International Journal of Advances in Medicine
Singh AK et al. Int J Adv Med. 2025 Mar;12(2):180-186
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20250370

Original Research Article

Assessing cognitive decline for effective screening: evaluating the efficacy of mini-mental status examination and Addenbrooke's cognitive examination in identifying minimal hepatic encephalopathy in patients with compensated liver cirrhosis

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Received: 23 November 2024
Accepted: 02 January 2025

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ABSTRACT

Background: Liver cirrhosis is a progressive disease marked by significant liver scarring and functional impairment. Minimal hepatic encephalopathy (MHE), a common complication, has a global prevalence of 30-84%, and in India, up to 59.7% among cirrhosis patients. Despite its prevalence, routine MHE screenings are infrequent, highlighting a significant gap in cirrhosis management. This study aims to evaluate the efficacy of the mini-mental status examination (MMSE) and the Addenbrooke's cognitive examination (ACE) in early detection of cognitive impairments in liver cirrhosis patients.
Methods: The study assessed cognitive function in 126 participants (63 males with compensated liver cirrhosis and 63 healthy male controls) using MMSE and ACE. Logistic regression analysis was employed to explore the relationship between cognitive impairment and MHE.
Results: MMSE scores were significantly lower in the cirrhosis group (M=23.73, SD=1.74) compared to controls (M=25.61, SD=1.07), indicating cognitive impairments, especially in orientation and language domains. ACE scores also showed a significant decline in the cirrhosis group (M=80.92, SD=2.66) compared to controls (M=84.98, SD=3.06), particularly in visuospatial abilities.
Conclusions: MHE significantly affects cognitive function in compensated liver cirrhosis patients. Both MMSE and ACE are effective in detecting cognitive impairments, with ACE showing greater sensitivity. Routine cognitive screening using ACE could improve early detection and intervention, enhancing cognitive function and quality of life for cirrhosis patients.

Keywords: Minimal hepatic encephalopathy, Mini-mental status examination, Addenbrooke's cognitive examination

INTRODUCTION

Liver cirrhosis is a progressive and severe disease characterized by extensive liver tissue scarring and significant functional impairment. Its complex pathophysiology and severe complications in advanced stages are major medical concerns.[1] One insidious complication is MHE, which involves subtle cognitive impairments often undetected in routine examinations, leading to underdiagnosis. This issue adversely affects patients' quality of life, underscoring the need for more sensitive diagnostic tools for early detection and management.[2-4]

The liver, the body's largest internal organ, is vital for metabolic and cognitive health, performing essential functions such as metabolizing carbohydrates, proteins, and fats, detoxifying metabolites, synthesizing vital

proteins, and producing bile for fat digestion. Its metabolic role ensures glucose homeostasis through glycolysis, gluconeogenesis, and glycogenolysis.[5,6] In cognitive health, the liver regulates systemic inflammation and maintains metabolic balance, influencing brain function.[6,7] Hepatic encephalopathy, a neuropsychiatric syndrome occurs when the liver fails to filter blood toxins, leading to cognitive impairments.[1,7-10] The liver's detoxification process is essential for both physical and cognitive health, as toxic substance accumulation adversely impacts brain health.[5]

Cirrhosis, the final stage of chronic liver disease, involves significant fibrosis and regenerative nodule formation, causing gradual liver function decline. Causes include chronic alcohol abuse, viral hepatitis (B and C), and non-alcoholic fatty liver disease (NAFLD).[10] Cirrhosis progression is insidious, leading to liver insufficiency and portal hypertension, with severe complications like variceal bleeding, ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy.[11,12] Cognitive impairment in cirrhosis arises from hyperammonemia and systemic inflammation, with ammonia buildup affecting the central nervous system.[13-16] Systemic inflammation exacerbates neuropsychological effects, compromising physical health and significantly impairing quality of life, highlighting the need for early diagnosis and management.[2,17]

MHE a major complication in cirrhosis patients, manifests as cognitive impairments detectable through specialized neuropsychological tests but not standard clinical exams. MHE prevalence ranges from 30-84% globally, with particularly high rates in India (59.7%).[12] Factors like smoking and alcohol consumption are associated with MHE, emphasizing the need for targeted interventions.[18] Despite high prevalence and serious implications, routine screenings for MHE are rare, creating a gap in cirrhosis management.[12,14] Systematic screening and management can enhance the quality of life and functional independence of cirrhosis patients, justifying routine MHE assessment in standard care protocols.[19]

Existing diagnostic tools, like the psychometric hepatic encephalopathy score (PHES), are effective but not routinely used due to the need for specialized training and significant time commitment.[17] These tools often require patient cooperation and understanding, challenging in high-volume or resource-limited settings. Hence, there's a need for accessible and sensitive diagnostic tools that integrate into standard evaluations, facilitating early MHE detection and timely interventions, improving patient outcomes and quality of life while reducing cirrhosis's socioeconomic impact.[9,11]

This study addresses this gap by enhancing MHE recognition, improving cirrhosis management and prognosis. It evaluates the efficacy of the MMSE and ACE-III in detecting MHE in compensated liver cirrhosis patients.

METHODS

The study was designed as a cross-sectional analysis, conducted at the department of medicine at KPS institute of medicine and the department of gastroenterology, GSVSPGI, GSVM medical college, Kanpur from February 2023 to April 2024. The research focused on assessing cognitive function in subjects with compensated cirrhosis of the liver, using two primary cognitive assessment tools: the MMSE and ACE.

Study sample size

A pilot study was conducted on 5 patients with CLD and 5 normal subjects. In CLD patients MMSE score was 28.3+1.8. In normal subjects, mean MMSE score was 27.2+1.7.

Using the formula for comparing means, $n=\frac{2\,(Z_{\alpha/2}+Z_{\beta})^2\ \sigma^2}{\delta 2}$

where: n=Sample size required for each group. $Z_{\alpha/2}$ Z value corresponding to the desired significance level (α). For a two-tailed test with α=0.05, $Z_{\alpha/2}$=1.96. Z_{β}: Z value corresponding to the desired power (1-β). For 80% power, Z_{β}=0.84. σ: Pooled standard deviation of the two groups. δ: Minimum detectable difference between the two group means, the sample size was calculated to be 63 in each group, at power 80% and level of significance 5%.

Study methodology

The 126 male participants with age between 18 and 65 years which consisted of 63 cases of compensated liver cirrhosis and 63 normal healthy participants serving as controls were taken. Both groups shared similar demographic characteristics were screened based on history and clinical examination on 1st visit after which cognitive assessments were done on 2nd visit within 7 days using MMSE and ACE.

The study employed following cognitive assessment tools:

ACE assesses various cognitive domains including attention, memory, verbal fluency, language, and visuospatial abilities. The test typically takes around 20-30 minutes to administer and involves tasks such as recalling words, following instructions, drawing diagrams, and answering questions about everyday scenarios.

MMSE consists of a series of questions and tasks, such as recalling words, counting backwards, naming objects, and following verbal and written commands. It typically takes around 5-10 min to administer and is scored out of 30 points, with higher scores indicating better cognitive function.

Data were collected through clinical assessments, cognitive assessments (MMSE and ACE). Diagnostic tests such as ultrasonography, upper GI endoscopy, and fibro

scan were used. Laboratory investigations included complete blood count (CBC), liver function test (LFT), kidney function test (KFT), thyroid function tests, fasting blood sugar level, HbA1C, PT/INR, and tests for HBsAg/anti HCV and HIV I/II.

Statistical analysis

Data were analyzed using SPSS version 27 and MS excel. Descriptive statistics summarized the demographic and clinical characteristics of the study population. Inferential statistics, such as correlation and regression analysis, were used to examine the relationship between cognitive impairment and the severity of cirrhosis. Statistical significance was determined at a $p<0.05$.

RESULTS

Total 126 male participants were included in the study of which 63 were cases of compensated liver cirrhosis and 63 normal healthy controls. Boths groups had statistically insignificant age and sex differences. The average age of participants in the case group was 43.65 years (±11.16), while the control group averaged 44.19 years (±13.2). The difference was not statistically significant, indicating a comparable age distribution between the groups. Base line characteristics of both groups incorporated in our study had no significant statistical difference (Table 1).

Table 1: Descriptive statistics of clinical and biochemical parameters for case and control group.

Variables	Case (Mean±SD)	Control (Mean±SD)
Age (in years)	43.65±11.16	44.19±13.2
S. bilirubin (T)	3.49±3.7	3.26±3.65
S. bilirubin (D)	1.18±1.27	1.24±1.38
S. bilirubin (I) (mg/dl)	2.31±2.51	2.36±2.59
SGOT (IU/l)	76.29±48.75	72.24±47.84
SGPT (IU/l)	52.41±10.92	52.92±9.88
S. albumin	3.26±0.47	3.21±0.51
S. total protein	5.8±0.74	5.64±0.52
PT	21±7.12	21.69±7.06
INR	1.43±0.15	1.43±0.15
S. Na	137.85±5.77	137.95±4.72
S. K	3.04±0.32	3.08±0.35
S. Ca	4.02±0.48	4.06±0.46
S. urea	41.62±10.13	41.32±10.24
S. creatinine	1.4±0.56	1.57±0.69
Hb. (g/dl)	11.39±0.84	11.41±0.79
TLC	4856.83± 975.44	4810.46± 930.26
Platelet count (in lacs)	0.88±0.56	1.1±0.7
S. TSH	4.54±1.56	4.27±1.38
F. T3	2.62±0.79	2.68±0.78
F. T4	1.02±0.47	1.05±0.54
HBA1c	5.2±0.64	5.17±0.59

MMSE scores were calculated and compared between the case and control groups across five cognitive domains: orientation, registration, attention and calculation, recall, and language (Table 2).

Table 1: Scores of MMSE in various cognitive domains.

Cognitive domain	Cases (Mean±SD)	Controls (Mean±SD)
Orientation	8.44±0.50	8.54±0.50
Registration	3.00±0.00	3.00±0.00
Attention and calculation	3.57±0.50	3.51±0.50
Recall	2.00±0.00	2.00±0.00
Language	6.71±1.90	8.51±1.05

The cognitive performance assessment revealed several differences between the case and control groups. In the orientation domain, the case group scored slightly lower (8.44±0.50) than the control group (8.54±0.50). Both groups scored equally in the registration domain with a mean score of 3.00±0.00. The attention and calculation domain showed a marginally higher mean score for the cases (3.57±0.50) compared to the controls (3.51±0.50). Both groups also scored equally in the recall domain with a mean score of 2.00±0.00. However, in the language domain, the case group scored lower (6.71±1.90) compared to the control group (8.51±1.05). These findings highlight notable differences in cognitive performance, particularly in the orientation and language domains where the case group exhibited lower scores**.**

ACE scores were calculated across various cognitive domains for both the case and control groups (Table 3). The scores are represented as mean ± standard deviation (SD).

Table 2: ACE Scores in various cognitive domains.

Cognitive domain	Cases (Mean±SD)	Controls (Mean±SD)
Attention and orientation	16.05±0.77	15.98±0.85
Memory	22.84±1.82	22.56±1.74
Fluency	11.48±1.06	11.46±1.09
Language	23.32±1.04	23.42±1.19
Visuospatial	7.35±3.48	11.34±3.82

The ACE scores were assessed across five domains: attention and orientation, memory, fluency, language, and visuospatial abilities. The case group scored higher in attention and orientation (16.05±0.77) and Memory (22.84±1.82) compared to the control group (15.98±0.85 and 22.56±1.74, respectively). Fluency scores were nearly identical (11.48±1.06 vs. 11.46±1.09). Language scores were slightly lower for the case group (23.32±1.04 vs. 23.42±1.19), and visuospatial scores were significantly lower (7.35±3.48 vs. 11.34±3.82). The MMSE scores also declined significantly in the case group (M=23.73,

SD=1.74) compared to controls (M=25.61, SD=1.07, t=-6.935, df=124, p<0.001). These findings indicate notable cognitive impairment in individuals with compensated cirrhosis.

Comparison of means of MMSE and ACE between case and control groups

In this study, we compared the cognitive function of subjects with compensated cirrhosis of the liver to a control group using MMSE and ACE (Table 4). MMSE scores for the case group (M=23.73, SD=1.74) were significantly lower than those of control group (M=25.61, SD=1.07). This difference was statistically significant with a t=-6.935 (df=124, p<0.001) under the assumption of equal variances. The mean difference of -1.79 points (95% CI: -2.30 to -1.28) indicates a notable reduction in cognitive function among the subjects with cirrhosis. This result was consistent even when variances were not assumed to be equal (t=-6.935, df=102.838, p<0.001).

Table 3: Comparison of mean values of MMSE score and Addenbrooke's score between case and control groups.

Score	Group	N	Mean±SD	Mean difference	T value	P value	Effect size (Cohen's d)
MMSE score	Case	63	23.73±1.74	-1.79	-6.935	<0.001	-1.236
	Control	63	25.61±1.07				
Addenbrooke's score	Case	63	80.92±2.66	-4.06	-7.956	<0.001	-1.418
	Control	63	84.98±3.06				

The ACE scores significantly declined in the case group (M=80.92, SD=2.66) compared to the control group (M=84.98, SD=3.06), with a t-value of -7.956 (df=124, p<0.001) and a mean difference of -4.06 points (95% CI: -5.07 to -3.05). Consistent findings were noted without assuming equal variances (t=-7.956, df=121.664, p<0.001).

Effect sizes for MMSE and ACE scores were substantial, with Cohen's d values of -1.236 and -1.418, Hedges' g values of -1.228 and -1.409, and Glass's delta values of -1.672 and -1.328, respectively. These results indicate significant cognitive impairment in individuals with compensated cirrhosis.

Analysis to evaluate predictive power of MMSE and ACE scores in determining the presence of MHE

To examine the relationship between cognitive impairment and MHE, a logistic regression analysis was performed using MMSE and Addenbrooke's scores as predictor variables. The analysis included 126 cases, with no missing values, ensuring the robustness of the results (Table 5).

Table 4: Results of logistic regression analysis of MMSE and ACE as predictor of MHE.

Variables	B	SE	Wald	Df	P value	Odds ratio
MMSE score	-0.859	0.214	16.107	1	0.000	0.423
Addenbrooke's score	-0.476	0.105	20.735	1	0.000	0.621
Omnibus tests of model coefficients						
Test		Chi-square		Df		P value
Step 1		76.088		2		0.000
Model summary						
-2 Log likelihood			Cox and Snell R square			Nagelkerke R square
98.585[a]			0.453			0.604
Hosmer and Lemeshow test						
Chi-square				Df		P value
9.056				7		0.249
Classification table						
Observed		Predicted no MHE		Predicted MHE		Percent correct
No MHE		50		13		79.40%
MHE		10		53		84.10%
Overall percent						81.70%

The logistic regression model was statistically significant (p<0.001), as indicated by the Omnibus tests of model coefficients (Chi-square=76.088, df=2, p<0.001). This demonstrates that the combined MMSE and Addenbrooke's scores are effective in predicting the likelihood of MHE. The coefficients for both scores were significant (p<0.001), with MMSE showing a coefficient of -0.859 (Wald=16.107), suggesting a 57.7% reduction in

the odds of developing MHE (Odds ratio=0.423). Similarly, Addenbrooke's score had a coefficient of -0.476 (Wald=20.735), indicating a 37.9% reduction in MHE odds (Odds ratio=0.621).

The model summary revealed a-2 log likelihood value of 98.585, a Cox and Snell R square of 0.453, and a Nagelkerke R square of 0.604, indicating the model explains 60.4% of the variance in MHE. The Hosmer and Lemeshow test further validated the model's fit (Chi-square=9.056, df=7, p=0.249). The classification table confirmed that the model accurately predicted 79.40% of cases with no MHE and 84.10% of cases with MHE, resulting in an overall accuracy of 81.70%.

These findings underscore the critical role of cognitive assessments in patients with compensated cirrhosis, highlighting the importance of early detection and intervention to prevent severe hepatic encephalopathy. and improving patient outcomes. MMSE exhibited a stronger negative association with MHE (lower odds ratio), making it slightly more effective in predicting a reduction in the likelihood of MHE whereas ACE has a higher Wald statistic, indicating it might be a more robust predictor in the context of logistic regression model used in the study.

DISCUSSION

Our study demonstrates significant cognitive impairments in patients with compensated cirrhosis of the liver, particularly in the domains of attention, memory, and psychomotor speed. The MMSE and ACE scores were substantially lower in the case group compared to the control group (Table 2-4), indicating the presence of MHE. In addition to this, our study demonstrates that ACE is more effective than MMSE (Table 4) in identifying cognitive impairments across multiple domains, making it a better tool for MHE detection.[20] These finding suggest that MMSE often fails to detect the early stages of MHE due to its broad scope and lack of specificity.[21]

Our findings are consistent with previous research that has highlighted the prevalence and impact of cognitive impairments in patients with liver cirrhosis. For instance, studies have shown that MHE is common in cirrhotic patients and significantly affects their quality of life and functional status.[22] Similar to our study, these studies found that conventional cognitive assessments, like the MMSE, often fail to detect the subtle impairments associated with MHE, while more comprehensive tools like the ACE and advanced neurophysiological assessments provide better diagnostic accuracy.[23] The MMSE has been widely used for the assessment of cognitive impairment. However, its utility in detecting MHE is limited. Studies have shown that MMSE lacks sensitivity in distinguishing MHE from other forms of cognitive dysfunction, with a sensitivity of 63% and specificity of 52% for diagnosing overt HE.[21] An MMSE score below the 26 has been suggested as a threshold for the identifying patients at the risk of hepatic encephalopathy, but it is not sufficient as a standalone diagnostic tool.[17]

In contrast, the ACE offers a more comprehensive assessment across multiple cognitive domains, including attention, memory, verbal fluency, language, and visuospatial abilities. ACE has demonstrated higher sensitivity and specificity compared to MMSE, making it more effective for diagnosing MHE.[24] However, it is more time-consuming and requires more detailed administration and interpretation.

This study emphasizes on early detection and management of MHE can mitigate these impacts, improving overall quality of life and reducing the socioeconomic burden associated with advanced hepatic encephalopathy.[25] Treatments such as lactulose and rifaximin have been shown to improve cognitive function and quality of life in patients with MHE.[26,27]

Limitations

Several limitations must be acknowledged:

Sample size: The study's sample size may limit the generalizability of the findings. Larger studies are needed to validate these results.

Study population consisted of exclusively males may limit the generalizability of the findings.

Cross-sectional design: The cross-sectional nature of the study prevents the assessment of causality. Longitudinal studies are required to establish causal relationships between liver function and cognitive impairment.

Diagnostic tools: While ACE proved effective in this study, the availability of comprehensive cognitive assessment tools may be limited in some clinical settings. For instance, psychometric tests, although standardized, may still be influenced by the patient's education level, cultural background, and motivation during testing.

Additionally, the study design did not control for all potential confounding factors such as concurrent medications, co-morbid conditions, and lifestyle factors like alcohol consumption and smoking, which are known to affect cognitive function.

CONCLUSION

The findings of this study provide strong evidence that cognitive impairments are prevalent in patients with compensated cirrhosis of the liver. The significant differences in MMSE and ACE scores between case and control groups highlight the necessity for regular cognitive assessments in these patients.

The ACE's superior sensitivity and specificity in detecting MHE suggest its incorporation into routine clinical

practice for early diagnosis and management. Early detection of MHE enables timely interventions, which can improve patient outcomes and quality of life.

ACKNOWLEDGEMENTS

Author would like to thank to multidisciplinary research unit, G. S. V. M. medical college, Kanpur and K. P. S. institute of medicine, G. S. V. M. medical college, Kanpur, for providing a conducive academic environment. Also, to Dr. Anup Kumar, and Mr. Akash pal, department of biostatistics, S. G. P. G. I., Lucknow.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Singh AK, Agarwal S, Kumar V, Giri R, Shrivastava S. Assessing cognitive decline for effective screening: evaluating the efficacy of mini-mental status examination and Addenbrooke's cognitive examination in identifying minimal hepatic encephalopathy in patients with compensated liver cirrhosis. Int J Adv Med 2025;12:180-6.