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A PROSPECTIVE STUDY TO ASSESS PREVALENCE OF MINIMAL HEPATIC ENCEPHALOPATHY IN CIRRHOTIC PATIENTS AND IMPACT OF PATIENT COUNSELLING IN IMPROVING BASELINE KNOWLEDGE OF CIRRHOTIC PATIENTS

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ABSTRACT
Aim: Psychometric hepatic encephalopathy score is considered as the simplest method for detection of MHE. This study aims to assess the prevalence of minimal hepatic encephalopathy in patients with liver cirrhosis, thus provide appropriate treatment and to prevent its progression to overt hepatic encephalopathy. **Materials and methods:** 52 patients with a mean age of 56.712±9.293years with liver cirrhosis who met up with the inclusion and exclusion criteria were included in the study. All subjects underwent psychometric tests which include number connection test A and B (NCT-A), figure connection test A (FCT-A) line tracing test (LTT), serial dotting test (SDT), and digital symbol test(DST) in the same day. **Result:** Prevalence of MHE was found to be 65.38% which was detected with a psychometric hepatic encephalopathy score ≤ - 5.Twelve patients with a mean age of 56.712±9.293 years completed all the five tests. 69.23% involved in the study were male respondents and 30.77% belongs to female population. The etiology for liver cirrhosis was found to be alcoholism (42.31%), hepatitis B (13.46%), hepatitis C (11.54%) and 32.69% due to primary sclerosing cholangitis, autoimmune hepatitis and steatohepatitis. Among subjects with MHE 50%belongs to CTP-A, 55.56% belongs to CTP-B and 93.75% belongs to CTP-C. The mean PHES was found to be -5.173±2.185points (median, -5; range, -2 to -10). **Conclusion:** MHE as undetectable mostly from any laboratory tests requires a validated diagnostic procedure but much more simple than critical flicker frequency in order to be performed in an outpatient setting. This defines the importance of PHES in MHE detection. More studies need to be conducted on this topic as PHES has prognostic significance on survival of liver cirrhotic patients.

INTRODUCTION
Cirrhosis, a final path way for wide variety of chronic liver disease is apathological entity that defined as diffuse hepatic fibrosis with the replacement of normal liver architecture by nodule. The principle complications of liver cirrhosis are:

☐ Hepatic encephalopathy
☐ Ascites
☐ Variceal bleeding
☐ Cholangio carcinoma
☐ Hepato pulmonary syndrome

Minimal hepatic encephalopathy (MHE) reflects the mildest form of spectrum of hepatic encephalopathy (HE). Patients with MHE do not manifest any recognizable clinical symptoms of HE like behavioral abnormalities, altered level of consciousness, neuromuscular dysfunction etc. But MHE patients have mild cognitive and psychomotor deficits, which may affect their reaction time, attention, coordination, vigilance, memory and fine motor abilities. MHE is

concerned with negative health related quality of life (HRQOL), driving impairments, which increases the risk of road/traffic accidents and also, it progresses to overt HE (OHE). Hence detection of MHE offers better treatment outcome in patients with liver cirrhosis.

MHE cannot be diagnosed with routine clinical and laboratory investigations. In 1998, the working party in World Congress of Gastroenterology recommended that psychometric hepatic encephalopathy score (PHES) can be considered as a gold standard diagnostic criteria for detecting MHE.[1] The PHES involves a set of five tests- number connection test A and B(NCT A/B), line tracing test(LTT), serial dotting test(SDT) and digital symbol test(DST). These are simple 'paper and pencil' tests used to assess the psychomotor speed and accuracy, visual perception, visuospatial orientation, concentration, attention and working memory.[2]

Different studies using PHES revealed that MHE is detected in 30-84% of patients with liver cirrhosis.[3,4]

Studies established the fact that dietary modification[5,6], branched chain amino acids[7,8], lactulose[9], lacitol[10] has an beneficiary effect in improvement of MHE. Early diagnosis of MHE helps in preventing progression to OHE and improves health-related quality of life in liver cirrhotic patients. The present pilot study aim to assess the prevalence of MHE in liver cirrhotic patients with aid of psychometric hepatic encephalopathy score

Diagnostic methods

Various tools have been evaluated for the diagnosis of MHE and include the neuropsychological tests, computerized tests, short neuropsychological and computerized test batteries and neurophysiological tests. Regional cerebral blood flow changes and magnetic resonance imaging and spectroscopy. Though useful for understanding pathogenic mechanisms, are currently not considered of di- agnostic value.[16]

There is no ideal test for the diagnosis of MHE. However, the Working Party recommends that the diagnosis of MHE requires a normal mental status examination and impairment in the performance of at least two of the following tests: number connection test-A (NCT-A), number connection test-B (NCT-B), block design test (BDT) and digit symbol test (DST). It also recommends the use of [PSE-Syndrome-Test or psychometric hepatic encephalopathy score (PHES)], a standardized test battery including (NCT-A) and B, the line-tracing test (LTT), the serial-dotting test (SDT), and DST. When possible, quantitative neurophysiologic tools (like EEG with mean dominant frequency, P300 auditory evoked potentials) should be used. There is no consensus regarding the frequency of testing, but experience has shown relative similarity in psychometric scores at this widely used for the assessment of cognitive function in clinical trials and the assessment of patient populations including those with hepatitis C.CDRS subtests reflect 5 cognitive domains, namely, power of attention, continuity of attention, quality of episodic memory, quality of working memory and speed of memory.

MATERIALS AND METHODS

A Prospective-observational study will be conducted in patients from department of Gastroenterology in Cosmopolitan Hospital who were diagnosed with Liver cirrhosis during the study period after obtaining permission for collection of data from Head of Gastroenterology Department. The Study will be conducted for a period of 6 months after obtaining clearance from the Institutional Ethics Committee. A written informed consent will be taken in prescribed format from patients with Cirrhosis satisfying the inclusion and exclusion criteria. All relevant demographic, laboratory and clinical parameters specified will be collected from case records and direct interview with patient with the help of physician. Data will be collected using a proforma. Psychometric hepatic encephalopathy scores (PHES) are used for diagnosis of Minimal hepatic encephalopathy in cirrhotic patients.

Five tests of PHES include Number connection test-A (NCT-A), Number connection test-B (NCT-B), Line tracing test, Digital symbol test (DST) and Serial dotting test. Relation of MHE with severity of liver injury can be assessed with the help of Child Pugh score. Patients were then assessed for their mental state using Mini Mental State Examination (MMSE) questionnaire. Those who scored greater than 25 points were considered to have normal mental status and were included in the study. Patients will be interviewed before and after counselling for their baseline knowledge on Cirrhosis within a 1-month period gap. Baseline knowledge is assessed using a questionnaire, which contain a total of 9 questions. Questionnaires were scored by allocating one point for a correct answer and no points for any other response, such as an incorrect answer, no answer or multiple options selected. Mean increase in knowledge after counselling is determined to assess the impact of patient counselling in improving the baseline knowledge of cirrhotic patients about their disease.

Inclusion criteria
1. Patients of both gender aged between 30 to 70 years diagnosed with liver cirrhosis
2. Patients who are willing to participate in the study with complete medical records.

Exclusion criteria
Presence of OHE, history of neurologic abnormalities like Alzheimer's disease, Parkinsonism, non hepatic metabolic encephalopathy, electrolyte disorders, history of taking lactulose or any antibiotics, gastrointestinal hemorrhage or spontaneous bacterial peritonitis during the past 30 days, hepatocellular carcinoma or other malignancy, psychoactive drug intake and visual impairment.

RESULT AND DISCUSSION
The proposed study entitled "A Prospective Study to assess the prevalence of Minimal Hepatic Encephalopathy in cirrhotic patients and impact of patient counseling in improving the baseline knowledge of cirrhotic patient" was a study carried out in a multispecialty tertiary care hospital. In this study we analyzed the data of 52 cirrhotic patients who visited department of Gastroenterology. This study has provided an overview of demographics and clinical characteristics of patients with liver cirrhosis, prevalence of MHE in in cirrhotic patients, relationship between MHE and CTP classification and the impact of patient counselling on improving the baseline knowledge of liver cirrhotic patients regarding their disease.
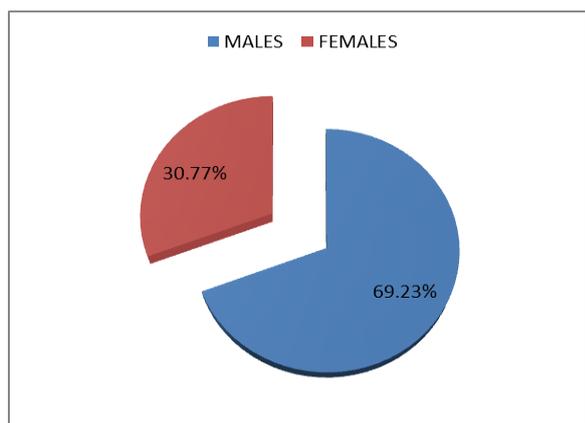
Fig.1: Gender distribution of cirrhotic patients.

The figure 1 represents the results on gender characterization among 52 cirrhosis patients and it reveals that out of 52 patients 36(69.23%) patients were males and 16(30.77%) were females. It suggests that majority of patients were males compared to females.
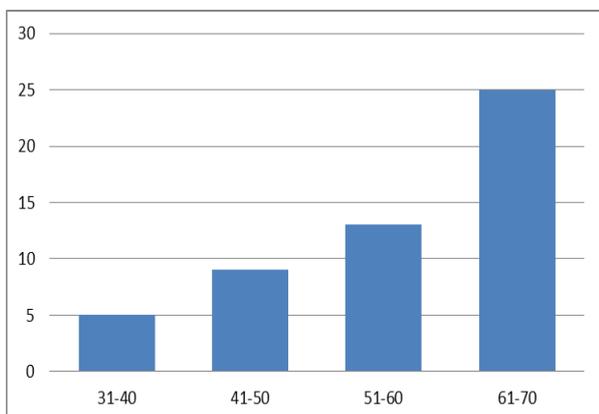

Fig 2: Age distribution of the subjects with liver cirrhosis.

Figure 2 represents the age group classification of cirrhosis patients included in the study. It suggests that majority of patients were in the age group between61-70 that is 25(48.08%) and the last were in the age group 31-40 that is 5 (9.62%) out of 52 patients. The patients in the age group of 41-50 years were 9(17.3%) and the patients in the age group of 51-60 years were 13(25%)
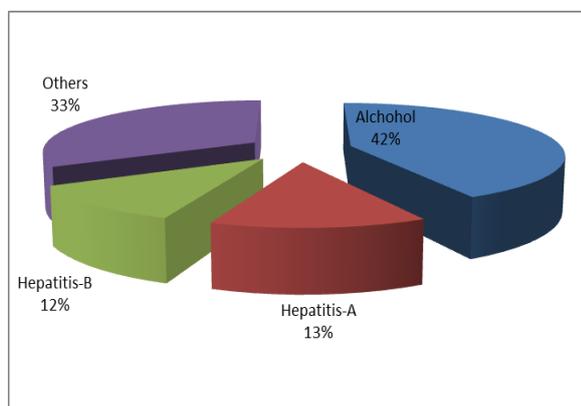

Fig 3: Etiology of liver cirrhosis.

The etiological factors that may be lead to liver cirrhosis are alcoholism, hepatitis A, hepatitis B and others (primary sclerosing cholangitis, autoimmune hepatitis and steatohepatitis) The study suggested that the main cause of cirrhosis is alcoholism and out of 52,22(43.31%) subjects were alcoholics, 7(13.46%) subjects were having Hepatitis A, 6(11.54%) subjects were having Hepatitis B and for 17(32.69%) subject cirrhosis occur due to other reasons
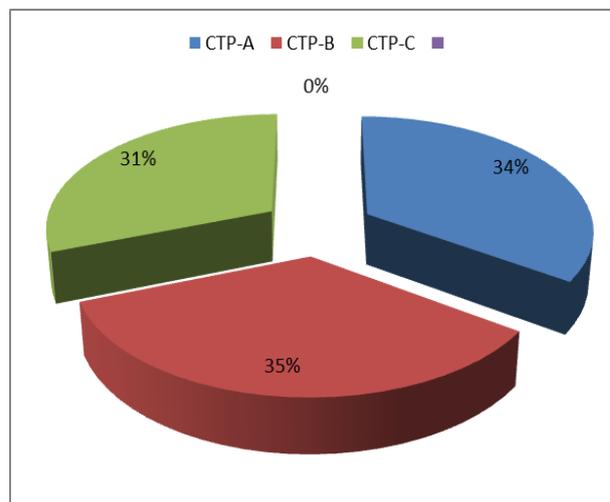

Fig 4: CTP classification of patients with liver cirrhosis.

Figure 4 shows that the classification of the 52 cirrhotic patient who participated in the study. The result shows that among 52 patients 18 (34.61%)were belongs to CTP-A,18(34.62%) belongs to CTP-B and 16(30.77%)belongs to CTP –C.
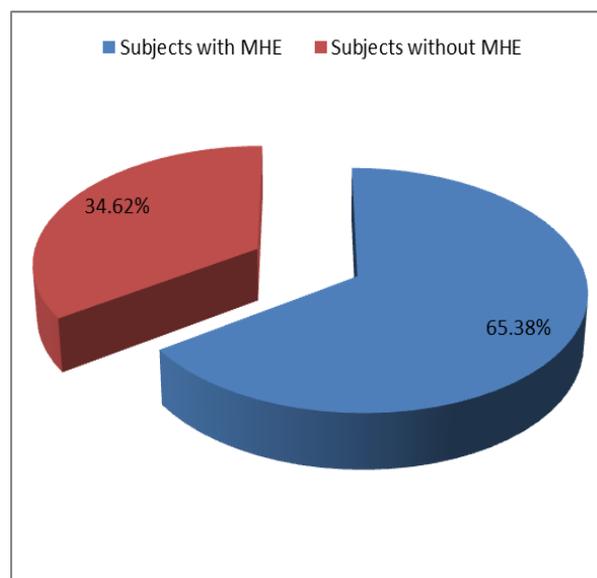

Fig 5: prevalence of MHE.

Figure 5 represent that the prevalence of MHE among patients with liver cirrhosis. It revels that among 52 patients 34 (65.38%)patients is having MHE. Remaining 18 subjects (34.62%) belongs to non MHE class.
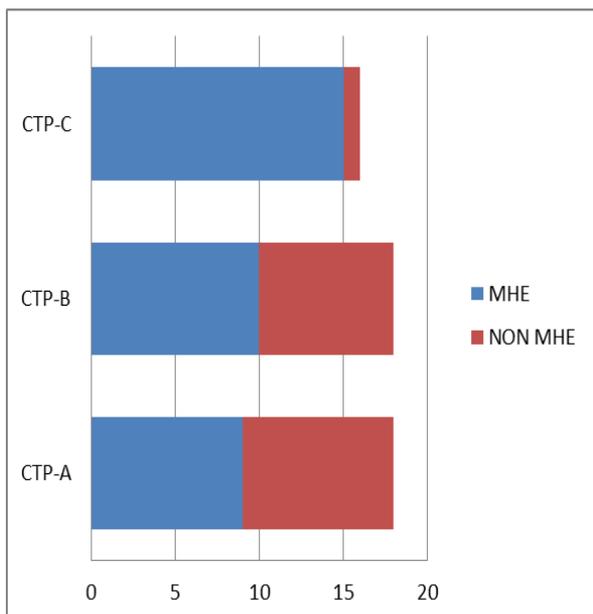
Fig 6: F Relation between MHE and CTP classification.

Fig 6 represents the relationship between severity of liver injury and prevalence of MHE. 19 subjects were involved in both CTP-A and CTP-B class and 16 of subjects belongs to CTP-C. Among 19 subjects of CTP-B 55.56% was positive for MHE. 15 of 16 subjects (93.75%) were detected with MHE. 50% of CTP-A and 55.56% of CTP-B were found to be positive for MHE
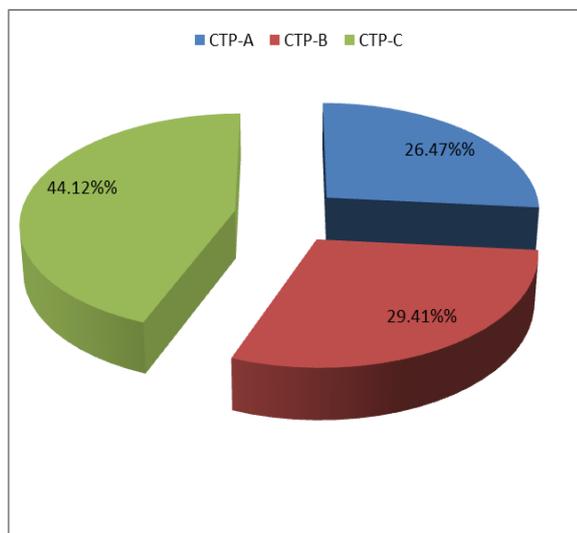

Fig 7: MHE Prevalence in each CTP Class.

34 subjects involved in the study were detected with MHE. Among these MHE positive subjects 44.12% belongs to CTP-C, 29.41% belongs to CTP-B and remaining 26.47% belongs to CTP-A classes respectively.
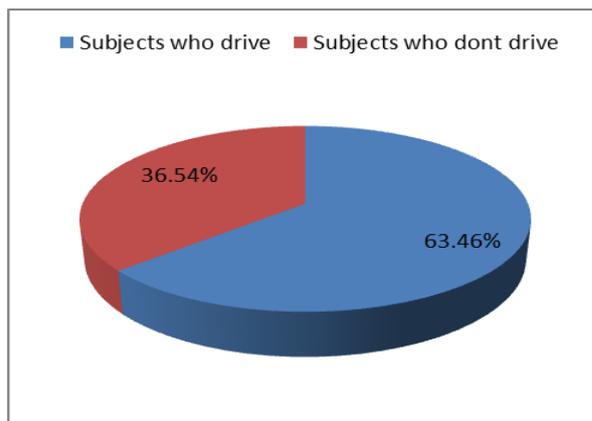
Fig 8: Subjects who drive and who don't drive.
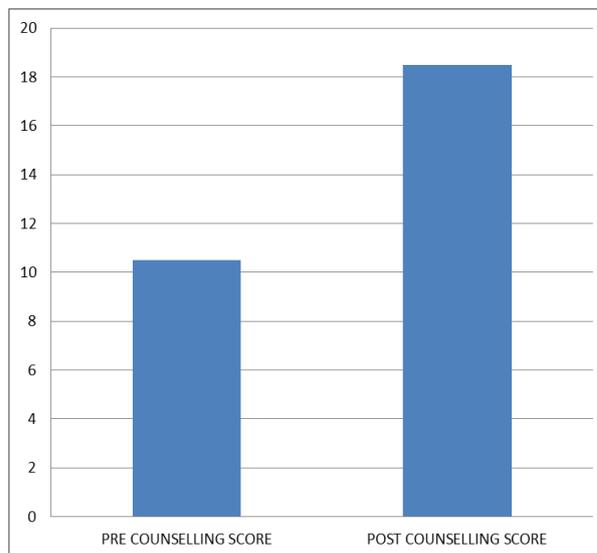
Among the subjects involved in the study, 33 subjects (63.46%) were involved in driving where as 36.54% don not drive.
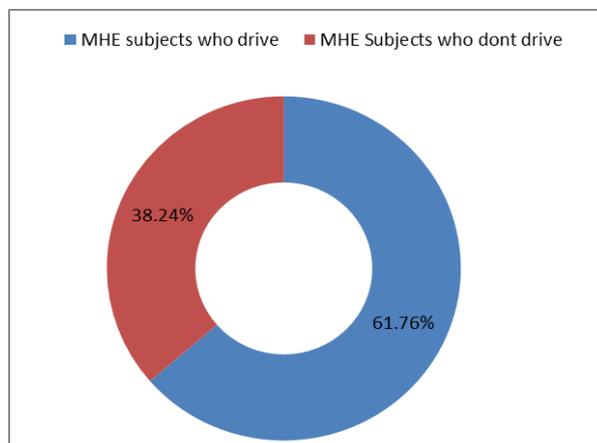
Fig 9: MHE- Driving relation.

Among 33 subjects who were performing driving, 61.76% (21) subjects were detected positive for MHE and are considered to be at high risk for road traffic accidents (RTA).

Fig 10: Impact of patient counselling.

Fig 12 represents impact of patient counseling in improving the baseline knowledge of cirrhotic patients. The maximum score of questionnaire was found out to be 20. Before counseling 52 subjects involved in the study achieved a mean score of 10.5 ± 3.05 and after counseling using leaflet the score was found to be 18.5 ± 1.45. Patient counseling was able to increase the baseline knowledge by an extent of 76.19%.

CONCLUSION

Detecting MHE in liver cirrhotic patients need to be considered with greater importance. Failure to detect MHE is considered as a medical error in most of the developed countries. Early detection of MHE helps in slowing down the progression of liver cirrhosis by modifying the treatment regimen with lactulose or rifixamin therapy.

This effectively prevents progression of MHE to OHE. Correlation between severity of liver injury and prevalence of MHE was found to be positive. MHE is found to be more prevalent in CTP-C, then CTP-B, and minimal in CTP-A class respectively. This implicates that more severe the liver injury, greater will be the prevalence of MHE. Since MHE impairs the mildest of neuro cognitive functions like attention, reaction time, vigilance etc. activities such as driving and handling complex machineries would be affected. The risk for RTA is greater in such individuals.

Patient counselling can effectively improve the baseline knowledge of liver cirrhotic patients. The impact of patient counselling to improve knowledge of cirrhotic patients regarding their disease is found to be positive. MHE subjects were also educated regarding the risk for RTA on driving and were informed not to drive.

CONFLICT OF INTEREST

There is no conflict of interest between the authors.

REFERENCE

1. Weissenborn K, Ennen JC, merus H, Neuropsychological characterization of hepatic encephalopathy Hepatol, 2001; 34: 768-63.
2. Cordoba J. New assessment of hepatic encephalopathy. J Hepatol, 2011; 54: 1030–1040.
3. Hartmann IJ, Groeneweg M, Quero JC, Beijeman SJ, de Man RA, Hop WC, etal. The prognostic significance of subclinical hepatic encephalopathy. Am J Gastroenterol, 2000; 95: 2029-34.
4. Poordad FF, Review article: The burden of hepatic encephalopathy. Aliment pharmacol Ther., 2007; 25: 13-19.
5. De Bruijn KM, Blendis LM, Zilm DH, Carlen PL, Anderson GH. Effect of dietry protein manipulations in subclinical portal-systemic encephalopathy. Gut, 1983; 24: 53-60.
6. Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy; detection prevalence and relationship to nitrogen metabolism. Gastroenterology, 1978; 75: 462-9.
7. Egberts EH, Schomerus H, Hamster W, Jurgens P. Branched chain aminoacids in the treatement of latent portosystemic encephalopathy. Gastroenterology, 1985; 88: 887-95
8. McClain CJ, Potter TJ, Kromhut JP, Zieve L. The effect of lactulose on psychometric performance tests in alcoholic cirrhosis without overt hepatic encephalopathy. J. Clin. Gastroenterol, 1984; 6: 325-9.
9. Salerno F, Moser P, Maggi A, Vitaliani G, Benetti G. Effects of long term administration of low dose lactitol in patients with cirrhosis but without overt encephalopathy. J. Hepatol, 1994; 21: 1092-6.
10. Groeneweg M, Moerland W, Quero JC, Hop WCJ, Krabbe P, Schalm SW. Screening of subclinical hepatic encephalopathy. *J Hepatol,* 2000; 32: 748–53.
11. Sharma P, Sharma BC, Tyagi P, Kumar M, Sarin SK. Neuropsychological impairment in severe acute viral hepatitis is due to minimal hepatic encephalopathy. *Liver Int,* 2008; 29: 260–4.
12. Butterworth RF. Pathophysiology of hepatic encephalopathy: a new look at ammonia Metabolism. Brain Disorders, 2002; 17: 221–7
13. Vaquero J, Chung C, Blei AT. Brain edema in acute liver failure. A window to the pathogenesis of hepatic encephalopathy. *Ann Hepatol,* 2003; 2: 12–22.
14. Dhiman RK, Kurmi R, Thumburu KK, Venkataramarao SH, Agarwal R, Duseja A, et al. Diagnosis and prognostic significance of minimal hepatic encephalopathy in patients with cirrhosis of liver. Dig Dis Sci., 2010; 55: 2381–2390.
15. Mullen KD. Review of the final report of the 1998 Working Party on definition nomenclature and diagnosis of hepatic en- cephalopathy. *Aliment Pharmacol Ther.,* 2007; 25(1): 11–6.
16. Ortiz M, Cordoba J, Doval E, Jacas C, Pujadas F, Esteban R, Guardia J. Development of a clinical hepatic encephalopathy staging scale. *Aliment Pharmacol Ther.,* 2007; 26: 859–67.
17. Gilberstedt SJ, Gilberstedt H, Zieve L, Buegel B, Collier RO, McClain CJ. Psychomotor performance defects incirrhotic patients without overt encephalopathy. Arch. Intern. Med., 1980; 140: 519-21.
18. Lockwood AH, Yap EW, Wong WH. Cerebral ammonia me- tabolism in patients with severe liver disease and minimal HE. *J Cereb Blood Flow Metab,* 1991; 11: 337–41
19. Fontana RJ, Bieliauskas LA, Lindsay KL, *et al.* Cognitive function does not worsenduring pegylated interferon and ribavirin retreatment of chronic hepatitis C.*Hepatology,* 2007; 45: 1154–63.
20. Sood GK, Sarin SK, Mahapatra J, Broor SL. Comparative efficacy of psychomotor tests in the detection of subclinical portal- systemic encephalopathy in non-alcoholic cirrhosis: search

for a rational approach. Am. J. Gastroenterol, 1989; 84: 156-9.

21. Romero Gómez M, Córdoba J, Jover R, del Olmo J, Fernández A, Flavia M, et al. Normality tables in the Spanish population for psychometric tests used in the diagnosis of minima hepatic encephalopathy. Med Clin (Barc), 2006; 127: 246-9.

22. Duarte-Rojo A, Estradas J, Hernández-Ramos R, Ponce-de-León S, Cordoba J, Torre A, Validation of the psychometric hepatic encephalopathy score (PHES) for identifying patients with minimal hepatic encephalopathy score. Dig Dis Sci., 2011; 56: 3014-23.

23. Li SW, Wang K, Yu YQ, Wang HB, Li YH, Xu JM, Psychometric hepatic encephalopathy score for diagnosis of minimal hepatic encephalopathy in China. World J Gastroenterol, 2013; 19: 8745-51.

24. Seo YS, Yim SY, Jung JY, Kim CH, Kim JD, Keum B, et al.Psychomotor hepatic encephalopathy for detection of minimal hepatic encephalopathy in Korean patients with liver cirrhosis Psychometric hepatic encephalopathy score for the detection of minimal hepatic encephalopathy in Korean patients with liver cirrhosis. J Gastroenterol Hepatol, 2012; 27: 1695-704.

25. Mina A, Moran S, Ortiz-Olvera N, Mera R, Urbine M.Prevalence of minimal hepatic encephalopathy and quality of life in patients with decompensated cirrhosis.Hepatol Res., Oct, 2014; 44(10): E92-9.

26. Maldonado-Garza HJ1, Vázquez-Elizondo G, Gaytán-Torres JO, Flores-Rendón AR, Cárdenas-Sandoval MG, Bosques-Padilla FJ. Prevalence of minimal hepatic encephalopathy in cirrhotic patients. Ann Hepatol, Jun, 2011; 10(2): S40-4.

27. Ji-Yao Wang, Ning-Ping Zhang, Bao-Rong Chi et al. Prevalence of minimal.