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Original article

Cognitive Impairment in Patients with Chronic Liver Diseases

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Abstract

Background and Aims: The aim of the study is assessment of cognitive functions in patients with chronic liver diseases (CLD) of various etiologies. **Patients and methods;** One hundred and twenty patients diagnosed with CLD of various etiologies were evaluated at the Hepatology and Gastroenterology clinics, at Beni-Suef University Hospital. They were recruited from November 2021 to April 2022. The Mini-mental state examination and Wechsler Adult Intelligence State score-4 were used to assess cognitive functions in the study group. **Results:** Out of one hundred and twenty patients (60 males and 60 females), 15 patients (12. 5%) of the study group showed cognitive dysfunction and 105 patients (87.5%) had normal cognitive function by Mini-Mental State Examination (MMSE). Whereas, 33 patients (27.5%) had cognitive impairment and 53 patients (44.2%) had attention and memory dysfunction detected by applying the Wechsler adult intelligence scale -4 (WAIS- 4). **Conclusion**: Based on the findings, the study concluded that patients with CLD have cognitive impairment in the form of dysfunction of (cognition, attention, memory, and executive functions)

1. Introduction:

Two million people die each year from liver disease, making chronic liver disease (CLD) a. leading cause of illness and death globally[1].The global tenth leading cause of mortality is CLD[2].The development of cirrhosis and liver cancer is the most prevalent and significant outcome of chronic liver disease (CLD)[3].

One of the most debilitating health conditions resulting from liver disease is hepatic encephalopathy (HE), also called portosystemic encephalopathy. This condition causes a broad range of neuropsychiatric symptoms and cognitive problems, such as difficulties with learning, attention, language, perception, psychomotor skills, and intellectual functions[4].

The degree of cognitive impairment varies from patient to patient; some may not exhibit any obvious symptoms at all, while others may develop life-threatening issues that put them into a coma [4] .

Occurring with liver disease and less severe forms of liver disease are the two main categories into which hepatic encephalopathy (HE) falls. Although the OHE is easily noticeable in clinical settings, the less severe HE has been gaining more attention as of late. Mild HE, sub-clinical HE, or latent HE are terms that describe this. Neuropsychiatric testing and neurophysiological evaluation may reveal that 30–84% of people with liver cirrhosis who do not exhibit clinical signs of HE nevertheless have MHE with mild cognitive impairment[5].

When patients with MHE operate heavy machinery or cars, they endanger not only themselves but also the community. The effects of MHE on everyday functioning and quality of life may be substantial[6].

Basic everyday taskssuch as hygiene, eating, clothing, etc. are unaffected by little hepatic encephalopathy, but complicated tasks requiring attention, information processing, and psychoemotional capacities (medium- or short-term planning, automobile driving, etc.) are. When compared to cirrhotic individuals without encephalopathy, those with MHE had much worse emotional behaviour, social relations, employment, and sleep quality, according to other clinical investigations[7].

It is common for MHE to go misdiagnosed due to the misconception that it does not significantly affect patients' quality of life (QOL) or functional capacity as it is not immediately noticeable[8].

Improving cognitive functioning and quality of life and preventing the development of overt HE may be achieved by early identification and care of MHE and associated risk factors[9]. Additionally, the likelihood of developing overt HE and overall mortality is higher in patients with MHE[10]. Curiously, there is no clear correlation between MHE and Child-Pugh scores, even though the former is greater in patients with MHE than in those without[11].

2. Patients and Methods:

This was a cross-sectional study that was conducted on 120 patients diagnosed with chronic liver disease of various etiologies. The patients were recruited from November 2021 to April 2022. All participants were recruited from Gastroenterology and Hepatology clinic Beni-Suef University Hospital.

To make sure that the same 15 patients wouldn't be included in the main trial, a pilot study was carried out in November 2021 in conditions that were identical to the main study. Both the technique and the tools were determined to be viable during the pilot research.

Ethics: After receiving clearance from the ethics council of Beni-Suef University Hospitals, the research was conducted following the declaration of Helsinki. All patients were asked to sign an informed consent form. The research only included patients who met the inclusion criteria. **The approval number was FMBSUREC/01112021/Ahmed**

2.1 Inclusion criteria:

1-All patients aged from 18 - 50 years old.

2-Both Sexes.

3- Patients with chronic liver diseases.

Exclusion criteria

Participants were carefully selected after thorough screening of their medical records to exclude any potential risk factors for cognitive impairment, including substance use disorders, alcohol abuse, current treatment with psychotropic medication, neurological diseases such as stroke, cerebrovascular disease, mental retardation, dementia, seizure disorders, liver cancer (HCC), cirrhosis (Child B/C), a history of hepatic encephalopathy, renal disease, acute fulminant hepatic failure, or psychiatric diseases. Additionally, patients who refused to participate were excluded from the study.

2.2 All patients were subjected to:

1. **Semi-structured sheet of Gastroenterology and hepatology clinic, Beni-Suef University:**

Unstructured health the following information was collected using standard questionnaires: age, sex, employment, medical history, current drugs, smoking, and alcohol intake.

2. **Physical Examination**

The neurological and abdominal systems of every patient were examined in detail.

3. **Laboratory investigations**

The evaluation included a complete blood count (CBC), liver function tests such as alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, serum albumin, and international normalization ratio (INR), as well as renal function tests (urea, creatinine) and blood sugar levels. Additionally, the Child-Pugh score was calculated for each participant.

4. **Radiological investigation:**

Abdominal ultrasonography was performed to detect advanced stages of hepatic cirrhosis and hepatic focal lesions.

5. The neuropsychological assessment includes

A-Mini Mental State Examination (MMSE)

The MMSE includes several short questions and tasks divided into eight categories: orientation to time and place, registration, attention and calculation, recall, language skills, repetition, and complex commands (such as writing a sentence of the patient's choice, reading a sentence, following a command, and copying pentagons). Each category is scored, and a total score of up to 30 points is calculated, with higher scores indicating better cognitive performance. For illiterate patients, the two points related to reading and writing were excluded, yielding a maximum score of 28 instead of 30 points[12]. A score of 24 or lower suggests cognitive impairment[13]. The MMSE was translated into Arabic by three individuals, and the Arabic version has been validated in Lebanon[14].

B-Wechsler adult intelligence scale-4:

The purpose of the WAIS is to evaluate the level of general cognitive function in people who are suffering from a range of neurological disorders. As an evaluation tool, WAIS may be used to:

1. Figure out where you excel and where you may need improvement in terms of learning, intelligence, and cognitive abilities.
2. Help in treatment planning and deciding where to put patients.
3. Give academic and neuropsychological assessments and clinical data.
4. Provide research with accurate and trustworthy data[15].

There are a total of fifteen subtests that make up the most recent iteration of the exam, the WAIS-IV, which came out in 2008. The Full-Scale IQ is derived from the sum of the scaled scores obtained from the ten core subtests. Index scores of 26 were substituted for verbal and performance IQ scores in the WAIS-IV. Seven people worked on the Arabic translation, and one person made edits and verified the final product.

Statistical methodology

A simple descriptive analysis was performed, using numbers and percentages for qualitative data, and arithmetic means and standard deviations to measure central tendency and dispersion for quantitative parametric data. For quantitative comparisons between two independent groups, the independent samples t-test was applied. For qualitative data, the Chi-square test was used to compare two or more groups, and the bivariate Pearson correlation test was employed to assess associations between variables. A P-value of less than 0.05 was considered statistically significant.

3. Results:

The current study was a cross-sectional study conducted on 120 patients diagnosed with chronic liver disease of various etiologies. The patients were recruited from Gastroenterology and Hepatology clinic at Beni-Suef University.

Hospital in the duration from November 2021 to April 2022 after obtaining an informed consent.

I -Descriptive data

A. Socio-demographic data

B. 1- Age:

The age of patients in this study ranged from (19 to 50) years with a mean value of 35.6 ± 9.3 years.

2- Gender: In the present study, 50% (n=60) of the included patients were females, and 50% (n=60) of patients were males.

C. Laboratory data:

Table (1): Description of routine investigations among study group The table illustrated that different routine investigations were normal as regards CBC, liver and kidney function tests. Also show normal levels of INR, HbA1c, and AFP.

Variables	Mean	± SD	Normal range
CBC			
Hb	12.9	± 1.6	(12-16) g/dl
WBCs	6.1	± 1.9	(4-11)x1000/mm3
PLT	255.9	± 66.04	150-450x1000/mm3
Liver function test			
Total bilirubin	0.74	± 0.35	(0.3-1.2) mg/dl
Direct bilirubin	0.40	± 1.8	(0.3) mg/dl
ALT	34.7	± 52.7	(0-40) U/L
AST	32.1	± 29.9	(0-40) U/L
Albumin	4.3	± 0.51	(3.5-5) g/dl
Kidney function			
Urea	23.1	± 4.6	(6-24) mg/dl
Creatinine	0.85	± 0.22	(0.4-1.3)mg/dl
Other investigations			
INR	1.07	± 0.12	1
AFP	4.5	± 8.6	(0- 40) ng/ml
HbA1c	5.2	± 0.82	Below (5.7%)

D. Radiological data

Table (2): Frequency of different ultrasonographic findings among the study group

The table illustrated that 40.8% of cases show bright liver in ultrasound, versus 59.2% had Chronic parenchymatous, for spleen 74.2% had normal spleen versus 25.8 % had splenomegaly.

Variables (n=120)	**Frequency**	
	Number	**%**
Liver		
Bright	49	40.8%
Chronic parenchymatous	71	59.2%
Spleen		
Normal	89	74.2%
Splenomegaly	31	25.8%

E. Psychometric assessment

All psychometric assessment tests were executed by clinical psychologists and these tests include the followings:

1- Mini-Mental State Examination (MMSE)

Table (3): Description of different MMSE domains among the study group

The table illustrated that the mean MMSE orientation domain was (9.2±0.80), the registration domain was (2.89±0.31), the attention and calculation domain was (4.15±0.93), the recall domain was (2.89±0.31), the mean language domain was (8±0.92), and finally the mean of the total score was (27.2±2.8). 12.5% of the study group show cognitive dysfunction by MMSE.

Variables	**Mean ± SD**	**Range**
MMSE (orientation)	9.2±0.80	5-10
MMSE (registration)	2.89±0.31	2-3
MMSE (attention and calculation)	4.15±0.93	2-5
MMSE (recall)	2.89±0.31	2-5
MMSE (language)	8±0.92	5-9
Total MMSE score	27.2±2.8	16-30
	No.	%
Dysfunction	15	12.5%
No Dysfunction	105	87.5 %

Table (4): Gender differences regarding MMSE different domains

The table illustrated that there was a statistically significant lower mean of all MMSE domains (orientation, registration, attention & calculation, recall, and language) among females with a p-value <0.05.

Variables	Sex				P-value	Sig.
	Male (N=60)		Female (N=60)			
	Mean	SD	Mean	SD		
MMSE (orientation)	9.46	0.62	8.97	0.88	**<0.001**	**HS**
MMSE (registration)	2.96	0.18	2.81	0.39	**0.008**	**HS**
MMSE (attention and calculation)	4.63	0.66	3.68	0.91	**<0.001**	**HS**
MMSE (recall)	2.97	0.18	2.81	0.39	**0.008**	**HS**
MMSE (language)	8.45	0.75	7.57	0.87	**<0.001**	**HS**
Total MMSE	28.5	2.1	25.8	2.9	**0.03**	**S**
	No.	**%**	**No.**	**%**	**P-value**	**Sig.**
Dysfunction	4	5%	11	18.3%	**0.04**	**S**
No Dysfunction	56	95%	49	81.7%		

2- Wechsler adult intelligence scale -4 (WAIS-4)

Table (5): Description of cognition function, attention and memory assessment by Wechsler adult intelligence scale -4 among the study group

The table illustrated that the mean first domain of the Wechsler adult intelligence scale was (7.9±2.5) and for the second domain, the main was (6.4±2.3). In domain 1 for cognition assessment, 27.5% show dysfunction, but dysfunction represents 44.2% in domain 2 for attention and memory.

Variables (n=120)	**Frequency**	
	Mean±SD	**Range**
Wechsler Adult Intelligence Scale -4		
Domain 1(**Cognition assessment**)	7.9±2.5	2-13
Domain 2 (**Attention and memory assessment**)	6.4±2.3	0-14
Cognition Assessment by Domain 1	**No.**	**%**
Dysfunction	33	27.5%
Normal	87	72.5%
Attention and memory assessment by Domain 2		
Dysfunction	53	44.2%
Normal	67	55.8%

F. Clinical assessment

Figure (1) illustrates that 5% of the study group had DM, and 7.5% had hypertension. For chronic liver disease etiology, figure (2) illustrated that 41.7% had HCV, followed by 30.8% with HBV and 25.9% were NAFLD.

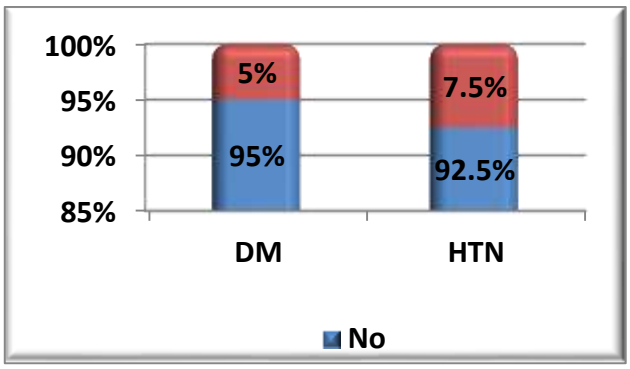

Figure (1) comorbidities

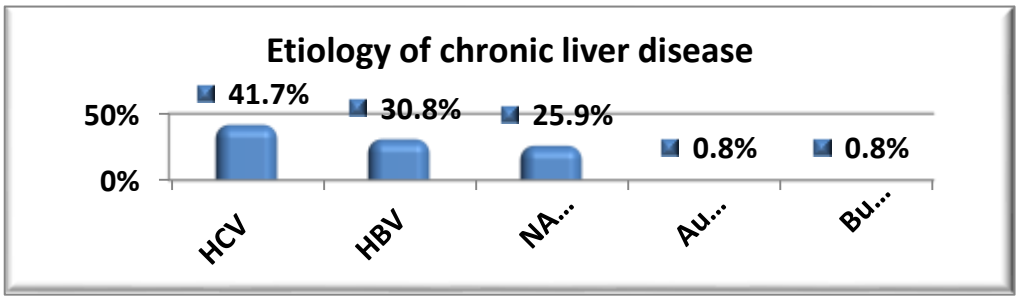

Figure (2) etiology of liver disease

II-Comparison Studies

Table (6): Comparison of demographic characters in different cognition dysfunction groups

Figure (3a) and (3b) illustrated that there was a statistically significant higher percentage of cognition dysfunction among females and cases of HCV with p-value <0.05. On the other hand, there was no statistically significant difference between cognition dysfunction groups with p-value >0.05 as regards age.

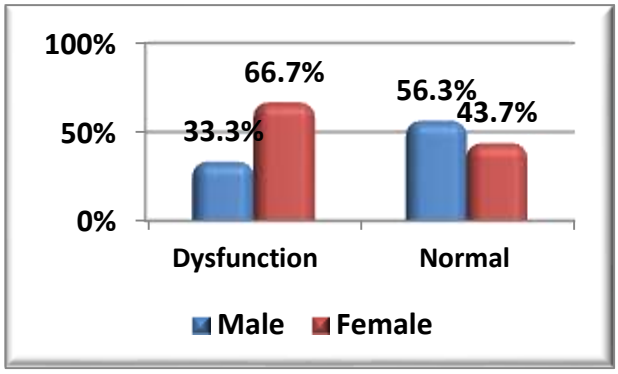

Figure (3a) cognitive dysfunction in relation to sex

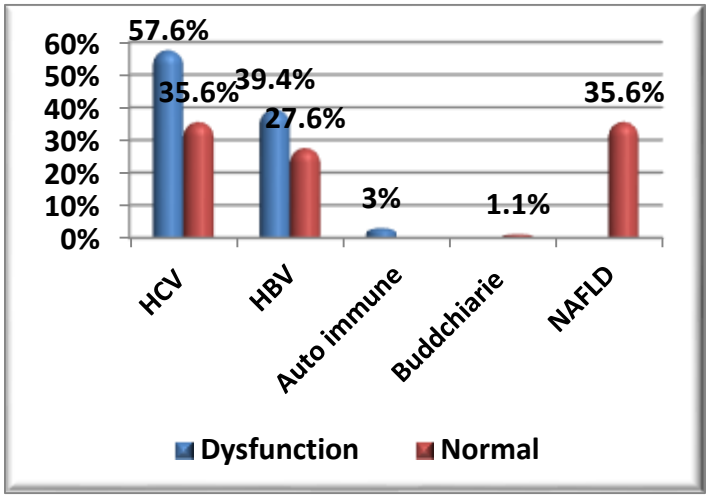

Figure (3b) cognitive dysfunction in relation to liver disease cause

III- Correlation Studies

Table (7): Correlation between MMSE domains with age and Wechsler adult intelligence scale among the study group

The table illustrated that there was a statistically significant **negative** correlation with p-value <0.05 between age and all MMSE domains. In addition, there was a statistically significant **positive** correlation with p-value <0.05 between the cognition score of WAIS-4 and all MMSE domains. On the other hand, there was no statistically significant correlation with a p-value >0.05 between the attention and memory domain score of WAIS-4 and all MMSE domains. That means an increase in all MMSE domain score in young age patients and in patients having high cognition scores by WAIS-4.

MMSE domains	**Variables**		
	Age (yrs)	**Domain 1 (Cognition)**	**Domain 2 (attention and memory)**
	r(p-value)	**r(p-value)**	**r(p-value)**
MMSE (orientation)	**-0.29(0.001*)**	**0.36(0.001*)**	0.05(0.6)
MMSE (registration)	**-0.32(0.001*)**	**0.19(0.03*)**	0.001(0.9)
MMSE (attention and calculation)	**-0.22(0.01*)**	**0.37(0.001*)**	0.06(0.5)
MMSE (recall)	**-0.32(0.001*)**	**0.19(0.03*)**	0.001(0.9)
MMSE (language)	**-0.20(0.03*)**	**0.37(0.001*)**	0.14(0.1)
Total MMSE	**-0.29(0.001*)**	**0.36 (0.001*)**	0.10(0.3)

4. Discussion:

The central nervous system is often implicated and impacted in people with CLD, regardless of the numerous reasons. Depending on how severe this impact is, it might produce a hepatic coma associated with irreparable brain damage, abnormalities in psycho motility, and disturbed mental function. The first symptoms are reversible neurological and mental disorders that are not immediately apparent in the patient's clinical symptoms and can only be diagnosed by psychometric testing. Subclinical or mild hepatic encephalopathy describes this state. [16]

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severe this impact is, it might produce a hepatic coma associated with irreparable brain damage, abnormalities in psycho motility, and disturbed mental function. The first symptoms are reversible neurological and mental disorders that are not immediately apparent in the patient's clinical symptoms and can only be diagnosed by psychometric testing. Subclinical or mild hepatic encephalopathy describes this state[17].

Since both cognitive impairment and depression are treatable conditions, it is critical to evaluate and track these symptoms in patients with chronic liver disease to detect them early and provide them with the appropriate therapy[18].

Our study was conducted on 120 patients with chronic liver disease. The majority of the patients with CLD were aged between 19-50 years. The mean age among the study group was (35.6±9.3) years. The proportion of males (50%) and females (50%) in terms of gender. These findings of socio-demographic variables are following other studies by Varghese ML et al[18]. that was a case-control study conducted on patients with CLD and healthy controls. A total of 41.8 per cent of the patients with CLD aged between 41-50 years and 33.6 per cent of the healthy controls aged between 31-40 years. Matching was done between patients with CLD and healthy controls in terms of age.

As regard the etiology of chronic liver disease 50 patients (41.7%) had HCV, 37 patients (30.8%) had HBV, 31patients (25.9%) had NAFLD, 1 patient (0.8%) had Autoimmune hepatitis and 1 patient (0.8%) had Budd Chiari syndrome. This agreed with the study conducted by **Sorrell JH et al[19].** who stated that the predominant cause of CLD was hepatitis C in the study done for evaluation of all consecutive adult outpatients with ESLD who presented for orthotopic liver transplantation at the University of Nebraska Medical Center.

Opposite results are obtained by the study conducted byVarghese ML, et al [18] that showed alcohol (47.3%) as the major cause of CLD.

Neuropsychological Assessment in the study group of patients:

1-Applying the Mini-Mental State Examination (MMSE) test

In the present study, after conducting the MMSE on patients with chronic liver disease by a clinical psychologist, the following results were obtained: The mean MMSE orientation domain was (9.2±0.80), the registration domain was (2.89±0.31), the attention and calculation domain was (4.15±0.93), recall domain was (2.89±0.31), the mean language domain was (8±0.92), and finally the mean of the total score was (27.2±2.8).

The result of the total score mean of our study was in agreement with the study conducted by Torres DS et al[20], as regarding the evaluation of global cognitive performance**,** patients with cirrhosis had a mean score of 27.5 ± 2.9 points (median of 28 points) on the MMSE**,** and also the results were in accordance with the study conducted by Corrias M et al[12], that was studied

on 191 patients with cirrhosis functionally**,** 67 patients (35%) were qualified as Child-Pugh class A, 86 patients (45%) were qualified as Child-Pugh class B and 38 patients (20%) were qualified as Child-Pugh class C. The average MMSE was 26.6 ±3.5 and 22 patients (19%) had abnormal MMSE based on the standard threshold of 24 [1,2,3] .

Our results indicated that 15 patients (12.5%) from the study group exhibited cognitive dysfunction as assessed by the MMSE. This could be attributed to the generally good liver function seen in Child A patients, which may explain the lower incidence of minimal hepatic encephalopathy (MHE). This finding aligns with a study conducted by N.Abdel et all[23], which involved 80 adult patients with hepatic cirrhosis, categorized into groups A, B, and C based on the Child-Pugh classification. The study aimed to evaluate cognitive functions in cirrhotic patients and found that those with cirrhosis (25.35 ± 1.63) had poorer cognitive performance compared to healthy controls (27.60 ± 1.93). A significant difference in cognitive function was noted between Child A patients compared to those in Child B and C, while no significant difference was found between Child B and C. Patients in Child-Pugh classes A and B had better MMSE results, both in total score and across most individual items, compared to those in Child-Pugh class C. However, similar results were observed between Child-Pugh classes A and B across most MMSE items. Additionally, 87.5% of patients with chronic liver disease (CLD) maintained normal cognitive function, which supports the findings of a study by Varghese Ml et al[18], which showed a significant association between cognitive function scores and liver cirrhosis (t=2.3, p=0.025). Patients with CLD but without cirrhosis had significantly higher cognitive function scores than those with cirrhosis. The cognitive function score was also significantly associated with minimal hepatic encephalopathy (t=4.8, p<0.001), with patients free from MHE showing higher cognitive function scores compared to those affected by MHE[18].

Our study illustrated that there was a statistically significant **negative** correlation with p-value <0.05 between age and all MMSE domains. That means an increase in cognition score and being younger in age is associated with an increase in MMSE scores in all domains. This result was in agreement with the study conducted by Soriano G et al[24], which stated that people with increasing age had cognitive dysfunction, and this result was in agreement with the study conducted by Varghese ML et al, **[18] that** showed poor cognitive function in the age group of 51-70 years (74.1±08.9) than 21-50 years (75.6±08.3).

Also, there was a statistically significantly lower mean of all MMSE domains (orientation, registration, attention & calculation, recall, and language) among females with a **p-value <0.05** than males. The total score in females was (25.8) while in males was (28.5), with a higher

percentage of cognitive dysfunction among females 18.3% versus 5% in males.

This result was in accordance with the study conducted by Elgohary MN et al[5], that was conducted on 302 patients with liver cirrhosis for the assessment of risk factors of MHE in patients with compensated liver cirrhosis. Of which 130 patients had Child A (compensated) liver cirrhosis and the results revealed that females perform worse than males in tasks that require visuospatial skills.

According to Asperholm M et all[25], the neurocognitive domains most affected in MHE include attention, visuospatial abilities, memory performance, and fine motor skills. This aligns with the findings of a study conducted by Koziarska D et al[26], on 101 consecutive patients with liver cirrhosis, which revealed that males performed significantly better than females in executing a complex command, such as writing a sentence (mean: 0.97 ± 0.37 vs. 0.84 ± 0.175 points, $p<0.03$).

5. Conclusion and Recommendations:

Deficits in quality of life are evident even in patients with chronic liver diseases, emphasizing the importance of a comprehensive assessment to address both physical and cognitive health. These findings point to the need for improving physical function and identifying and treating cognitive dysfunction. The study recommends incorporating neurophysiological assessments, such as the MMSE and WAIS-IV, to effectively detect cognitive impairment in patients with chronic liver disease.

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