Prevalence of Minimal Hepatic Encephalopathy in Patients With Liver Cirrhosis: A Cross-Sectional, Clinicoepidemiological, Multicenter, Nationwide Study in India: The PREDICT Study

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Background: The study aimed at assessing the prevalence and clinical profile of minimal hepatic encephalopathy (MHE) in patients with cirrhosis using neuropsychological assessment and at understanding the management practices of MHE in the Indian clinical setting. **Methods:** This cross-sectional, clinicoepidemiological study conducted at 20 sites enrolled liver cirrhosis patients with Grade 0 hepatic encephalopathy according to West-Haven Criteria. Patients were subjected to mini-mental state examination and those with a score of ≥ 24 were assessed using psychometric hepatic encephalopathy score. Short Form-36 questionnaire was administered to assess the impact on health-related quality of life. **Results:** Of the 1260 enrolled patients, 1114 were included in the analysis. The mean age was 49.5 years and majority were males (901 [81%]). The prevalence of MHE was found to be 59.7% (665/1114) based on the psychometric hepatic encephalopathy score of ≤ -5 . Alcohol-related liver disease was the most common etiology (482 [43.27%]) followed by viral infection (239 [21.45%]). Past smokers as well as those currently smoking were more likely to have MHE than nonsmokers. A significant association was found between tobacco chewing, smoking, alcohol consumption, diabetes, and the presence of MHE. Multivariable analysis revealed smoking as the only parameter associated with MHE. A total of 300 (26.9%) patients were on prophylaxis with lactulose/lactitol or rifaximin. These patients were less likely to have MHE as compared to those not on prophylaxis (odds ratio, 0.67; 95% confidence interval, 0.50-0.88; $P = 0.005$). **Conclusion:** The disease burden of MHE is quite substantial in patients with cirrhosis with no apparent cognitive defect. Smoking, whether past or current, has significant association with the presence of MHE. Although MHE has been shown to adversely affect quality of life, prophylaxis for MHE is not routinely practiced in the Indian setting.

The study has been registered under clinical trials registry of India (CTRI/2014/01/004306). (J CLIN EXP HEPATOL 2019;9:476–483)

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Abbreviations: ALD: alcohol-related liver disease; CI: confidence interval; DST: Digit Symbol Test; FCT: figure connection test; HE: hepatic encephalopathy; HRQL: health-related quality of life; MCS: mental component summary; MELD: model for end-stage liver disease; MHE: minimal hepatic encephalopathy; MMSE: mini-mental state examination; NCT: number connection test; PCS: physical component summary; PHES: psychometric hepatic encephalopathy score; SF-36: Short Form-36

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Hepatic encephalopathy (HE) is a major complication in patients with acute or chronic liver disease caused by metabolic disturbances in the central nervous system.¹ Minimal hepatic encephalopathy (MHE) is the mildest form of HE that presents without any apparent clinical disturbance (normal mental and neurologic status on clinical examination) and requires specific psychometric tests for diagnosis. It is characterized by subtle motor and cognitive deficits with impairment of health-related quality of life (HRQL).²⁻⁴

Worldwide, the prevalence of MHE varies from 30% to 84% in cirrhotic patients.⁵ Studies from India report a prevalence of 53%-62%.^{6,7} Prevalence of MHE is influenced by history of overt HE, severity of liver disease, age, alcoholic etiology, and surgical portosystemic shunts.⁵ Furthermore, patients with MHE have a higher incidence of overt HE and mortality than those without MHE.⁸⁻¹⁰ Recognizing MHE at an early stage is important to initiate timely treatment to improve cognitive functions and HRQL and prevent progression to overt HE.

Diagnosis of MHE requires specialized neuropsychological and neurophysiological tests. As these are often impaired in patients with other causes of cognitive impairment, the mini-mental state examination (MMSE) is used for screening and excluding advanced cognitive impairment in high-quality studies before administering diagnostic tests for MHE.^{9,11,12} Various diagnostic tools such as standard neuropsychological tests, psychometric hepatic encephalopathy score (PHES), computerized test batteries, and neurophysiological tests have been evaluated for the diagnosis of MHE.¹³ Among these tests, PHES is the most extensively validated.¹⁴

Lactulose, rifaximin, and probiotics have all been shown to reverse MHE and improve quality of life in these patients.¹⁵⁻²¹ However, despite the high prevalence, impact on quality of life, and availability of effective treatment, MHE often goes undiagnosed and untreated. The aim of this study was to assess the prevalence and clinical profile of MHE in Indian patients with underlying cirrhosis by using a structured algorithm of West-Haven grading, followed by MMSE and PHES, and to understand the management practices of MHE patients in the Indian clinical setting.

METHODS

Study Population

This multicenter, cross-sectional, clinicoepidemiological study was conducted at 20 centers across India. Consecutive adult patients with an established diagnosis of liver cirrhosis with Grade 0 of West-Haven criteria, without any overt symptoms of HE at the time of screening, and who gave consent for the study were included. The diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonography or liver histologic data. Patients were

excluded if they had a history of recent alcohol intake (<12 weeks)/substance abuse or gastrointestinal bleeding (<4 weeks), serious infection, use of drugs affecting psychometric performances (<4 weeks), severe medical problems that could influence HRQL measurement, and inability to perform neuropsychometric tests or complete the Short Form-36 (SF-36) questionnaire.

The ethical committee of Postgraduate Institute of Medical Education and Research approved the study (Ethical clearance no. P-570). Local independent ethics committee of all centers also approved the study protocol. The study was conducted in accordance with the ethical principles having their origin in the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, all applicable government regulations, and institutional research policies and procedures. All patients provided written consent in the patient authorization form to participate in the study.

Laboratory testing and Medical History documentation

Demographic data such as age, sex, and education level were collected. Etiology for cirrhosis as labeled by a physician was recorded. Recent laboratory investigations such as hemogram, serum electrolyte levels, renal and liver function tests, and coagulation profile results were noted if available and were used for calculating model for end-stage liver disease (MELD) scores. Details of comorbid conditions and concomitant medications were also noted. All enrolled patients underwent screening of mental state by using a standard MMSE questionnaire. Only patients having an MMSE score of ≥ 24 were evaluated with the PHES questionnaire. The SF-36 questionnaire was completed by interviewing all patients for HRQL assessment (Figure 1) (Figure 2).

Psychometric testing

The PHES consists of 5 paper-pencil tests including the number connection test (NCT)-A, figure connection test (FCT), line-tracing test for time (t) and error (e), serial-dotting test, and digit symbol test.⁹ PHES has been extensively validated in Spanish, German, and Indian populations and can be performed in 15-20 min.²² In the Indian version, NCT-B has been replaced by FCT, as some patients may not be familiar with English numerals and therefore may find it difficult to complete the NCT.⁹

Assessment of HRQL

The HRQL was assessed using the SF-36 questionnaire, which is a quality of life scale to measure the health status or dysfunction caused by a disease. It measures the patients' perceived health status and is sensitive enough to detect changes or differences in their health status.

Figure 1 Study design. HRQL, health-related quality of life; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; MMSE, mini-mental state examination; PHES, psychometric hepatic encephalopathy score; SF-36, Short Form 36.

Training of Site Coordinators

As the questionnaires used in this study had exacting requirements in terms of explanation, the recording of time intervals, and interpretation, a special training workshop was conducted for all site coordinators and/or personnel administering the various questionnaires used in this study. Additionally, the site personnel had to complete administering a sample set of questionnaires, especially the PHES, to both normal individuals and cirrhotic patients (ratio of 1:3), and the same was reviewed and approved by the lead investigator. Once approved, the site personnel were considered ready to administer the questionnaire to the enrolled patients.

Outcome Measures

The primary outcome measure was to assess the prevalence of MHE among all cirrhotic patients who visited the healthcare setup without any evidence of clinically evident HE. The secondary outcome measures were demographic and clinical characteristics of the patients with cirrhosis, and the etiology and comorbid conditions associated with cirrhosis. The HRQL in MHE patients was assessed using the SF-36 questionnaire.

Statistical Analysis

The data were presented as the mean and 95% confidence intervals (CIs) for quantitative variables and as proportions

with 95% CI for qualitative variables. Chi-square test was used to assess the difference between categorical variables and the unpaired *t*-test to analyze the difference between continuous variables. A multivariable logistic regression analysis using the block method was performed on variables reaching a significance of $P \leq 0.10$ on univariate analysis to determine the influence on the presence of MHE. A *P* value of ≤ 0.05 was considered statistically significant. Statistical analysis was performed using SAS® software for Windows, version 9.2.

RESULTS

Of the 1260 cirrhotic patients who were enrolled, 1114 patients were considered evaluable for primary and secondary outcome measures. Excluded patients ($n = 146$ [12.4%]) included 107 patients with errors in PHES administration, 34 patients for whom erroneous PHES scores were recorded in 2 of the modules (NCT and FCT), and 5 patients with MMSE score < 24 .

Prevalence and Characteristics of MHE

Of the 1114 evaluable patients, 665 had a PHES score ≤ -5 , indicating MHE, with a prevalence rate of 59.7%.

Demographic and Clinical Characteristics

The mean age was 49.5 years (range, 18-65 years) and most patients were males (81%). The most common underlying

Figure 2 Prevalence of MHE in major cities in India. MHE, minimal hepatic encephalopathy.

etiology of cirrhosis was alcohol-related liver disease (ALD) (43.3%) followed by viral infection (21.5%). ALD was more common among patients with MHE (47.7%) than among those patients without MHE (36.8%; $P = 0.003$). Most of the patients (77.7%) were nonsmokers. Smokers, whether past or current, were more likely to have MHE than nonsmokers (Table 1). The average MELD score was comparable between the MHE and non-MHE groups. A significant association was found between variables like tobacco use, alcohol consumption, smoking, diabetes, and the presence of MHE (Table 2). Multivariable analysis also revealed that smokers were 1.8 times more likely to have MHE than non-

smokers. However, none of the other parameters retained significance with MHE after the multivariable analysis (Table 2).

HRQL Using SF-36 Questionnaire

MHE patients had significantly lower scores compared with non-MHE patients in the overall physical component summary (PCS; 46.0 ± 6.61 vs. 47.5 ± 6.5 ; $P < 0.001$) and mental component summary (MCS; 46.0 ± 8.9 vs. 48.7 ± 8.8 ; $P < 0.001$). PHES was found to be significantly but weakly correlated with PCS ($r = 0.1$; $P = 0.0014$) and MCS ($r = 0.1$; $P < 0.0001$).

Table 1 Demographic and Clinical Characteristics of the Study Population.

Parameter	Overall (N = 1114)	MHE (N = 665)	Non-MHE (N = 449)	P value
Age in years, mean (95% CI)	49.52 (48.9-50.1)	50.48 (49.7-51.2)	48.1 (47.1-49.1)	<0.001 ^a
Male, n (%)	901 (80.9)	553	348	0.02 ^b
Female, n (%)	213 (19.1)	112	101	
Education level (years of education)	12.4	12.4	12.5	0.61 ^a
Mean (95% CI)	(12.2–12.6)	(12.1–12.6)	(12.2–12.78)	
Etiology				0.003 ^b
Alcoholic liver disease, n (%)	482 (43.3)	317 (47.7)	165 (36.8)	<0.001 ^b
Viral hepatitis, n (%)	239 (21.5)	136 (20.5)	103 (22.9)	0.32 ^b
NASH/NAFLD, n (%)	125 (11.2)	70 (10.5)	55 (12.3)	0.37 ^b
Other, n (%)	268 (24.1)	142 (21.4)	126 (28.1)	0.01 ^b
Smoking status				
Past/current smoker	249	181 (72.7%)	68 (27.3%)	<0.001 ^b
Nonsmoker	865	484 (56.0%)	381 (44.1%)	
Diabetes mellitus	197	105 (53.3%)	92 (46.7%)	0.04 ^b
Tobacco chewing status	130	90 (69.2%)	40 (30.7%)	0.012 ^b
MELD score	15.12	15.26	14.97	0.85 ^a
Mean (95% CI)	(14.5–15.8)	(14.31–16.2)	(14.05–15.9)	

CI, confidence interval; MHE, minimal hepatic encephalopathy; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; MELD, model for end-stage liver disease.

^aAnalyzed using Wilcoxon sum test.

^bAnalyzed using chi-square test.

Management

Of the 1114 enrolled patients with cirrhosis, who did not have any overt evidence of encephalopathy or cognitive

dysfunction, 300 (26.9%) patients were already on secondary HE prophylaxis: 274 (24.6%) on lactulose/lactitol, 68 (6.1%) on rifaximin, with 42 (3.8%) on both drugs.

Table 2 Univariate and Multivariate Analyses.

Variable (univariate)	Odds ratio	95% Wald confidence limits	P value ^a
Age (years)	1.023	1.011–1.035	<0.001
Etiology (alcohol vs. nonalcohol)	1.568	1.227–2.003	<0.001
Education level	0.986	0.947–1.026	0.48
Tobacco chewing	1.600	1.080–2.372	0.02
Smoking (past/current)	2.095	1.538–2.855	<0.001
Diabetes mellitus	0.728	0.534–0.992	0.04
Sodium (mmol/L)	0.949	0.892–1.010	0.10
MELD score	1.040	0.989–1.095	0.13
Variable (multivariate)	Odds ratio	95% Wald confidence limits	P value ^a
Age	1.02	0.99–1.05	0.07
Diabetes mellitus	0.84	0.604–1.163	0.29
Tobacco chewing	1.37	0.912–2.068	0.13
Smoking status (past/current)	1.84	1.326–2.556	<0.01
Etiology (alcohol vs. nonalcohol)	1.20	0.780–1.854	0.40

MELD, model for end-stage liver disease.

^aAnalyzed using logistic regression.

Table 3 Encephalopathy Prophylaxis Prescription Patterns at Initial Evaluation.

Medication	Overall (N = 1114)	%	MHE (N = 665)	%	Non-MHE (N = 449)	%
Lactulose	205	18.40	132	19.85	73	16.26
Lactitol	69	6.19	51	7.67	18	4.01
Rifaximin	68	6.10	48	7.21	20	4.45
Lactulose/lactitol only	232	20.83	152	22.86	80	17.82
Rifaximin only	26	2.33	17	2.56	9	2.00
Rifaximin + lactulose/lactitol	42	3.77	31	4.66	11	2.45
Total on HE prophylaxis	300	26.93	200	30.08	100	22.27
No prophylaxis	814	73.07	465	69.92	349	77.73

MHE, minimal hepatic encephalopathy; HE, hepatic encephalopathy.

Rifaximin was used as monotherapy in 26 patients. Patients who were on prophylaxis were significantly less likely to have MHE at presentation (odds ratio, 0.67; 95% CI, 0.50-0.88; $P = 0.005$). Among these patients, the prevalence of MHE was similar in patients who were on lactulose/lactitol rifaximin, or a combination of both ($P = 0.63$). After diagnosis of MHE, an additional 83 patients were administered lactulose (Table 3).

DISCUSSION

This study highlights the high prevalence rates of cognitive dysfunction in the form of MHE in the cirrhotic population without any clinically overt manifestation of HE. As MHE is difficult to diagnose and requires special psychometric tests for detection, it is seldom, if ever, screened for in-routine clinical practice. However, in this multicenter, cross-sectional study performed at 20 centers across the country, we found that a majority (59.7%) of cirrhotic patients visiting healthcare setups without any apparent cognitive dysfunction showed evidence of MHE. The reported prevalence rate in our study is in line with the reported prevalence rates of 30%-84% in other studies involving patients with liver cirrhosis.^{10,23}

In this study, cirrhotic patients had a mean age of 49.5 years, with males being predominant (81%). The patients with MHE were slightly older than those without MHE (50.5 vs. 48.1 years, $P < 0.001$). ALD was the most common etiology of cirrhosis overall (43.3%). ALD as the etiology of cirrhosis was more common in the MHE group compared to those without MHE. Patients with ALD were 1.6 times more likely to have MHE. No such preponderance was seen in cirrhosis with other etiologies.

Univariate analysis revealed that age, tobacco chewing, alcohol consumption, and diabetes mellitus also had a significant association with MHE. Smoking, whether past or current, predicted increased likelihood of having MHE. In the multivariable analysis, only smoking retained its significant association with MHE. Thus, smoking seems to be

the single most important factor that predicts the development of MHE in patients with cirrhosis. In the past, only one small, single-center study has studied the association of smoking with MHE, where they found smoking to be a significant risk factor for MHE.²⁴

Smoking has been shown to increase the risk of cognitive decline and dementia.²⁵ It leads to faulty processing of amyloid precursor protein, reduces A β microglia clearance, and potentiates microglial inflammation.²⁶ Smoking has been implicated as a risk factor leading to reduction in cerebral perfusion, and for development of leukoaraiotic changes and cerebral atrophy.²⁷ This might be a direct consequence of the oxidative damage caused by smoking on the central nervous system, or secondary to microvascular changes.²⁸ This cognitive decline might have contributed to the lower PHES scores. It is possible that smoking may worsen the cognitive dysfunction, leading to the development of MHE.

Cognitive impairment in MHE patients contributed to impaired quality of life.²⁹ The overall PCS and MCS scores in SF-36 in our study population were significantly lower in MHE patients compared with non-MHE patients. However, there was only a weak correlation of PHES with both PCS and MCS. Studies have shown that MHE is the leading cause of cognitive dysfunction in cirrhotic patients, with marked impairment in both HRQL and job performance.³⁰ Increased blood ammonia level is present in about 90% of the MHE patients and is considered to play a major role in the development of MHE.³¹

Accurate and early diagnosis, and timely initiation of treatment are key to the management algorithm of MHE. Pharmacotherapy of MHE is largely directed at reduction of gut-derived ammonia. Lactulose has been shown to be beneficial for patients with MHE. Various studies have reported marked improvement in MHE and HRQL in patients with chronic liver disease after treatment with lactulose.^{24,32} Lactulose has also been shown to improve psychometric performance in patients with MHE. However, almost a third of the patients may be unable to tolerate lactulose due to bloating, diarrhea, or sweet taste. Thus, prescribing

lactulose for these patients is still a matter of individual patient and physician preference.

Our study illustrates that a majority of the patients were not receiving any prophylactic treatment for MHE. Only about one-fourth (26.9%) of the patients were on prophylaxis with lactulose/lactitol or rifaximin. These patients were two-thirds as likely to have MHE as compared to those not on prophylaxis (odds ratio, 0.67). After diagnosis of MHE, an additional 83 patients were administered lactulose. Overall, there was a wide treatment gap identified, as a majority of the studied patients were not prescribed any pharmacological treatment for MHE after diagnosis.

Years of education, sodium levels, and MELD scores were not found to have a significant association with MHE. There are conflicting results in literature regarding the correlation between severity of liver disease and prevalence of MHE. Many studies have shown correlation between cognitive impairment determined by psychometric and neurophysiological tests and increasing severity of liver disease assessed by Child-Pugh classification, while others have found no such correlation.³³ In our study, there was no significant difference in the MELD scores between MHE and non-MHE groups.

Our study was performed in over 20 centers from various parts of the country, involving 1260 patients ranging from 18 to 65 years of age. Thus, we were able to study a diverse population of patients with cirrhosis. To the best of our knowledge, this is the largest sample size for the study of MHE. The diagnosis of MHE was made upon the basis of a full PHES battery, and a strict training protocol was followed for its administration. However, a complete assessment of the severity of liver disease was not available for all of our patients due to missing data. Also, although smoking was determined to be the single most important factor in association with MHE, a detailed smoking history in terms of duration was not available. Furthermore, the study excluded 146 (11.6%) patients, which was slightly higher than the presumed exclusion of <10%. This was mainly due to errors in PHES administration. As a complete, error-free PHES battery is a prerequisite for the correct classification of MHE, a slightly higher than expected exclusion rate seems justifiable.

In conclusion, a significant disease burden of MHE among Indian cirrhotic patients was observed, which may adversely affect the HRQL in these patients. Patients on prophylaxis with lactulose had lower prevalence of MHE, indicating a role of lactulose therapy in these patients. However, most of the patients in India are not being treated for the same. Smoking emerged as the single most important parameter that was significantly associated with MHE.

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CONFLICTS OF INTEREST

The authors have none to declare.

CRediT authorship contribution statement

Sahaj Rathi: Formal analysis. **Madhu Chopra:** Validation. **Gourdas Choudhuri:** Data curation, Writing - review & editing. **Praveen Sharma:** Data curation, Writing - review & editing. **Kaushal Madan:** Data curation, Writing - review & editing. **Mohinish Chhabra:** Data curation, Writing - review & editing. **Ramesh R. Rai:** Data curation, Writing - review & editing. **Anurag Govil:** Data curation, Writing - review & editing. **Asokananda Konar:** Data curation, Writing - review & editing. **Mahesh Goenka:** Data curation, Writing - review & editing. **Manoj Agarwal:** Data curation, Writing - review & editing. **Jayanta Mukherjee:** Data curation, Writing - review & editing. **Vinay Thorat:** Data curation, Writing - review & editing. **Sanjay Salunkhe:** Data curation, Writing - review & editing. **Philip Abraham:** Data curation, Writing - review & editing. **Aabha Nagral:** Data curation, Writing - review & editing. **Ajay Jhaveri:** Data curation, Writing - review & editing. **Naresh Bhat:** Data curation, Writing - review & editing. **Joy Varghese:** Data curation, Writing - review & editing. **Arun R.S.:** Data curation, Writing - review & editing. **Ravishankar:** Data curation, Writing - review & editing. **Deevaguntla C. Reddy:** Data curation, Writing - review & editing. **Radha K. Dhiman:** Investigation, Writing - original draft, Data curation.

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