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Relationship between Sarcopenia and minimal hepatic encephalopathy in patients with cirrhosis: a prospective observational study

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Abstract

Background Sarcopenia, characterized by loss of muscle mass and function, has gained importance in the evaluation of cirrhotic patients. Evidence suggests its role in adverse clinical outcomes, including minimal hepatic encephalopathy (MHE). This study aimed to investigate the association between sarcopenia and MHE in patients with cirrhosis.

Methods We prospectively enrolled outpatients with cirrhosis to assess sarcopenia using the 2019 criteria from the Asian Working Group for Sarcopenia. MHE was diagnosed through the Psychometric Hepatic Encephalopathy Score.

Results Of the 210 cirrhotic patients (57.1% male, mean age 62.7 ± 9.6 years), 54 (25.7%) had sarcopenia, with 26 (12.3%) classified as severe. Thirty-seven patients (17.6%) were diagnosed with MHE. Sarcopenia prevalence was significantly higher in patients with MHE compared to those without MHE (45.9% vs. 21.4%). MHE was significantly associated with age, education level, Mini-Mental State Examination score, and a history of hepatic decompensation. No significant associations were found regarding gender, body mass index, comorbidities, sleep quality, and the etiology of cirrhosis. Multivariable logistic regression showed that MHE was significantly associated with age (adjusted odds ratio [aOR] 1.08, 95% CI 1.02–1.13), sarcopenia (aOR 3.29, 95% CI 1.44–7.50), history of overt hepatic encephalopathy (aOR 7.40, 95% CI 1.20-45.56), and variceal bleeding (aOR 3.13, 95% CI 1.38–7.10). Severe sarcopenia was also independently associated with MHE (aOR 3.64, 95% CI 1.32–10.05).

Conclusions Sarcopenia is prevalent in cirrhotic patients and is associated with an increased risk of MHE. Our findings emphasize the importance of assessing sarcopenia to potentially mitigate MHE risk in managing patients with cirrhosis.

Keywords Cirrhosis, Hepatic decompensation, Minimal hepatic encephalopathy, Psychometric hepatic encephalopathy score, Sarcopenia

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Introduction

Sarcopenia is characterized by loss of skeletal muscle mass, strength, and physical performance [1, 2]. This condition has gained importance in the evaluation of patients with liver diseases, especially cirrhosis [3, 4]. It is prevalent in cirrhotic patients and associated with high risk of overt hepatic encephalopathy (OHE) and mortality [4, 5]. Thus, treatment and prevention of sarcopenia are pivotal to improving quality of life and prognosis.

Minimal hepatic encephalopathy (MHE) is a neuropsychiatric abnormality caused by liver insufficiency and portosystemic shunting that involves subtle cognitive deficits such as diminished attention, vigilance, and integrative function [6]. Unlike OHE, MHE lacks overt clinical symptoms, making it difficult to detect in daily practice [6]. MHE is typically diagnosed using neuropsychological tests like the Psychometric Hepatic Encephalopathy Score (PHES), regarded as the gold standard [7]. While OHE affects approximately 15–20% of cirrhotic patients [8], MHE is present in 25–50% of those without OHE [9, 10]. MHE has been shown to impact health-related quality of life and driving skills negatively and is linked to a higher risk of hepatic decompensation and mortality [6, 11, 12]. The severity of liver disease, as indicated by factors such as the Child-Turcotte-Pugh (CTP) score, Model for End-Stage Liver Disease (MELD) score, total bilirubin, international normalized ratio (INR), and albumin levels, is associated with the development of MHE [9, 10, 13]. Emerging evidence suggests that sarcopenia may elevate the risk of MHE [14]. Merli et al. [5] reported an association between MHE and reduced muscle mass measured via mid-arm muscle circumference. Similarly, Hanai et al. [9] identified a link between MHE and sarcopenia, characterized by low muscle mass and strength, though their findings relied on retrospective data. Nardelli et al. [15] supported this association; however, they were limited by a small sample size and reliance on computed tomography-based muscle mass evaluation, emphasizing muscle depletion over other sarcopenia components, thereby restricting their conclusions.

This prospective study employs a comprehensive assessment—integrating muscle mass, strength, and function—to investigate the relationship between sarcopenia and MHE in cirrhotic patients. Additionally, it seeks to determine the prevalence of these conditions, addressing prior limitations and providing a deeper understanding of their interplay to inform clinical management strategies.

Methods

Participants

We prospectively enrolled outpatients aged 18 years or older with liver cirrhosis of any etiology from a specialized liver clinic of a metropolitan tertiary teaching hospital, Siriraj Hospital, from April 2023 to October 2023. Eligible patients had liver cirrhosis as diagnosed based on clinical, biochemical, endoscopic, and radiological data and, if available, liver histology. Patients exhibiting clinical manifestations of OHE according to the West-Haven criteria were excluded. To further confirm the absence of OHE, we administered the Mini-Mental State Examination (MMSE), including only those with scores of 24 or higher [16]. Since fluid overload interferes with body composition assessment, patients with clinically detectable ascites were excluded from the study.

Other exclusion criteria were as follows: history of decompensation events (e.g., OHE, variceal bleeding, spontaneous bacterial peritonitis) within the past 3 months; current use of lactulose, rifaximin, or L-ornithine-l-aspartate; history of liver transplantation; the presence of transjugular intrahepatic portosystemic shunts; neuropsychiatric conditions affecting memory and behavior (e.g., Alzheimer's disease, Parkinson's disease, schizophrenia, cerebrovascular disease, metabolic encephalopathy); use of psychoactive medications (e.g., benzodiazepines, barbiturates, first-generation antihistamines, selective serotonin reuptake inhibitors, and tricyclic antidepressants); uncontrolled decompensated comorbidities (e.g., chronic heart failure at NYHA stages 3–4, end-stage renal disease requiring dialysis, chronic obstructive pulmonary disease classified under Gold D); active infections; active extrahepatic malignancy undergoing chemotherapy; pregnancy; and breastfeeding.

The study protocol was approved by the ethics committee of the Faculty of Medicine Siriraj Hospital (COA no. Si 174/2023) and carried out following the 1975 Declaration of Helsinki. All patients provided written informed consent for participation.

Clinical and laboratory assessment

An interview was initiated to collect data regarding demographics, clinical history, and current daily use of medications. All participants underwent the anthropometric tests, including body weight, height, body mass index (BMI), and waist and hip circumference. Blood samples were obtained from each patient after 12 h of overnight fasting for hematological and biochemical evaluation. Complete blood count, prothrombin time, INR, liver biochemistry (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, albumin, and globulin), creatinine, sodium, and potassium were evaluated by routine laboratory methods. The CTP and MELD scores were calculated to assess liver disease severity. The Bilirubin-Albumin-Beta blocker-Statin (BABS) score was calculated as previously described [17].

All patients underwent liver stiffness measurement (LSM) with transient elastography to define clinically

significant portal hypertension (CSPH) according to the Baveno-VII criteria [18]. Transient elastography (FibroScan® 502 Touch, Echosens, Paris, France) was performed by a single experienced operator. Subjects fasted for at least 3 h before the examination. The elastography results obtained with ten valid measurements with a success rate of ≥ 60% and an interquartile range/median ratio of ≤30% were considered reliable. The liver stiffness was expressed in kilo Pascal (kPa), and CSPH was defined with LSM > 25 kPa [18].

Assessment of minimal hepatic encephalopathy and sleep quality

MHE was evaluated using the validated Thai version of the paper-pencil PHES, which included the digit symbol test (DST), number connection tests (NCT) A and B, serial dotting test (SDT), and line tracing test (LTT) [7]. Scores for each test, ranging from − 3 to + 1, were adjusted for age and educational levels based on Thai normative values. A total PHES score of ≤ -5 indicated MHE [7].

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), with scores above 5 indicating poor sleep quality [19].

Diagnosis of Sarcopenia and severe Sarcopenia

Sarcopenia was diagnosed based on the 2019 criteria from the Asian Working Group for Sarcopenia [2]. Sarcopenia was defined as low muscle mass with either low physical performance or low muscle strength, and severe sarcopenia was defined as low muscle mass with both low physical performance and low muscle strength [2]. Muscle mass was assessed by appendicular skeletal muscle mass (ASM) using bioelectrical impedance analysis (BIA, InBody 770, Cerritos, CA, USA). ASM was calculated as the sum of the muscle mass of the four limbs and was then normalized by the height squared (m^2) to give the skeletal muscle index (SMI, kg/m^2). Low muscle mass was defined as SMI < 7.0 kg/m^2 for men and < 5.7 kg/m^2 for women. Muscle strength was assessed by handgrip strength of the dominant using a digital grip strength dynamometer (Model EH101, Zhongshan Camry Electronic Co., Ltd, China), and low muscle strength was defined as handgrip strength < 28 kg for men and < 18 kg for women. Gait speed was measured via a 6-minute walk test, and low physical performance was defined as gait speed < 1 m/s. BIA-derived whole-body phase angle is considered an index of overall muscle quality. The bioelectrical values with a current at a single frequency of 50 kHz were used to calculate the phase angle.

Statistical analysis

Continuous variables were reported as means with standard deviations or medians (interquartile range) and compared using Student's t-test or Mann–Whitney test, as appropriate. Categorical variables were expressed as percentages and compared using the chi-square or Fisher's exact test. Logistic regression analysis was used to estimate the odds ratio (OR), corresponding to a 95% confidence interval (CI) for factors associated with MHE. Variables with a probability threshold < 0.10 in univariate analysis were included in multivariable analysis with stepwise selection. All statistical tests were conducted at a 2-tailed α level of 0.05 using MedCalc software, version 22 (MedCalc Software Ltd, Ostend, Belgium).

Results

The study population

A total of 220 cirrhotic outpatients were screened, and 10 were excluded due to MMSE scores below 24 (range 15 to 23). Thus, 210 patients were enrolled in the study. Figure 1 illustrates the flow chart of patient selection. The mean age of the participants was 62.7 ± 9.6 years, with 57.1% being male. The MELD score of the cohort was 8.96 ± 2.56. Most patients (92.9%) were classified as CTP class A, while 7.1% were classified as CTP class B. The most common etiology of cirrhosis was hepatitis B virus (42.9%), followed by hepatitis C virus (35.7%), autoimmune liver disease (6.7%), alcohol-related liver disease (6.2%), metabolic dysfunction-associated steatohepatitis (5.7%), and others (2.9%). A history of decompensation events—hepatic encephalopathy, ascites, and variceal hemorrhage—was documented in 2.9%, 13.3%, and 29.0% of cases, respectively, all occurring more than three months before the inclusion period. Nonselective beta-blockers, diuretics, and statins were taken by 21.9%, 6.7%, and 33.3%, respectively. None of the patients received an infusion of human albumin and branched-chain amino acids (BCAAs) supplementation. The median LSM was 17.0 kPa (range 8.1–30.9), with valid LSMs obtained from 203 patients, and 36% of them were diagnosed with CSPH.

Clinical and laboratory characteristics of cirrhotic patients with and without MHE

In this cohort, 37 patients (17.6%) were diagnosed with MHE, with a prevalence of 16.3% in patients with CTP class A and 33.3% in those with CTP class B. MHE was more common in patients with CSPH than those without CSPH (24.7% vs. 13.1%, $p = 0.037$).

Table 1 compares patient characteristics between those with and without MHE. Patients with MHE were older, had lower educational levels, and had a higher frequency of underlying thyroid disease and a history of hepatic decompensation, including OHE and variceal bleeding, compared to those without MHE. There were no significant differences in gender, underlying etiology of cirrhosis, comorbidities (except thyroid disease), medication

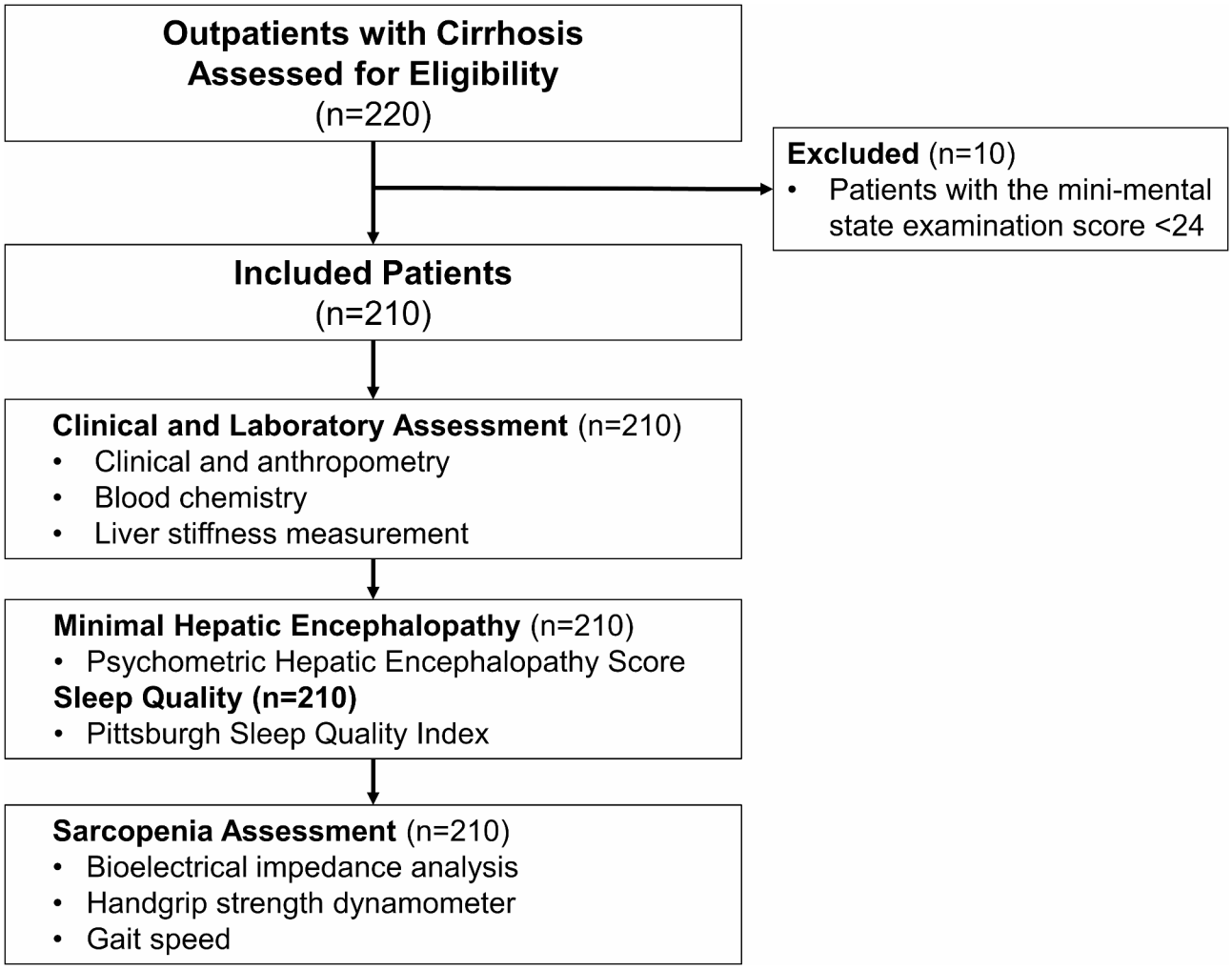

Fig. 1 The flow chart of patient selection and assessment

use, and the severity of liver disease as indicated by CTP and MELD scores. Patients with MHE had significantly higher levels of total bilirubin, globulin, and INR and lower levels of albumin, platelets, and leukocyte counts. BMI, waist and hip circumference, body fat, and visceral fat levels were not significantly different between the groups. Patients with MHE had significantly lower muscle mass, ASM, and SMI than those without MHE. Additionally, they had lower handgrip strength (19.8 ± 6.8 kg vs. 24.0 ± 7.0 kg; $p = 0.001$) and gait speed (0.8 ± 0.2 m/sec vs. 1.0 ± 0.2 m/sec; $p < 0.001$). A lower phase angle was observed in cirrhotic patients with MHE compared to those without MHE (4.2 ± 0.6 vs. 4.6 ± 0.7; $p = 0.001$).

Figure 2A shows that the mean PSQI scores for patients with MHE and non-MHE were 8.8 ± 4.4 and 8.1 ± 3.6, respectively ($p = 0.297$). Similarly, there was no significant difference in the prevalence of MHE between patients with poor and good sleep quality (Fig. 2B). The mean BARB scores also did not differ between patients with and without MHE (Fig. 2C). However, there was a trend toward higher MHE prevalence across low (< 0), intermediate (0–20), and high BARB (> 20) scores (p for trend = 0.065) (Fig. 2D).

Sarcopenia and sarcopenic components

The mean SMI of the study cohort was 6.9 ± 1.2 kg/m^2, the mean handgrip strength was 23.3 ± 7.2 kg, and the mean gait speed was 1.0 ± 0.2 m/sec. Low SMI, low muscle strength, and low physical performance were observed in 29.5%, 78.6%, and 39.5% of the study cohort, respectively. Sarcopenia was presented in 54 patients (25.7%), with 26 (12.3%) classified as having severe sarcopenia. Patients aged over 65 years had a higher prevalence of sarcopenia compared to those under 65 years (32.6% vs. 20.3%; $p = 0.044$). No statistical difference in the prevalence of sarcopenia was evident between men and women (21.7% vs. 31.1%; $p = 0.122$).

Table 2 compares anthropometric data, sleep quality, and PHES of cirrhotic patients with and without sarcopenia. Patients with sarcopenia had significantly lower

Table 1 Characteristics of cirrhotic patients with and without minimal hepatic encephalopathy

	Total (*n* = 210)	**MHE (*n* = 37)**	**Non-MHE (*n* = 173)**	***P* value**
Age, years	62.7 ± 9.6	67.4 ± 8.0	61.7 ± 9.6	0.001
Female, n (%)	90 (42.9)	20 (54.1)	70 (40.5)	0.130
Education level, n (%)				0.007
Primary school	63 (30.0)	19 (51.4)	44 (25.4)	
High school	82 (39.0)	11 (29.7)	71 (41.0)	
University	65 (31.0)	7 (18.9)	58 (33.5)	
Etiology of cirrhosis, n (%)				0.105
Hepatitis B virus	90 (42.9)	13 (35.1)	77 (44.5)	
Hepatitis C virus	75 (35.7)	13 (35.1)	62 (35.8)	
Alcohol	13 (6.2)	2 (5.4)	11 (6.4)	
MASLD	12 (5.7)	4 (10.8)	8 (4.6)	
Autoimmune liver disease	14 (6.7)	5 (13.5)	9 (5.2)	
Others	6 (2.9)	0 (0)	6 (3.5)	
Comorbidity, n (%)				
Type 2 diabetes mellitus	72 (34.3)	13 (35.1)	59 (34.1)	0.905
Hypertension	114 (54.3)	16 (43.2)	98 (56.6)	0.138
Hypercholesterolemia	75 (35.7)	11 (29.7)	64 (37.0)	0.404
Chronic pulmonary disease	10 (4.8)	2 (5.4)	8 (4.6)	0.840
Thyroid disease	17 (8.1)	6 (16.2)	11 (6.4)	0.047
Extrahepatic malignancy	16 (7.6)	2 (5.4)	14 (8.1)	0.577
Hepatocellular carcinoma	101 (48.1)	29 (53.7)	72 (46.2)	0.340
History of decompensation†, n (%)				
Ascites	28 (13.3)	7 (18.9)	21 (12.1)	0.272
Overt hepatic encephalopathy	6 (2.9)	3 (8.1)	3 (1.7)	0.035
Variceal hemorrhage	61 (29.0)	19 (51.4)	42 (24.3)	0.001
Medication use				
Nonselective beta-blockers	46 (21.9)	9 (24.3)	37 (21.4)	0.696
Diuretics	14 (6.7)	2 (5.4)	12 (6.9)	0.735
Statins	70 (33.3)	11 (29.7)	59 (34.1)	0.609
Anthropometry data				
BMI, kg/m^2	26.1 ± 5.0	25.8 ± 4.4	26.2 ± 5.1	0.668
Waist circumference, cm	91.4 ± 12.9	90.9 ± 11.1	91.5 ± 13.3	0.813
Hip circumference, cm	98.6 ± 10.4	98.6 ± 9.3	98.6 ± 10.7	0.994
Body fat, kg	24.7 ± 9.9	24.6 ± 8.0	24.8 ± 10.3	0.909
Visceral fat level	11.7 ± 4.9	12.2 ± 4.6	11.6 ± 4.9	0.520
Muscle mass, kg	23.3 ± 5.4	21.4 ± 5.1	23.7 ± 5.4	0.016
Appendicular skeletal muscle, kg	18.3 ± 4.7	16.6 ± 4.6	18.6 ± 4.7	0.018
Skeletal muscle index, kg/m^2	6.9 ± 1.2	6.5 ± 1.2	7.0 ± 1.2	0.030
Laboratory data				
Hemoglobin, g/dl	13.1 ± 1.8	12.8 ± 1.6	13.1 ± 1.9	0.364
Leukocyte, cell/mm	5,584 ± 1,750	4,927 ± 1,674	5,739 ± 1,737	0.012
Platelet, 10^6 cell/mm^3	147 ± 66	126 ± 59	152 ± 66	0.028
Aspartate aminotransferase, U/L	39 ± 23	43 ± 26	38 ± 22	0.283
Alanine aminotransferase, U/L	29 ± 17	26 ± 15	29 ± 17	0.283
Gamma-glutamyltransferase, U/L	48 (29–75)	51 (21–82)	45 (30–74)	0.869
Total bilirubin, mg/dl	0.7 (0.5–1.1)	0.9 (0.6–1.3)	0.7 (0.5-1.0)	0.045
Albumin, g/dl	4.1 ± 0.5	3.9 ± 0.5	4.1 ± 0.5	0.026
Globulin, g/dl	3.7 ± 0.6	4.0 ± 0.7	3.7 ± 0.6	0.029
INR	1.13 ± 0.13	1.16 ± 0.13	1.12 ± 0.13	0.181
Creatinine, mg/dl	0.94 ± 0.27	0.92 ± 0.27	0.94 ± 0.27	0.704
Sodium, mEq/L	139.0 ± 2.7	139.2 ± 3.4	138.9 ± 2.6	0.661
Potassium, mEq/L	4.2 ± 0.4	4.3 ± 0.5	4.2 ± 0.4	0.461

Table 1 (continued)

	Total (*n* = 210)	MHE (*n* = 37)	Non-MHE (*n* = 173)	*P* value
MELD score	9.0 ± 2.6	9.3 ± 2.3	8.9 ± 2.6	0.376
CTP score	5.3 ± 0.6	5.1 ± 0.3	5.2 ± 0.6	0.212
Liver stiffness, kPa	17.0 (8.1–30.9)	26.7 (8.6–35.2)	16.2 (8.1–29.4)	0.234

Abbreviations: CTP, Child-Turcotte-Pugh; INR, international normalized ratio; MASLD, Metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; MHE, minimal hepatic encephalopathy

[†]History of decompensation events occurring more than three months prior to the inclusion period

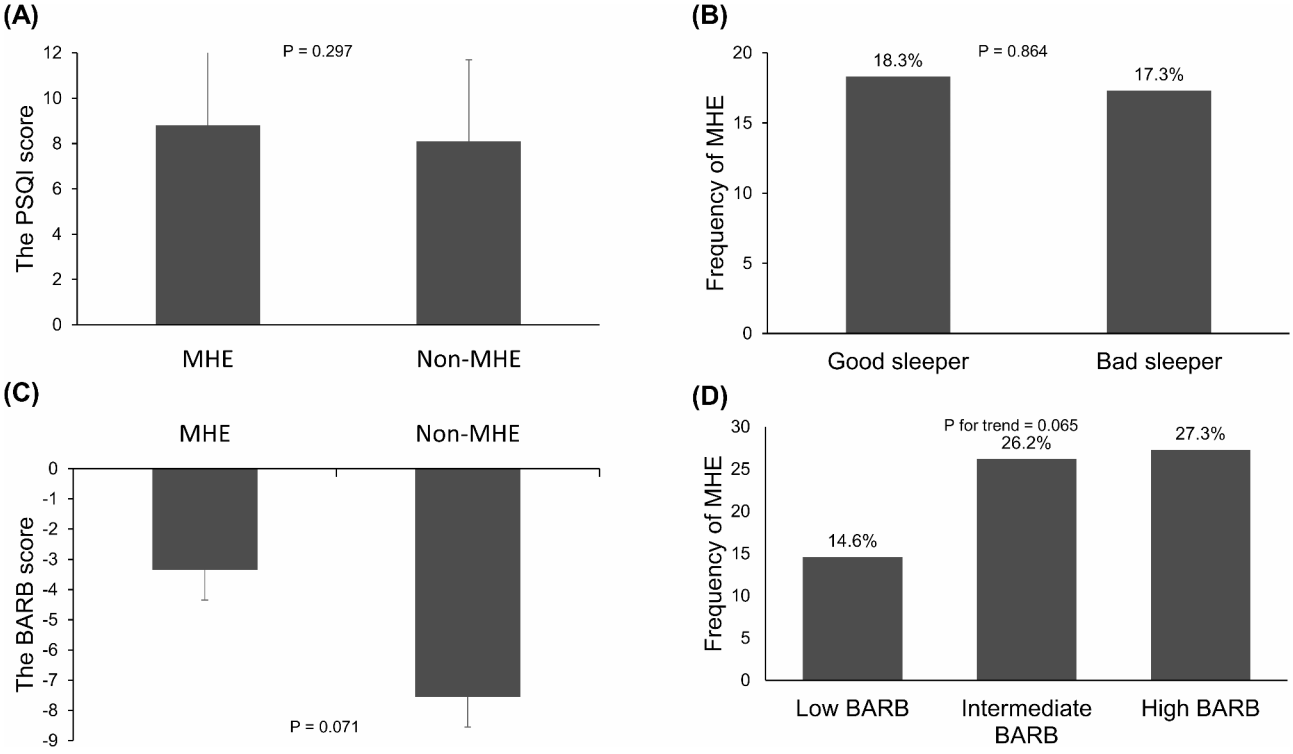

Fig. 2 Association between MHE, Sleep Quality, and BARB Score in Cirrhotic Patients. (**A**) Comparison of PSQI scores between cirrhotic patients with and without MHE; (**B**) Frequency of MHE among patients classified as good or poor sleepers; (**C**) Comparison of BARB scores between cirrhotic patients with and without MHE; (**D**) Frequency of MHE among patients with low, intermediate, and high BARB scores

BMI, waist and hip circumference, body fat, visceral fat levels, muscle mass, ASM, and SMI than those without sarcopenia. No significant difference in the PSQI scores was observed between patients with and without sarcopenia. Psychometric test scores, including total PHES, NCT A, NCT B, SDT, and LTT, were significantly lower in the sarcopenic group. Figure 3 illustrates the frequency of MHE stratified by the presence of sarcopenia and sarcopenic components. The proportion of MHE in patients with and without sarcopenia was 31.5% and 12.8%, respectively ($p = 0.002$). The presence of low SMI and slow gait speed was significantly associated with a higher frequency of MHE (Fig. 3B and D). However, no significant difference in MHE prevalence was observed between patients with normal and weak handgrip strength (Fig. 3C).

Association between MHE and Sarcopenia in patients with cirrhosis

As shown in Table 3, univariate regression analysis revealed significant associations between MHE and age ($p = 0.001$), education levels ($p = 0.009$), history of variceal bleeding ($p = 0.001$), muscle mass ($p = 0.018$), whole-body phase angle ($p = 0.002$), sarcopenia ($p = 0.003$), and MMSE score ($p = 0.021$). Multivariable logistic regression analysis, which included variables with p-values less than 0.10 from the univariate analysis, indicated that age (adjusted odds ratio [aOR] 1.08, 95% CI 1.02–1.13), sarcopenia (aOR 3.29, 95% CI 1.44–7.50), history of OHE (aOR 7.40, 95% CI 1.20-45.56), and variceal bleeding (aOR 3.13, 95% CI 1.38–7.10) were independently associated with the presence of MHE. Similarly, when using severe sarcopenia instead of sarcopenia in the multivariable model,

Table 2 Anthropometric data, sleep quality, and psychometric hepatic encephalopathy score of cirrhotic patients with and without Sarcopenia

	Total (*n* = 210)	Sarcopenia (*n* = 54)	No sarcopenia (*n* = 156)	*P* value
Anthropometric data				
Body mass index, kg/m^2	26.1 ± 5.0	22.4 ± 3.6	27.4 ± 4.7	< 0.001
Waist circumference, cm	91.4 ± 12.9	82.9 ± 9.3	94.3 ± 12.7	< 0.001
Hip circumference, cm	98.6 ± 10.4	91.6 ± 8.7	101.1 ± 9.9	< 0.001
Body fat, kg	24.7 ± 9.9	19.7 ± 7.6	26.5 ± 10.1	< 0.001
Visceral fat level	11.7 ± 4.9	10.2 ± 4.8	12.3 ± 4.8	0.005
Muscle mass, kg	23.3 ± 5.4	18.8 ± 3.6	24.9 ± 5.1	< 0.001
Appendicular skeletal muscle, kg	18.3 ± 4.7	14.3 ± 3.2	19.7 ± 4.4	< 0.001
Skeletal muscle index, kg/m^2	6.9 ± 1.2	5.7 ± 0.8	7.3 ± 1.1	< 0.001
Sleep quality				
PSQI score	8.20 ± 3.74	8.11 ± 3.92	8.23 ± 3.69	0.840
Psychometric hepatic encephalopathy score				
Total score	-2.17 ± 2.45	-3.20 ± 2.65	-1.81 ± 2.28	< 0.001
DST score	-0.34 ± 0.58	-0.43 ± 0.57	-0.31 ± 0.59	0.199
NCT A score	-0.52 ± 0.82	-0.80 ± 0.94	-0.43 ± 0.75	0.011
NCT B score	-1.11 ± 1.08	-1.48 ± 1.06	-0.99 ± 1.07	0.004
SDT score	-0.10 ± 0.42	-0.28 ± 0.45	-0.03 ± 0.38	< 0.001
LTT score	-0.10 ± 0.49	-0.22 ± 0.57	-0.05 ± 0.45	0.049

Abbreviations: DST, digit symbol test; LTT, the line tracing test; NCT A, number connection tests A; NCT B, number connection tests B; PSQI, Pittsburgh Sleep Quality Index; SDT, serial dotting test

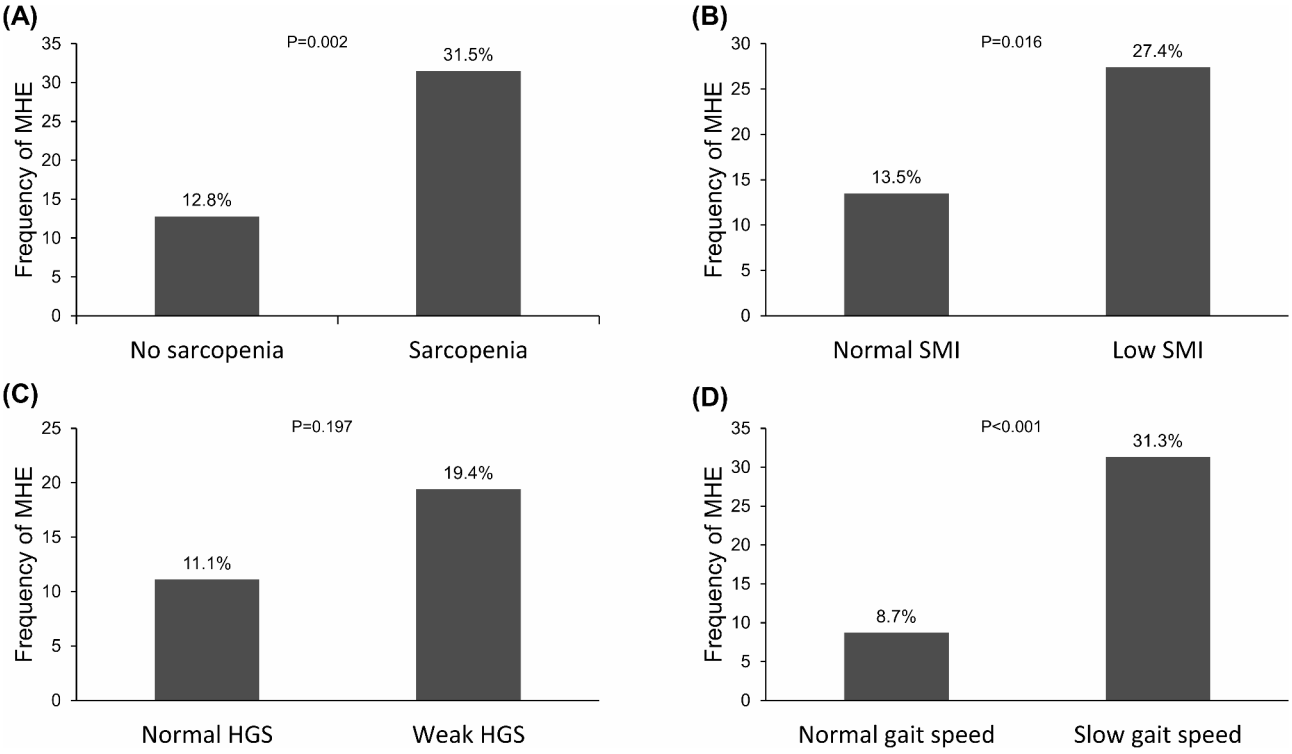

Fig. 3 Frequency of MHE in Cirrhotic Patients with Sarcopenia. (**A**) Frequency of MHE in cirrhotic patients with and without sarcopenia; (**B**) Frequency of MHE in patients with normal versus low skeletal muscle index (SMI); (**C**) Frequency of MHE in patients with normal versus weak handgrip strength (HGS); (**D**) Frequency of MHE in patients with normal versus slow gait speed

Table 3 Factors associated with minimal hepatic encephalopathy in cirrhotic patients

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Age, year	1.08 (1.03–1.13)	0.001	1.08 (1.02–1.13)	0.005
Female gender	1.73 (0.85–3.54)	0.132		
Education level				
Primary school	reference			
High school	0.36 (0.16–0.82)	0.016		
University	0.28 (0.11–0.72)	0.009		
Anthropometric data				
Body mass index, kg/m^2	0.98 (0.91–1.06)	0.666		
Waist circumference, cm	0.99 (0.96–1.02)	0.812		
Hip circumference, cm	0.99 (0.97–1.03)	0.994		
Body fat, kg	0.99 (0.96–1.03)	0.908		
Visceral fat level	1.02 (0.95–1.10)	0.518		
Muscle mass, kg	0.92 (0.85–0.98)	0.018		
Whole body phase angle	0.42 (0.24–0.72)	0.002		
Sarcopenia	3.12 (1.49–6.56)	0.003	3.29 (1.44–7.50)	0.005
Etiology of cirrhosis				
Hepatitis B virus	0.68 (0.32–1.41)	0.298		
Hepatitis C virus	0.97 (0.46–2.04)	0.935		
Alcohol	0.84 (0.18–3.97)	0.827		
Comorbidity				
Type 2 diabetes mellitus	1.05 (0.50–2.20)	0.905		
Hypertension	0.58 (0.28–1.19)	0.140		
Hypercholesterolemia	0.72 (0.33–1.56)	0.404		
Chronic pulmonary disease	1.18 (0.24–5.79)	0.840		
Thyroid disease	2.85 (0.98–8.28)	0.054		
Extrahepatic malignancy	0.65 (0.14–2.99)	0.579		
Hepatocellular carcinoma	1.17 (0.58–2.38)	0.663		
History of decompensation				
Ascites	1.69 (0.66–4.33)	0.275		
Overt hepatic encephalopathy	5.00 (0.97–25.83)	0.055	7.40 (1.20-45.56)	0.031
Variceal hemorrhage	3.29 (1.58–6.85)	0.001	3.13 (1.38–7.10)	0.006
Medication use				
Nonselective beta-blockers	1.18 (0.51–2.72)	0.695		
Diuretics	0.77 (0.16–3.58)	0.735		
Statins	0.82 (0.38–1.77)	0.609		
MELD score	1.07 (0.92–1.24)	0.376		
CTP score	1.38 (0.85–2.24)	0.194		
Liver stiffness ≥ 25 kPa	2.18 (1.04–4.55)	0.039		
Mini-mental state examination score	0.77 (0.62–0.96)	0.021		
PSQI score	1.05 (0.96–1.16)	0.296		
BARB score				
Low risk (< 0)	Reference			
Intermediate risk (0–20)	2.07 (0.91–4.68)	0.082		
High risk (> 20)	2.18 (0.54–8.85)	0.274		

Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh; PSQI, HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; OR, odds ratio; PSQI, Pittsburgh sleep quality index

severe sarcopenia remained an independent factor associated with MHE (aOR 3.64, 95% CI 1.32–10.05).

Discussion

This study examined the relationship between MHE and sarcopenia in 210 cirrhotic outpatients. We found that MHE was present in 17.6% of patients, while 25.7% had sarcopenia, including 12.3% with severe sarcopenia. Sarcopenia was more prevalent in older patients, and those with MHE had significantly lower muscle mass, muscle strength, and physical performance. Age, sarcopenia, history of OHE, and variceal bleeding were significant risk factors for MHE. The findings highlight sarcopenia as a critical risk factor for MHE in cirrhotic patients.

Hepatic encephalopathy is a devastating complication of liver cirrhosis, significantly impairing cognitive function and quality of life [20]. It has been shown that patients with MHE are at increased risk of progressing to OHE [21]. Detection and treatment of MHE are essential to prevent cognitive decline, emphasizing the need for routine screening in cirrhotic patients. The diagnosis of MHE is currently made by performing specialized psychometric testing. Our study using the PHES found an MHE prevalence of 18%, lower than the reported 25–50% range [7, 9, 10], possibly due to stricter diagnostic criteria and the predominance of patients in CTP class A. Specifically, our stringent exclusion of OHE using MMSE scores and the inclusion of a higher proportion of patients (90%) in CTP class A likely contributed to this discrepancy. Our findings of 16% MHE prevalence in CTP A patients are consistent with other studies reporting 15–20% [7, 9, 22]. Variations in prevalence across studies are likely due to differences in diagnostic methods and patient selection criteria.

We found significant relationships between MHE and several patients' characteristics. Age and education level remained significant factors, even after adjusting for these variables in the PHES. Younger patients with higher education levels may have greater cognitive reserve, providing some protection against MHE, akin to other cognitive disorders like dementia [23]. Consistent with previous research [9, 13], our study also showed that patients with MHE had more severe liver disease indicators, such as higher total bilirubin and INR and lower albumin levels. However, in logistic regression analysis, neither CTP nor MELD scores emerged as significant predictors of MHE. This may be due to most participants being classified as CTP class A, which limited the variability of both CTP and MELD scores. Nevertheless, a history of decompensation events, including OHE and variceal bleeding, was strongly associated with MHE, emphasizing that advanced liver disease plays a significant role in MHE development. This aligns with earlier studies [7, 10], highlighting the importance of careful monitoring and early intervention for these patients.

Growing evidence indicates that sarcopenia is prevalent among cirrhotic patients and negatively impacts their prognosis and mortality [24–27]. While computed tomography is commonly used to estimate muscle mass at the third lumbar vertebrae, its limitations—such as availability, radiation exposure, and cost—necessitate alternative methods [28]. BIA provides a simpler, safer, and more affordable way to measure the SMI, aiding sarcopenia diagnosis in cirrhosis [29]. Combining BIA with assessing muscle strength (handgrip) and physical performance (gait speed) allows for comprehensive muscle health evaluation, enabling timely diagnosis and management of sarcopenia. Our study excluded patients with clinically significant fluid retention and ascites to minimize the limitations of BIA. However, patients with a history of ascites, who effectively managed with low-dose diuretics, were not excluded. This approach allowed us to include a broader cirrhotic population while avoiding the confounding effects of significant fluid retention. Using BIA, handgrip strength, and gait speed, we found a 26% sarcopenia prevalence, consistent with previous reports of 26–34% in cirrhotic patients [9, 30]. The higher prevalence of sarcopenia in cirrhotic patients compared to the general population (10%) is expected [31] due to mechanisms in advanced liver disease that accelerate muscle loss, including imbalanced protein metabolism, hormonal changes and malnutrition [32, 33].

Our study found that sarcopenia significantly increases the risk of MHE in cirrhotic patients, with an adjusted OR of 3.29. This finding is consistent with a meta-analysis of three studies showing a pooled OR of 3.34 (95% CI 1.68–6.67) [14]. All sarcopenic indices, including SMI, handgrip strength, and gait speed, were significantly lower in cirrhotic patients with MHE. Additionally, a lower phase angle derived from BIA was observed in the MHE group, supporting sarcopenia as a predictor of MHE [34, 35]. The mechanism linking sarcopenia to MHE likely involves reduced skeletal muscle mass leading to decreased glutamine synthetase activity, impairing ammonia metabolism, and causing hyperammonia [14, 36], which disrupts astrocyte function and contributes to hepatic encephalopathy [37]. Conversely, hyperammonemia can inhibit protein synthesis by increasing myostatin via nuclear factor-κB, further exacerbating muscle loss [38]. A deficiency of BCAAs, crucial for maintaining muscle mass and strength, is also involved [39]. While BCAA supplementation may improve sarcopenia parameters, the results are inconsistent [40]. Due to resource limitations and the variability of routine clinical practice, we did not measure serum ammonia or BCAA levels. Future studies should incorporate these parameters for a more thorough understanding. Furthermore, a prior

history of OHE and variceal hemorrhage were significantly associated with higher MHE risk, suggesting that advanced liver disease and significant portal hypertension exacerbate ammonia levels, promoting MHE. Our findings emphasize the need for comprehensive muscle health assessments and interventions to mitigate MHE risk in managing cirrhotic patients.

Stratifying patients for the risk of OHE by identifying MHE is crucial, as recommended by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism [12]. Although the PHES is the gold standard for detecting cognitive dysfunction in liver disease, its complexity and cost make it impractical for routine use. Implementing simpler, validated tests is essential. Our study found no significant difference in PSQI scores between MHE and non-MHE patients, indicating that sleep quality is not a reliable marker. Risk scores like the BABS score are valuable in clinical practice [17]. However, our results exhibited only a trend toward increased MHE prevalence with higher BABS scores, highlighting the need for more refined risk stratification tools. Point-of-care tests could enhance MHE screening in outpatient settings, broadening the scope of early detection and intervention [41, 42].

Our study has several important strengths that distinguish it from previous research on the relationship between sarcopenia and MHE in cirrhotic patients. Using the 2019 Asian Working Group for Sarcopenia criteria, which assesses muscle mass, strength, and function, our approach provides a more comprehensive evaluation than earlier studies focusing mainly on muscle mass [5, 9, 15]. Furthermore, our study addresses a gap in the literature by focusing on an Asian population, offering valuable regional insights into the prevalence and clinical significance of sarcopenia and MHE. A key methodological strength is the prospective design, which allowed for comprehensive data collection and minimized data loss. We utilized standardized diagnostic criteria for MHE and sarcopenia, reducing misclassification risk. Extensive adjustments for potential confounders between MHE and sarcopenia support the validity of our observed associations. However, limitations include the predominance of milder cirrhosis cases (90% CTP class A) due to strict eligibility criteria, which may not reflect the broader cirrhotic population with more advanced disease. Additionally, the cross-sectional nature of the study precludes establishing causality between sarcopenia and MHE.

In conclusion, this study demonstrates that sarcopenia is a significant and independent risk factor for MHE in cirrhotic patients. The findings emphasize the importance of assessing and addressing sarcopenia in this patient population to potentially mitigate the risk of MHE. Clinically, routine screening for sarcopenia should be incorporated into the management of cirrhotic patients, and interventions to improve muscle mass and function could be beneficial. Further research should evaluate the efficacy of specific nutritional and physical interventions in reducing the incidence of MHE in cirrhotic patients with sarcopenia.

Abbreviations

aOR	Adjusted odds ratio
ASM	Appendicular skeletal muscle mass
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CI	Confidence interval
CSPH	Clinically significant portal hypertension
CTP	Child-Turcotte-Pugh
BABS	Bilirubin-albumin-beta blocker-statin
DST	Digit symbol test
INR	International normalized ratio
kPa	Kilo Pascal
LSM	Liver stiffness measurement
LTT	Line tracing test
MELD	Model for end-stage liver disease
MHE	Minimal hepatic encephalopathy
MMSE	Mini-mental state examination
NCT	Number connection tests
OHE	Overt hepatic encephalopathy
OR	Odds ratio
PSQI	Pittsburgh sleep quality index
SDT	Serial dotting test
SMI	Skeletal muscle index

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Author contributions
All authors contributed to the study conception and design. Data acquisition was performed by Wasit Wongtrakul and Wimolrak Bandidniyamanon. Statistical analysis was performed by Phunchai Charatcharoenwitthaya. The first draft of the manuscript was written by Wasit Wongtrakul. Phunchai Charatcharoenwitthaya commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The dataset that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate
The research was performed according to the Declaration of Helsinki and approved by the ethics committees of the Faculty of Medicine Siriraj Hospital. All subjects provided informed written consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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