

Prevalence and risk factors of subclinical hepatic encephalopathy in patients with cirrhosis

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Abstract

Background Subclinical hepatic encephalopathy (SHE) is considered an early stage of clinical encephalopathy and has been associated with shortened lifespan and increased healthcare-associated burden. We aimed to assess the prevalence of SHE in patients with cirrhosis and to elucidate the potential factors related to its occurrence.

Methods Thirty consecutive patients with cirrhosis were evaluated between March and July 2017. The exclusion criteria included overt hepatic encephalopathy, recent gastrointestinal hemorrhage, neurological disease, and the use of lactulose or non-absorbable antibiotics. After exclusion, 23 patients were included in this study. Twenty healthy age- and sex-matched controls were also included. SHE was assessed using the number connection test (NCT) and the inhibitory control test (ICT).

Results The NCT completion time was significantly longer in cirrhotic patients than in controls (77 ± 45 vs. 27 ± 6 sec, $P<0.001$), with 78.3% of cirrhotic patients showing abnormal results. ICT correct target recognition was also significantly lower in cirrhotic patients ($18.5\pm 21.8\%$ vs. $56.2\pm 15.8\%$, $P<0.001$), with 60.9% showing abnormal results. By combining NCT and ICT, 39.1% of patients with cirrhosis were diagnosed with SHE. No significant associations were detected between the Child-Turcotte-Pugh class or baseline parameters and the presence of SHE. At the 3-month follow up, the SHE diagnosis remained consistent, with 66.7% of those diagnosed at baseline still exhibiting SHE.

Conclusions SHE is prevalent in patients with cirrhosis and significantly affects cognitive and psychomotor abilities. Although the study sample was small, these findings highlight the necessity of regular psychometric testing in cirrhotic patients to identify and manage SHE.

Keywords Subclinical hepatic encephalopathy, cirrhosis, prevalence, risk factors

Ann Gastroenterol 2026; 39 (2): 1-6

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Conflict of Interest: None

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Received 28 December 2024; accepted 27 November 2025; published online 12 February 2026

DOI: <https://doi.org/10.20524/aog.2026.1045>

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Introduction

Hepatic encephalopathy (HE) is a major complication of cirrhosis and is associated with greater hospitalization, healthcare costs, and mortality [1]. It refers to a wide range of neuropsychiatric abnormalities caused by advanced hepatic impairment, and/or dysfunction of normal hepatic circulation or portal vein hypertension [2,3]. HE is broadly classified as overt, presenting with neurological and neuropsychiatric abnormalities detected by inpatient examinations and tests, and minimal or subclinical HE (SHE), presenting with abnormalities detected only by psychometric tests [4]. Overt HE occurs in approximately 30-40% of patients with cirrhosis during their disease [2]. However, SHE is estimated to occur in more than 60% of patients with cirrhosis, with a prevalence

ranging between 20% and 80%, depending on the population studied and the diagnostic tool used [5,6]. SHE patients do not have clinical or laboratory abnormalities compatible with HE patients, and are spatiotemporally oriented, with no wing-beating tremor or obvious underlying pathology [7]. However, SHE patients show interference with the performance of psychometric tests, such as working memory, psychomotor speed and audiovisual ability, as well as electrophysiological and other functional measures of the brain [8]. It is argued that patients are unable to perform delicate manipulations or complex mental work, and they can become dangerous to themselves and public health [9]. Moreover, SHE is considered an early stage of clinical encephalopathy, and has been associated with a shortened lifespan [10]. Additionally, it results in an increased healthcare-associated burden [11]. Recently, SHE has been attracting more research and clinical interest, as it seems to affect patients' daily activities and quality of life [12]. This study aimed to assess the prevalence of SHE in patients with cirrhosis and to elucidate possible factors related to its occurrence.

Patients and methods

Patients

Thirty consecutive patients with cirrhosis who attended outpatient clinics between March and July 2017 were recruited. Cirrhosis was diagnosed after a liver biopsy or compatible ultrasonographic and/or endoscopic features. Exclusion criteria for the study included current diagnosis or history of overt HE, history of spontaneous bacterial peritonitis, gastrointestinal hemorrhage during the previous month, Wilson's disease, neurological disease, metabolic encephalopathy of non-hepatic etiology, treatment with lactulose, use of non-absorbable antibiotics or psychotropic drugs, uremia, and refusal to sign informed consent for participation in the study. All patients underwent a thorough clinical examination at baseline and were required to have a normal neurological examination: alert, without flapping, ataxia or dysarthria. After evaluation, 23 patients with cirrhosis were found to be eligible for recruitment into the study (5 patients were excluded for overt encephalopathy and 2 for the use of non-absorbable antibiotics). All patients were asked to undergo a follow-up examination 3 months after the baseline visit. Twenty healthy subjects matched to the study patients for age and sex were included as controls.

This study was approved by the Ethics Committee of the hospital. All study patients and controls provided written informed consent, which was in line with the ethical guidelines issued by the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki.

Clinical and laboratory data

Clinical and laboratory data and routine blood tests, including full blood count, prothrombin time, serum

albumin, serum creatinine, international normalized ratio, serum aspartate aminotransferase, alanine aminotransferase, and bilirubin levels were measured at baseline and follow-up visits. Likewise, the presence of ascites or clinical HE was recorded at both visits. The severity of liver disease was determined using the Child-Turcotte-Pugh (CTP) score, and the model for end-stage liver disease (MELD) score was calculated according to the United Network for Organ Sharing (UNOS) formula.

Psychometric tests

The number connection test (NCT) and inhibitory control test (ICT) were performed in all patients to assess the presence of SHE. The NCT is a standard psychometric test that measures cognitive motor ability. It has been used and validated in multiple studies to assess the presence of SHE. It consists of 25 numbers scattered on 1 page, and requires the patient to link them with a pen in the shortest possible time. The test completion time was recorded in seconds. Each subject completed 2 consecutive NCT tests (NCT-A and NCT-B) [13].

ICT is a straightforward electronic psychometric assessment. In the present study, a modified version of this test was utilized, which is accessible online and can be easily installed on any computer system [14]. The primary advantage of this program lies in its user-friendliness, which negates the need for specialized personnel, thereby reducing costs and enabling broad applicability. A brief training session lasting 30 min was provided by the research team to familiarize patients with the procedure.

During each stage of the test, letters from the alphabet are presented on the computer screen at intervals of 500 msec, with the letters "x" and "y" included in the sequence. In the initial phase, participants are instructed to respond by pressing the mouse button whenever they observe the letter "x" or "y." Subsequently, participants are required to respond only when the letter "x" is immediately followed by the letter "y" (target), and to refrain from responding when this sequence does not occur (lure).

Upon completion of the preliminary phase, the participant was prepared to undergo ICT. The test typically comprised 6 cycles, each lasting approximately 2 minutes. The program recorded the percentages of correct responses to target sequences and misleading stimuli (lures), as well as the reaction times associated with each. The final ICT score was considered satisfactory when characterized by a low response rate to misleading stimuli (ICT1) and a high response rate to target sequences (ICT2).

The diagnosis of SHE was considered positive if both psychometric tests were abnormal. Values greater than 2 standard deviations (SD) of the mean value corresponding to people of the same sex and age, without a history of liver disease, psychiatric or neurological disease, or alcohol abuse in the last 3 months, were considered abnormal.

Statistical analysis

Statistical analyses were performed using SPSS V23 (SPSS software; SPSS Inc., Chicago, IL, USA). Data are expressed as frequencies, mean \pm SD, or median (interquartile range [IQR]), as appropriate. Quantitative variables were compared between groups using Student's t-test or the Mann-Whitney test, for normally distributed and non-normally distributed variables, respectively. Qualitative variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Associations between quantitative variables were assessed using Spearman's correlation coefficient. All tests were 2-sided, and statistical significance was set at $P < 0.05$.

Results

Subject characteristics

No significant differences were noted between patients with cirrhosis and controls in terms of age or sex distribution. Most patients with cirrhosis had compensated cirrhosis of CTP class A, while chronic viral hepatitis (B or C) was the leading cause of liver disease, followed by nonalcoholic fatty liver disease. Baseline epidemiological and laboratory characteristics of the enrolled patients are presented in Table 1. NCT and ICT were performed in all patients and controls.

NCT

The NCT completion time was significantly longer in patients with cirrhosis than in controls (77 ± 45 vs. 27 ± 6 s, $P < 0.001$). Considering the mean NCT completion time of controls ± 2 SD as the normal cutoff limit of NCT, 18 (78.3%) of the 23 patients with cirrhosis had abnormal NCT. NCT completion time did not differ between patients with CTP classes A and B (76 ± 43 vs. 78 ± 50 sec, $P = 0.935$) and was not correlated with patients' MELD score ($r = 0.217$, $P = 0.332$).

ICT

The percentage of correct target recognition was significantly lower in patients with cirrhosis than in controls ($18.5 \pm 21.8\%$ vs. $56.2 \pm 15.8\%$, $P < 0.001$). Considering the value of the mean ± 2 SD of correct recognition of targets in controls as the normal cutoff limit of ICT, 14 (60.9%) of the 23 cirrhotic patients had abnormal ICT. The percentage of correct target recognition was arithmetically, though not significantly, higher in cirrhotic patients with CTP class A than B ($24.7 \pm 6.6\%$ vs. $15.4 \pm 6.6\%$, $P = 0.257$). There was no correlation between the number of correct targets recognized by the patients and their MELD score ($r = 0.308$, $P = 0.163$).

Table 1 Main epidemiological and laboratory characteristics of patients with cirrhosis and healthy controls

Characteristics	Patients with cirrhosis (n=23)	Controls (n=20)
Male sex	15 (65%)	9 (35%)
Age, years	63 \pm 11 (39-78)	56 \pm 15 (41-80)
Liver disease etiology	Chronic viral hepatitis: 14 (61%) Non-alcoholic fatty liver disease: 4 (17%) Alcoholic liver disease: 3 (13%) Other: 2 (9%)	N/A
CTP class, A / B	15 (61%) / 8 (39%)	N/A
MELD score	10 \pm 6 (5-26)	N/A
Hemoglobin, g/dL	13.0 \pm 1.8 (9-16)	N/A
Platelets, $\times 10^9/L$	121 \pm 56 (33-233)	N/A
INR	1.4 \pm 0.4 (1.0-2.3)	N/A
AST, IU/L	70 \pm 46 (19-163)	N/A
ALT, IU/L	50 \pm 34 (11-131)	N/A
Total bilirubin, mg/dL	1.9 \pm 2.1 (0.3-8.7)	N/A
Creatinine, mg/dL	0.9 \pm 0.3 (0.3-1.6)	N/A
Albumin, g/dL	3.7 \pm 0.9 (1.9-4.8)	N/A
Sodium, mEq/L	139 \pm 3 (132-143)	N/A
CRP (ULN: <5 mg/L)	1.2 \pm 0.9 (0.4-2.2)	N/A

Quantitative variables are expressed as mean \pm SD (minimum-maximum).

Qualitative variables are expressed as n (%)

CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease;

INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; ULN, upper limit of normal

The percentage of incorrect lures did not differ between patients with cirrhosis and controls ($90.0 \pm 16.3\%$ vs. $83.0 \pm 4.3\%$, $P = 0.868$). In addition, no difference in the percentage of incorrect lures was observed between patients with CTP classes A and B ($P = \text{NS}$); therefore, no further analysis was performed. The percentage of incorrect lures was strongly correlated with the percentage of correct targets in the total study population (k-statistics: 0.475, $P = 0.001$).

Combination of NCT and ICT

Nine (39.1%) of the 23 patients with cirrhosis had abnormal findings for both NCT and ICT, and were diagnosed with SHE according to the study definition. Neither CTP class nor any other baseline parameters were associated with the presence of SHE (Table 2). Correct target recognition was inversely correlated with the NCT completion time ($r = -0.389$, $P = 0.016$).

Table 2 Association between the presence of subclinical hepatic encephalopathy (SHE) and patients' characteristics in 23 patients with cirrhosis

Characteristics	SHE (n=9) (both NST and ICT abnormal)	NST abnormal (n=18)	ICT abnormal (n=14)	No SHE (n=14)	P-value (SHE vs. no SHE)
Sex, males/females	6/3	12/6	10/4	9/5	>0.99
Age, years	66±11 (40-78)	65±10 (40-78)	65±12 (39-78)	61±11 (39-75)	0.317
Liver disease etiology:					0.820
Chronic viral hepatitis	5 (56%)	11 (61%)	8 (57%)	9 (65%)	
Non-alcoholic fatty liver disease	2(22%)	4(22%)	2(14%)	2(14%)	
Alcoholic liver disease	1(11%)	1(6%)	3(22%)	2(14%)	
Other	1(11%)	2(11%)	1(7%)	1(7%)	
CTP score	6.0±1.0	6.0±1.1	6.1±1.1	6.3±1.5	0.596
CTP class:					0.505
A	5 (56%)	11 (61%)	7 (50%)	9 (64%)	
B	4 (44%)	7 (39%)	7 (50%)	5 (36%)	
MELD score	10.3±5.2	11.4±6.6	9.1±4.7	10.6±6.9	0.919
Hemoglobin, g/dL	12.5±1.4	12.8±1.9	12.9±1.4	13.3±2.1	0.367
Platelets, ×10 ⁹ /L	105±47	109±66	99±57	111±78	0.860
INR	1.3±0.2	1.4±0.3	1.3±0.2	1.5±0.5	0.496
AST, IU/L	77±52	71±47	67±48	64±42	0.533
ALT, IU/L	45±21	57±34	43±28	53±43	0.624
Total bilirubin, mg/dL	2.8±3.4	2.1±2.3	2.2±2.8	1.4±0.9	0.225
Creatinine, mg/dL	0.8±0.2	0.9±0.3	0.9±0.2	0.99±0.36	0.319
Albumin, g/dL	3.2±1.2	3.5±1.1	3.5±1.0	3.8±0.8	0.235
Sodium, mEq/L	138±4	138±3	136±3	139±2	0.402
CRP (ULN: <5 mg/L)	0.8±0.6	1.2±0.9	0.8±0.6	2.2±0.8	0.307

Quantitative variables are expressed as mean ± standard deviation

CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; ULN, upper limit of normal

Follow up

Of the 23 cirrhotic patients, 16 (70%) were reevaluated using both ICT and NCT 3 months after the baseline visit. Eight (50%) of these 16 patients had abnormal NCT results, while 8 of the 16 patients also had abnormal ICT results, as expressed by the percentage of correct target recognition. The NCT values at the 3-month follow-up visit were significantly correlated with the baseline values ($r=0.665$, $P=0.007$). In contrast, there was no significant correlation between the percentage of correct targets detected by ICT at the baseline and 3-month visits ($r=0.359$, $P=0.172$).

Of the 6 patients diagnosed with SHE at baseline (both NCT and ICT abnormal) who were reevaluated at follow up, 4 (66.7%) had SHE at the 3-month follow-up visit, while none of the 10 patients without SHE at baseline were diagnosed with SHE at the 3-month follow-up visit. Thus, the diagnosis of SHE at baseline was strongly correlated with the diagnosis of SHE at 3 months (k -statistics: 0.714, $P=0.008$).

Discussion

The prevalence of SHE depends strongly on the definition and diagnostic criteria applied to each cohort. To correctly determine the presence of SHE, its diagnosis was made when both ICT and NCT were abnormal, as suggested by several previous studies [15-18]. Based on this definition, the prevalence of SHE in our patients with cirrhosis was found to be as high as 39%, which is within the range of previously reported prevalence rates (22-52%) in patients with cirrhosis [15,19,20]. Such a wide variation in the prevalence of SHE among different studies may be due to the different tools used for SHE diagnosis in each study and the heterogeneity of the patient populations.

The association between the presence of SHE and the severity of liver impairment, as expressed by CTP class and MELD score, remains controversial. Previous studies reported no correlation between MELD score and the presence of SHE [20]. In contrast, SHE was reported to be more frequent in patients with CTP B/C than in those with A cirrhosis (48%

vs. 15%), while the presence of SHE diagnosed by critical flicker frequency was found to have a weak but significant correlation with CTP score ($r=0.22$; $P=0.018$) [20,21]. In our study, there was no correlation between NCT or ICT values and the MELD score or CPT class, while only an arithmetically but not significantly lower correct target recognition in the ICT test was observed in patients with CPT B than in those with A class. The inability to identify a difference in the SHE prevalence rates between different CTP classes may be due to the small sample size, but also due to the inclusion of patients without advanced liver impairment (mostly CTP class A and perhaps B), as it is uncommon to encounter patients with advanced liver impairment who have not yet developed overt HE.

According to our findings, no new case of SHE was diagnosed at the 3-month follow-up evaluation. It must be emphasized that no significant clinical events were observed in our study population during the 3-month follow-up period. This observation supports the hypothesis that the development is a complex and slowly progressive process. In contrast, two thirds of our patients with SHE at baseline continued to have SHE at the 3-month follow-up visit. Thus, cognitive impairment in patients with cirrhosis seems to persist without significant fluctuations, at least in the short term. In a study by Sharma *et al*, no significant differences in the correct target recognition of ICT were reported between 2 sequential evaluations at 4-h intervals in patients with primary SHE [15]. Similarly to our study, a few cases of abnormal psychometric tests at baseline and normal tests at follow up were identified, and were attributed to potential learning effects and increased familiarity with the procedure. In the latter study, with only a 4-h interval between the 2 tests, the learning effect might have been stronger and potentially associated with a significant reduction in the completion time of NCT-A and a higher percentage of correct lures in the follow-up test in patients with cirrhosis.

The number of ICT lures did not differ between patients with cirrhosis and healthy controls, and was not associated with the presence of SHE. In addition, we observed a strong correlation between the number of correct targets detected by our patients and controls and their incorrect cure rates. These data are in accordance with the findings from the study by Amodio *et al*, in which the incorrect cure rates exhibited a U shape [22]. The relationship between the rate of correct targets and incorrect lures implies that testing inhibition in the context of insufficient attention produces unreliable results. The low incorrect lure recognition in our cases might also be associated with the fact that older Greeks tend to have a lower level of education and less familiarity with computers, as was also observed in the Italian control cohort of Amodio *et al* [22], findings that were in contrast to those from American cohorts in the studies of Sharma *et al* and Baja *et al* [15,23].

This study has several limitations that should be acknowledged. The relatively small sample size reflects

the limited number of eligible cirrhotic patients routinely followed in our tertiary Hepatology Clinic, as well as the limited 4-month enrolment period. While this reduced the statistical power of the analysis, and may have prevented the detection of certain associations (type II error), the findings nonetheless provide valuable preliminary insight into the prevalence and persistence of SHE in a real-world outpatient population. Additionally, one third of the participants were lost to follow up, and the 3-month observation period may not fully capture the long-term evolution or fluctuation of SHE. Data on markers of portal hypertension and systemic inflammation were not available in the present cohort, which is an additional limitation. Finally, although metabolic and nutritional parameters, such as sarcopenia, are known to influence the risk of HE, including its subclinical form (SHE), the present study primarily focused on behavioural and psychometric characteristics associated with SHE. Therefore, the assessment of body mass index or muscle mass indices was beyond the intended scope of this work.

In conclusion, our study underscores the significant prevalence of SHE among patients with cirrhosis, with 39% of our cohort displaying signs of SHE. This finding aligns with previous research, illustrating that SHE is a common and persistent issue within this patient population. The diagnosis of SHE, determined using both the NCT and the ICT, was found to be stable over a 3-month period, suggesting that cognitive impairment in cirrhotic patients persists over time without significant fluctuations.

Despite the lack of correlation between SHE and the severity of liver impairment (as measured by MELD score and CTP class), our results highlight the importance of consistent and comprehensive screening for SHE in patients with cirrhosis. The persistence of cognitive impairment calls for ongoing monitoring and management to improve patient outcomes and quality of life. It is noteworthy that no new cases of SHE were diagnosed during the follow-up period, reinforcing the idea that SHE develops progressively and may not fluctuate significantly in the short term.

Moving forward, it is crucial to further explore the underlying mechanisms of SHE and its impact on patients' daily functioning and overall health. Future research should aim to refine diagnostic tools and establish standardized criteria for SHE diagnosis to reduce variability in prevalence rates across studies. Additionally, larger and more diverse cohorts are needed to better understand the relationship between liver impairment severity and SHE.

Moreover, interventions targeting cognitive impairment in cirrhotic patients should be developed and tested, with an emphasis on early detection and treatment. Enhancing patient and caregiver education about SHE and its potential consequences can also play a pivotal role in managing this condition effectively. Our study's results underscore the necessity for a holistic approach in managing SHE, involving regular screening, patient education and targeted interventions to mitigate its impact on patients' lives.

Summary Box

What is already known:

- Hepatic encephalopathy (HE) significantly impacts patients with cirrhosis, leading to greater hospitalization, healthcare costs and mortality rates
- HE can present as overt or subclinical, with the latter, known as subclinical HE (SHE), being more prevalent and harder to detect
- SHE impairs performance on psychometric tests and affects daily functioning and quality of life, potentially serving as an early warning sign for clinical encephalopathy

What the new findings are:

- In our study, we found that 39.1% of patients with cirrhosis exhibited signs of SHE, demonstrating its significant presence among this population
- By using both the number connection test and the inhibitory control test, we effectively identified patients with SHE, highlighting the utility of these combined diagnostic tools
- The persistence of SHE was evident, as initial diagnoses at baseline were strongly correlated with diagnoses at the 3-month follow up, indicating that SHE remains a stable condition over time

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