

Two hundred patients underwent a combination of psychometric test including the Number Connection Test-A and Digit Symbol Test. The Number Connection Test (NCT) is the most universally used in the psychometric evaluation of cirrhotic patients. It was established to be capable of detecting mild mental dysfunction in cirrhotic patients. The subject is shown a sheet of paper with 25 numbered circles that are randomly spread over the paper. The task given was to connect the circles from 1-25 as quickly as possible. The test results are the time needed by subject including error correction time [15], (Figure 1).

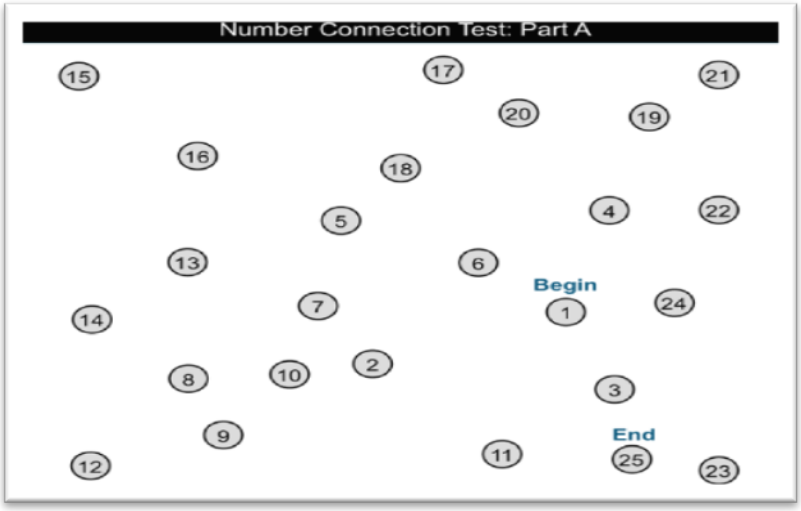

Figure 1: Number connection test

The Digit Symbol Test (DST) - the subject is given a succession of double-boxes with a number given in the upper part. The task is to draw a symbol relevant to this number into the bottom part of the boxes. Nine fixed pairs of digits and symbols are given at the top of the test sheet. The number of boxes of the test results is correctly filled within 90 seconds. The test score is the time required to complete the test, including the time needed to correct any errors (Figure 2). Tests were considered abnormal when the test score was more than mean ± 2 SD, from the age and education matched controls[9]. Minimal hepatic encephalopathy was diagnosed if two or more psychometric tests were abnormal.

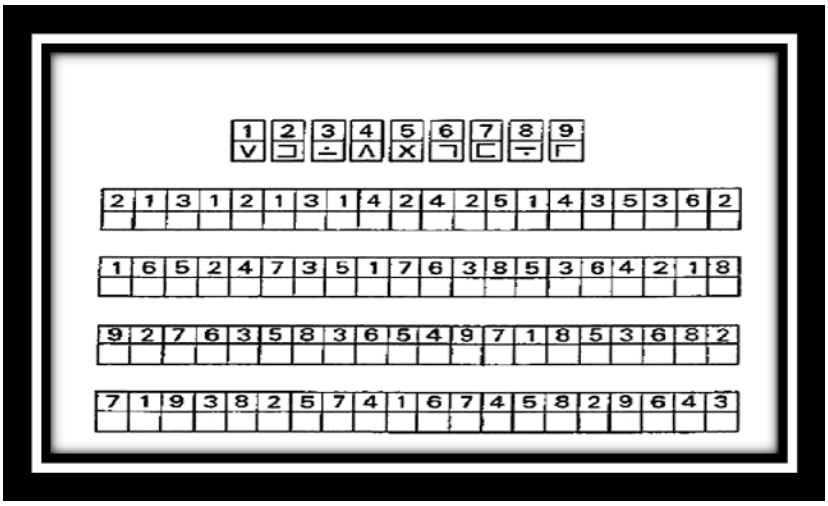

Figure 2: Digit symbol test

Biochemical examination:

Blood samples for AST, ALT, and TBIL, albumin, INR, sodium, creatinine, PT, INR, PTA, and ammonium were analyzed by conventional methods and abdominal ultrasound and computed tomography for ascites.

Calculation of MELD and CTP score:

Both the scores were calculated on the day of the assessment of MHE. CTP score was achieved according to the classification presented by Pugh[10]. The MELD score was calculated according to the following formula: MELD = (0.957 × Log [creatinine in mg/dL] + 0.378 × Log [bilirubin in mg/dL] + 1.12 × Log International normalized ratio [INR] + 0.643)× 10.The maximal serum creatinine level contemplated within the MELD score equation is 2.0 mg/dL [11].

Statistics analysis:

Data were expressed as mean ± S.D. for a comparison of categorical variables, chi-square test, and T-test. Receiver operating characteristic (ROC) analysis was used to distinguish the threshold values. The area under the curve (AUC), sensitivity and specificity for cutoff points obtained were reported. A logistic regression model was used to calculate multivariate odds ratios (ORs), and their 95% confidence intervals (CIs) were used to identify factors associated with MHE. Kappa statistics were used to study the agreement between the NCT-A and DST.A two-sided P value less than 0.05 was purposeful statistically significant. The statistical analysis was done using SPSS version 10 software (SPSS, Chicago, IL).

RESULTS

Between December 2018 to December 2019,200 patients with clinically stable liver cirrhosis (age, 50.22±10.53 years; M: F ratio, 147:53), child-Pugh class A: 67, child –Pugh class B: 85, child –Pugh class C: 48 were included. Two hundred patients met the inclusion criteria and were included in the study. The causes of

cirrhosis were: Chronic Hepatitis B (n=116), Chronic Hepatitis C (n=21), Primary Biliary Cirrhosis (n=23), Alcoholic Cirrhosis (n=18), Autoimmune Hepatitis (n=11) and Cryptogenic Cirrhosis (n=11). The demographic and clinical features of the patients enrolled are shown in Table 1.

Parameters	Cirrhotic (mean ±S. D) n=200
Age (years)	50.22 ±10.53
Sex: M/F (%)	147 (73.5): 53 (25.5)
Education 1-6years/7-9years/10-12years/>12years, n(%)	76(38%)/ 37(18.5%)/32(16%)/ 55(27.5%)
AST (U/L)	77.21±110.86
ALT (U/L)	68.75±133.19
TBIL (µmol/L)	56.99±83.77
Creatinine (µmol/L)	64.06±30.77
NA^+ (µmol/L)	139.22±4.09
Ammonia (µmol/L)	39.31±30.94
PTA (%)	65.91±20.67
INR (sec.)	1.39±0.37
Child-Pugh class A: B: C (%)	67 (33.5):85 (42.5):48 (24)

Table 1: Demographic and clinical characteristics of the study population

Abbreviations: AST – Aspartate aminotransferase; ALT – Alanine aminotransferase; TIBL – Total Bilirubin; NA^+ - Sodium; PTA – Prothrombin Activity; INR – International Normalized Ratio.

Results of psychometric tests:

In total, 200 liver cirrhosis patients, 76 patients were primary school, 37 patients were secondary school, 32 patients were high school, and 55 patients were university students, of the 200 patients taking the NCT-A and DST .128 patients had abnormal psychometric tests and 72 patients had normal psychometric test results. 128 patients (64%) were diagnosed as MHE based on two or more abnormal (± 2SD control) psychometric tests (Tables 2 and 3). The age and education years of the 200 were range 50.22±10.53 (range 18-64), respectively, and 147 were men (73.5%) and 53 were female (26.5%).The distribution of subjects according to age was as follows: 18-34 years, 19(9.5%); 35-44 years, 35(17.5%): 45-54 years, 65(32.5%); and 55-64 years, 81 (40.5%) (Figure 3). The educational years according to age is presented in Figure 4.

The results of NCT-A and DST were 84.91± 34.06, 20.99 ±7.35, respectively. The results of the two tests were significantly correlated with age and education, and Pearson's Correlation Coefficients are shown in Table 4. There was a significant correlation with age and educational years between psychometric tests (p-value is <0.05).

Parameters	MHE (n=128)	Non-MHE (n=72)	P-value
NCT-A (sec.)	84.91 ± 34.06	43.63 ± 6.80	0.001
DST (score)	20.99 ±7.35	44.04 ± 9.28	0.009

Table 2: Psychometric tests in patients with MHE and Non-MHE

Abbreviations: NCT-A – Number Connection Test; DST – Digit Symbol Test.

Predictors associated with MHE:

Ammonia (49.02±33.41vs22.06±14.67; P= 0.001), Child-Pugh score (P= 0.001), MELD score (7.60±4.58vs6.10±3.77; P=0.040) and AST (85.24±121.55vs62.94±87.71; P=0.028) were significantly higher in patients with MHE as compared to patients without MHE (Table 3).

On Multivariate Analysis Venous Ammonia and Child-Pugh Score were significantly associated with MHE (Table 5). Receiver Operating Characteristic (ROC) analysis was done to identify cutoff for CTP, MELD Score, and Venous Ammonia (Table 6, Figure 5). 128 patients (64%) had CTP score >7.5, MELD score >5.31 and venous ammonia >26.50µmol.

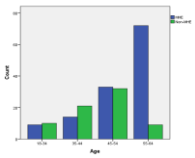

Figure 3: Allocation of the patients according to age

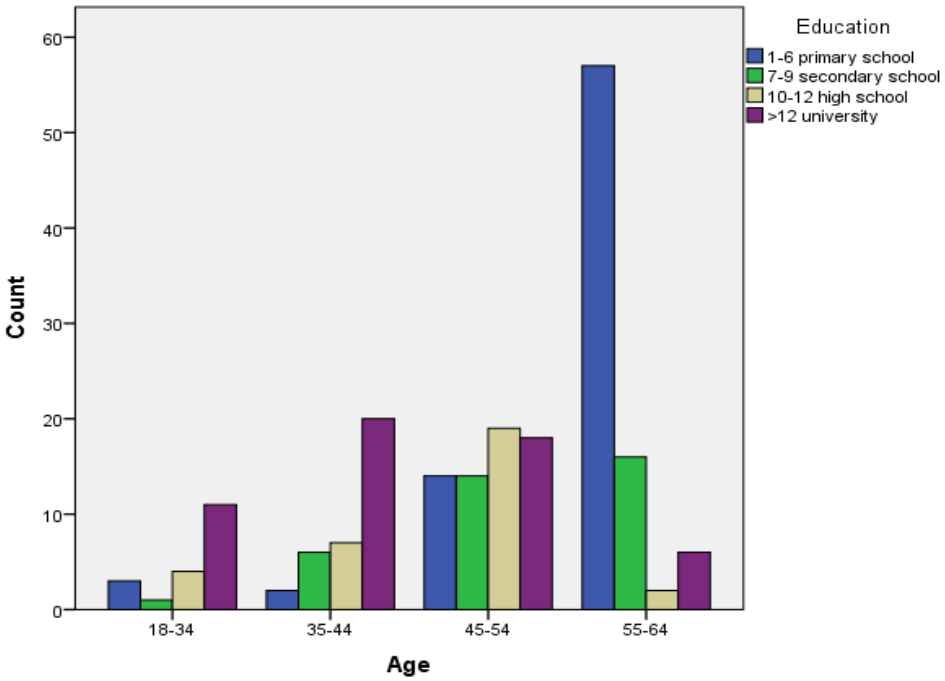

Figure 4: Comparison of education years between stable Cirrhotic patients of different age groups ($p<0.05$)

Parameters	MHE (n=128)	Non-MHE (n=72)	P-value
Sex: m/f (%)	90(70.31):38(29.69)	57(79.17):15(20.83)	0.173
AST (U/L)	85.24±121.55	62.94±87.71	0.028
ALT (U/L)	63.02±124.57	78.92±147.66	0.084
NA^+ (mmol/L)	139.24±4.09	139.18±4.12	0.976
Ammonia (µmol/L)	49.02±33.41	22.06±14.67	0.001
PTA (%)	63.74±20.65	69.76±20.27	0.985
MELD score	7.60±4.58	6.10±3.77	0.040
Child-Pugh Classification			0.004
Child-A	32	35	
Child-B	65	20	
Child-C	31	17	
Education years			0.001
1-6	74	2	
7-9	24	13	
10-12	18	14	

>12	12	43	
Age years			0.001
18-34	9	10	
35-44	14	21	
45-54	33	32	
55-64	72	9	

Table 3: Demographic and clinical characteristics of patients with MHE and Non-MHE

Abbreviations: AST – Aspartate aminotransferase; ALT – Alanine aminotransferase; NA^+ - Sodium; PTA – Prothrombin Activity; MELD – Model for End-Stage-Disease.

	NCT-A		DST	
	R	P -value	R	P -value
Age	0.418	0.001	-0.526	0.001
Education years	-0.592	0.001	0.715	0.001

Table 4: Correlation between psychometric tests and age and education

Abbreviations: NCT-A – Number Connection Test; DST – Digit Symbol Test.

Variable	OR	95%C.I. for EXP (B)		P -value
		Lower	Upper	
Ammonia	0.960	0.946	0.974	0.001
CTP score	0.849	0.739	0.976	0.021
MELD score	0.915	0.849	0.988	0.022

Table 5: Multivariate analysis of predictors of minimal hepatic encephalopathy

Abbreviations: CTP – Child-Turcottee-Pugh; MELD – Model for End-Stage-Disease.

Parameter	Cutoff	AUC (95%Cl)	Sensitivity %	Specificity%	P-value
Ammonia	26.5	0.772	76.6	41.7	0.001
CTP score	7.5	0.602	75.0	51.4	0.017
MELD score	5.31	0.615	60.9	50.0	0.007

Table 6: Receiver operating curve for venous ammonia, score, and Model for End-Stage Liver Disease for the diagnosis of MHE

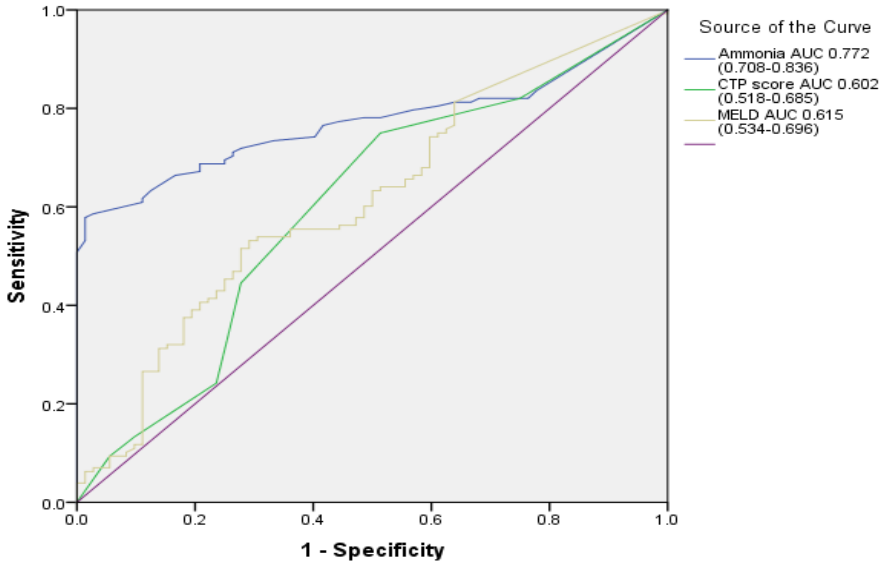

Figure 5: Receiver operating characteristic curve (ROC) of analyses of ammonia, CTP score, and MELD score. Receiver operating characteristics of ammonia, CTP score, MELD score, and AST as a predictor for mortality in cirrhotic patients.

Comparisons of psychometric tests including NCT-A and DST:

The international consensus recommends that at least two of the NCT-A, NCT-B, DST and Block-Design Tests (BDT) should be used for the diagnosis of MHE[8].Because we compared the psychometric test assessment by using the NCT-A and DST[12]. Utilization of NCT-A and DST enabled diagnosis of MHE with a sensitivity of (96.9, 23) and a specificity of (37.5, 69.4% (AUC =0.970, 0.001, 0.001) if at least one of the two tests was abnormal (Table 7).

Parameter	Sensitivity	Specificity	AUC	P- value
NCT-A	0.969	0.375	0.970	0.001
DST	0.023	0.694	0.020	0.001

Table 7: Comparisons between psychometric tests including NCT-A and DST

Abbreviations: NCT-A – Number Connection Test; DST – Digit Symbol Test; AUC – Area under the curve.

DISCUSSION

MHE is manifested by subtle cognitive and psychomotor deficiencies and the absence of significant clinical signs and symptoms of HE and is documented by neuropsychometric (NP) tests and neurophysiological tests. Minimal Hepatic Encephalopathy cases vary worldwide between 30 to 84% in cirrhotic patients. MHE is associated with impaired quality of life and driving ability and is a predictor of the development of overt hepatic encephalopathy (OHE). Complications of liver cirrhosis such as ascites, variceal

bleeding, infection and HE are predictors of an unfavorable prognosis in patients with cirrhosis [2, 4]. Validation of reference standard for neuropsychological tests may increase the detection of MHE. The PHES is a neuropsychological test that was specifically designed and recommended for the diagnosis of MHE[10, 15]. Weissenborn *et al*. assembled the first age calibrated normative data for the German population [12]. Recently, the PHES has also been generally endorsed in Spanish [13], Italian [14], Mexico [15], India [15] and Korean [16] populations. A PHES endorsement studies in Germany [12] and India [15] showed that the age of the patient influences PHES, and following validation studies in Spain, Italy, Mexico and Korea circulated that level of education also influences PHES [14,17,16].

In our study, we also detected that the results of psychometric tests including NCT-A and DST were affected by age and education years. We also found that age and education years were predictors of all two tests included in psychometric tests (NCT-A, DST). However, differences in age and education years were found between the MHE and Non-MHE groups (P=<0.05). The proportion of patients with MHE was associated with the intensity of liver dysfunction. Age and educational rank are generally recognized to have corresponded with the results of neuropsychological tests and accordingly age and education matched standard values of healthy controls are recommended [10]. In the study from Spain, the NCT-A and NCT-B results were greater in males than in females.

In our study, the two neuropsychological tests of the NCT-A and DST were impacted by age and education. Although, they did not vary between males and females in all age categories. As such, age and education, which influenced the results of the neuropsychological tests, were included in the multiple linear regression models and formulas used to establish the expected values. In this study, prescriptive data that was matched for age and education years were used, and differences were found between patients with and without MHE.

The international consensus recommends the use of the PHES for diagnosing MHE [10, 18]. The Vienna consensus recommends that at least two of four tests (NCT-A, NCT-B, DST, and BDT) should be used for the diagnosis of MHE [16]. In some studies, MHE was diagnosed when both of the two tests were abnormal [19]. In others, MHE was diagnosed when at least one of the two tests was abnormal [20].

The present study compared Psychometric tests with NCT-A and DST for the diagnosis of MHE. The diagnosis of MHE based on NCT-A and DST showed positive agreement with Psychometric tests. If at least one of the NCT-A and DST tests was abnormal, MHE could be diagnosed with a sensitivity of 96.9, 23% and a specificity of 37.5, 69.4% to PHES (AUC =0.970, 0.020; K =0.001, 0.001). Based on our study, we conclude that NCT-A and DST, which can be completed in minutes, are simple tools for screening MHE patients with liver cirrhosis.

Ammonia is a significant contributor to the pathogenesis of MHE in various studies. Ammonia and other neurotoxins act synergistically to induce low-grade cerebral edema as a result of swelling of astrocytes, which is mainly due to increased intracellular content of glutamine, secondary to ammonia metabolism [21]. In our study also, venous ammonia was significantly higher in MHE patients as compared to Non-MHE

patients (49.02±33.415*vs*22.06±14.670.; *P* = 0.001), which correlates well with findings from other studies [21]. Venous ammonia was found to be correlated with MHE (r=-0.041; *P*= 0.001), and its sensitivity and specificity were 76.6% and 41.7%, respectively, with AUC of 0.772 (95% CI, 0.946-0.974; *P* = 0.001). It was found to be associated with MHE on multivariate analysis also.

When contrasted with patients in CTP class A, those in classes B and C were at a higher risk of suffering from MHE with an odds ratio of 3.72 and 15.072 (p = < 0.001 for both) respectively. Disagreement persists in the literature about the ability of the CTP score to predict MHE. While many studies have shown that cirrhotic patients with CTP classes B and C have a higher prevalence of MHE compared to CTP class A [22],only a few do not [23]. Das et al. reported that though the prevalence of MHE was similar across all CTP classes, the severity of MHE as determined by the number of abnormal psychometric tests was greater in patients with more severe liver disease [24]. While all patients with cirrhosis need to be screened for MHE, it is clear from our results that the highest benefit of screening will accrue in those with CTP classes of B and C.

In our study, the proportion of patients with MHE increased with the increase in the Child-Pugh grade as follows: 128 patients had MHE was present in CTP class A(32,25%),CTP class B (65,50.7%) and CTP class C (31,15.5%). The prevalence rate of MHE in CTP class B cirrhosis patients was significantly higher than CTP class A and CTP class C. so more patients with Child class B had MHE as compared to the number of patients with Child class A and CTP class C grade (*P* < 0.05). When we analyzed the CTP score association with MHE, a cutoff of 7.5 showed a sensitivity of 77.3% and a specificity of 44.4% with ROC of 0.602 (95% CI, 0.518-0.685; *P* = 0.017) and odds ratio of 0.961 (p=<0.001).

One of the major aspects of the MELD score which is calculated from three biochemical variables (serum bilirubin, prothrombin time and creatinine) is that it has continuous variables and accounts for the spectrum of disease severity. Although, using the most differentiate cutoff from the receiver operating characteristic curve may provide a model that might be a useful strategy in selecting candidates for any cirrhosis-related complication [25]. In a study by Praveen Sharma and others, MHE was significantly associated with the MELD score and was following the incidence of MHE. Similarly, Meyer and co-workers found that the higher MELD score the more trail-making test A and B impaired [18].

In our study, the MELD score of 5.31 or above was found to be associated with MHE with a sensitivity of 60.9% and a specificity of 50.0% with an ROC of 0.615 (95% CI, 0.534-0.696; *P* = 0.007). Although patients with higher MELD scores (>5.31) have a high prospect of having MHE.

CONCLUSION

Based on our study evaluation, the combination of NCT-A and DST has significant association in cirrhotic patients and can be used for the diagnosis of MHE**.**

The Psychometric tests including NCT-A and DST showed excellent correlation with age and education.

The prevalence of MHE in this study was 64%. Ammonia>26.5µmol/L, Child- Pugh score>7.5, and

MELD score>5.31 were predictive of MHE.

REFERENCES

1. Mullen KD and Prakash RK: New perspectives in hepatic encephalopathy. *Clin Liver Dis*. 2012, 16:1–5
2. Labenz C *et al.*: Epidemiology of hepatic encephalopathy in german hospitals - the EpHE study. *Z Gastroenterol*. 2017, 55: 741–747
3. Bajaj JS *et al.*: The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *Am. J. Gastroenterol.* 2011, 106:1646–1653
4. Mookerjee RP *et al.*: Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. *Hepatology*. 2007, 46: 831–840
5. Romero-Gómez M, Boza F, García-Valdecasas MS , García E, and Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. *Am. J. Gastroenterol.* 2001, 96: 2718–2723
6. Kamath PS, Kim WR, and Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). *Hepatology*. 2007, 45: 797–805
7. Jalan R, Shawcross D, and Davies N. The molecular pathogenesis of hepatic encephalopathy. *Int. J. Biochem. Cell Biol.* 2003, 35: 1175–1181
8. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, and Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology*. 2002, 35: 716–721
9. Dhiman RK, Saraswat VA, Verma M, and Naik SR. Figure connection test: a universal test for assessment of mental state. *J. Gastroenterol. Hepatol.*1995, 10: 14–23
10. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, and Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973, 60: 646–649
11. Freeman RB *et al.*: The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl.* 2002, 8: 851–858
12. Weissenborn K, Ennen JC, Schomerus H, Rückert N, and Hecker H. Neuropsychological characterization of hepatic encephalopathy. *J. Hepatol.* 2001, 34: 768–773
13. Romero Gómez M *et al.*: Normality tables in the Spanish population for psychometric tests used in the diagnosis of minimal hepatic encephalopathy. *Med Clin (Barc)*. 2006, 127: 246–249
14. Amodio P *et al.*: Detection of minimal hepatic encephalopathy: normalization and optimization of the Psychometric Hepatic Encephalopathy Score. A neuropsychological and quantified EEG study. *J. Hepatol.*2008, 49: 346–353
15. Dhiman RK *et al.*: Diagnosis and prognostic significance of minimal hepatic encephalopathy in patients with cirrhosis of liver. *Dig. Dis. Sci.* 2010, 55: 2381–23
16. Seo YS *et al.*: Psychometric Hepatic Encephalopathy Score for the detection of minimal hepatic

encephalopathy in Korean patients with liver cirrhosis: PHES in Korea. *Journal of Gastroenterology and Hepatology*. 2012, 27: 1695–1704

17. Li SW. Psychometric hepatic encephalopathy score for diagnosis of minimal hepatic encephalopathy in China. *World Journal of Gastroenterology*.2013, 19: 8745
18. Meyer T, Eshelman A, and Abouljoud M. Neuropsychological changes in a large sample of liver transplant candidates. *Transplant. Proc.* 2006, 38: 3559–3560
19. Romero-Gómez M. Critical flicker frequency: it is time to break down barriers surrounding minimal hepatic encephalopathy. *J. Hepatol.* 2007, 47:10–11 Jul. 2007, do
20. Tan HH, Lee GH, Thia KTJ, Ng HS, Chow WC, and Lui HF. Minimal hepatic encephalopathy runs a fluctuating course: results from a three-year prospective cohort follow-up study. *Singapore Med J*. 2009, 50: 255–260
21. Kircheis G, Wettstein M, Timmermann L, Schnitzler A, and Häussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. *Hepatology*. 2002, 35: 357–366
22. Groeneweg M, Moerland W, Quero JC, Hop WC, Krabbe PF, and Schalm SW. Screening of subclinical hepatic encephalopathy. *J. Hepatol.* 2000, 32: 748–753
23. Rikkers L, Jenko P, Rudman D, and Freides D. Subclinical hepatic encephalopathy: Detection, prevalence, and relationship to nitrogen metabolism. *Gastroenterology*. 1978, 75: 462–469
24. Das A, Dhiman RK, Saraswat VA, Verma M, and Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. *J. Gastroenterol. Hepatol 2001,*16: 531–535
25. Huo TI *et al.*: Evaluation of the increase in model for end-stage liver disease (DeltaMELD) score over time as a prognostic predictor in patients with advanced cirrhosis: risk factor analysis and comparison with initial MELD and Child-Turcotte-Pugh score. *J. Hepatol.* 2005, 42: 826–832