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Impact of pre-sarcopenia on outcomes of transarterial chemoembolization in unresectable hepatocellular carcinoma

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Sarcopenia's impact on hepatocellular carcinoma (HCC) outcomes is well-documented, but the effects of pre-sarcopenia remain unclear. This study investigates the impact of pre-sarcopenia on tumor response and survival in patients with unresectable HCC undergoing transarterial chemoembolization (TACE). We retrospectively evaluated muscle volume using the SliceOmatic software in patients with unresectable HCC treated with TACE. Pre-sarcopenia was defined by Japan Society of Hepatology standards (men: 42 cm^2/m^2; women: 38 cm^2/m^2). Pre-sarcopenia and non-pre-sarcopenia groups were compared, and Cox proportional hazards model was used to identify survival-influencing variables. Subgroup analysis was conducted stratified by the tumor burden, using serum alpha-fetoprotein (AFP) levels at a diagnostic cutoff value of 200 ng/mL. Of the 100 patients, 39 had pre-sarcopenia. The presence of pre-sarcopenia was not associated with tumor complete response achievement. The median overall survival (OS) was significantly lower in the pre-sarcopenia group (18 months) than in the non-pre-sarcopenia group (30 months; log-rank $P = 0.039$). Subgroup analysis among 77 patients with AFP < 200 ng/mL revealed that OS was particularly poor in the pre-sarcopenia group (16 vs. 34 months; log-rank $P < 0.001$). Multivariate analysis identified increased AFP (adjusted hazard ratio [HR] per 10-unit increase 1.142; $P < 0.001$), higher Model for End-Stage Liver Disease score (adjusted HR per 1-unit increase 1.176; $P < 0.001$), and pre-sarcopenia (adjusted HR 2.965; $P < 0.001$) as predictors of shorter OS. Pre-sarcopenia is a significant predictor of increased mortality in patients with unresectable HCC undergoing TACE, especially in those with AFP < 200 ng/mL, suggesting its potential as a target for early intervention.

Keywords Hepatocellular carcinoma, Muscle mass, Pre-sarcopenia, Survival, Transarterial chemoembolization

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer-related deaths worldwide[1]. The prognosis of HCC remains poor despite improvements in therapy; this may be because most HCC patients exhibit an advanced stage at diagnosis, leaving palliative treatment as their only option[2,3]. Transarterial chemoembolization (TACE) is currently the mainstream therapeutic strategy for patients with unresectable HCC with preserved liver function[2,3]. The prognosis following TACE primarily depends on both tumor- and host-related factors: hepatic function and the patient's general condition are important influencing factors[4,5].

Sarcopenia is defined as the loss of skeletal muscle mass and functional capacity (including muscle strength or physical function), whereas pre-sarcopenia is specifically defined as low muscle mass without an impact on muscle strength. Sarcopenia is classified as either primary (associated with aging) or secondary (associated with chronic illness)[6]. HCC is closely associated with chronic liver disease and cirrhosis[7], and is often associated with protein-energy malabsorption and sarcopenia[8]. Thus, unsurprisingly, the prevalence of sarcopenia in patients with HCC is high[9,10]. Notably, sarcopenia has attracted attention as a predictor of poor prognoses in patients

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with HCC. In recent years, evidence has increasingly supported the negative impact of reduced muscle mass on the clinical outcomes of patients with chronic liver disease and HCC[11–15]. Several studies have demonstrated the negative impact of sarcopenia on the prognosis of patients with HCC after treatment. However, data on the effect of pre-sarcopenia on the survival outcomes of patients with HCC remain limited. The presence of pre-sarcopenia has been shown to correlate with a poor prognosis in patients with HCC after radiofrequency ablation and sorafenib treatment[16–18]. Nevertheless, information on the prevalence and significance of pre-sarcopenia in patients with unresectable HCC treated with TACE is limited, and no previous study has evaluated the impact of pre-sarcopenia on treatment outcome.

Therefore, the present study aimed to investigate the impact of pre-sarcopenia on treatment response and survival outcomes in patients with unresectable HCC who underwent conventional TACE.

Methods

Study design

This retrospective, single-center, observational cohort analysis was conducted at Hatyai Hospital, a leading referral center in southern Thailand, from January 2014 to December 2021. The Institutional Review Board of the Hatyai Hospital (Human Research Ethics Committee Hatyai Hospital, approval number HYH EC 019-65-01) approved this study and waived the requirement for obtaining informed consent because of its retrospective nature. This study adhered to the ethical principles outlined in the Declaration of Helsinki. All data were anonymized prior to analysis to maintain patient confidentiality.

Patient population

Eligible participants were individuals aged 18 years and older, diagnosed with HCC based on histological evidence or non-invasive criteria, presenting with unresectable disease or contraindications for surgical resection, and who underwent TACE as the initial treatment modality. Included patients were at Barcelona Clinic Liver Cancer (BCLC) stage 0, A, B, or C. We excluded patients who underwent any curative treatment post-initial TACE and those with infiltrative tumor types; incomplete abdominal computed tomography (CT) examination including L3; renal, cerebral, or cardiopulmonary dysfunction; Child–Turcotte–Pugh (CTP) stage C; extrahepatic metastasis at diagnosis; or incomplete datasets.

Data collection

Data were retrospectively compiled, including clinical and anthropometric parameters at diagnosis (age, sex, body mass index [BMI], comorbidities, hepatitis infection status, alcohol consumption history, laboratory findings, and tumor characteristics) and clinical outcomes (total number of treatments and post-treatment response). Data acquisition was performed by two independent investigators, each with more than a decade of experience in hepatology, ensuring consensus to reconcile any discrepancies.

Skeletal mass index and pre-sarcopenia definition

Skeletal muscle evaluation was conducted using CT scans at the time of diagnosis, focusing on the third lumbar vertebra level where the transverse processes were distinctly visible. The total cross-sectional muscle area (cm^2) was quantified using SliceOmatic version 5.0 software (Tomovision, Montreal, QC, Canada) by demarcating the muscular boundaries within Hounsfield unit (HU) thresholds of − 29 to + 150[19]. The psoas, erector spinae, quadratus lumborum, transversus abdominis, external oblique, internal oblique, and rectus abdominis muscles were analyzed[20]. The skeletal muscle index (SMI) was calculated as the aggregate muscle area divided by height squared[21]. Based on the sarcopenia criteria for liver disease proposed by the Japan Society of Hepatology[22], the threshold for pre-sarcopenia was defined as an SMI below 42 cm^2/m^2 for men and below 38 cm^2/m^2 for women. Based on these criteria, patients were classified into "pre-sarcopenia" and "non-pre-sarcopenia" cohorts.

Treatment and assessment of tumor response

After deliberation by a multidisciplinary team, TACE was performed on eligible patients. This decision-making process involved achieving a consensus between healthcare professionals and patients, adhering to established local protocols[23]. Following TACE, the assessment of treatment response was systematically conducted 4-weeks post-procedure via multiphasic hepatic CT scans or magnetic resonance imaging (MRI) in accordance with the modified Response Evaluation Criteria in Solid Tumors[24].

In alignment with the European guidelines on HCC management[2], the option to repeat TACE was considered 2 months after the initial treatment if a partial response was observed on post-treatment imaging with preserved hepatic function. This decision was contingent upon re-evaluation by a multidisciplinary tumor board. Patients who achieved a complete response (CR) underwent routine surveillance involving dynamic contrast-enhanced CT or MRI and serum alpha-fetoprotein (AFP) measurement every 3 months during the first year after treatment, transitioning to biannual follow-up provided no indications of HCC recurrence were found.

Definitions and outcomes

HCC was diagnosed in accordance with the international diagnostic criteria by employing the Barcelona Clinic Liver Cancer (BCLC) system for tumor staging[2,3]. Viral hepatitis was diagnosed based on serological evidence of hepatitis B virus (HBV) surface antigen or hepatitis C virus (HCV) antibody, further confirmed by the detection of HBV DNA or HCV RNA. Alcohol-related liver disease was determined in cases in which individuals had documented daily alcohol consumption of at least 40 g over a period of 5 years[25,26]. The diagnosis of cirrhosis was substantiated by clinical features, radiological findings, and/or histopathological examination. Portal

hypertension was defined as the presence of one or more of the following: ascites, esophageal or gastric varices, or splenomegaly, with a platelet count < 100,000/mm^3. Hepatic function was appraised using CTP and Model for End-Stage Liver Disease (MELD) scores[27,28]. The Eastern Cooperative Oncology Group Performance Status scale was utilized to categorize patient's functional status[29].

Overall survival (OS) was defined as the interval from the HCC diagnosis date to the endpoint of either mortality or the most recent follow-up. We determined patients' vitality status at the time of data censoring (January 1, 2023) using records obtained from the Thai civil registration system.

Statistical analyses

Qualitative variables are expressed as numbers and percentages and were tested for equality using Pearson's χ^2 test or Fisher's exact test. All quantitative data were presented as mean ± standard deviation (SD) or median and interquartile range, depending on their distribution. The significance of differences between groups was established using Student's *t*-test or the Wilcoxon rank-sum test, as appropriate. Logistic regression analyses were performed to determine factors affecting CR achievement. OS rates were estimated using the non-parametric Kaplan–Meier method, and group differences were evaluated using the log-rank test. A Cox proportional hazards model was used to explore the potential impact of pre-sarcopenia on survival outcomes. Hazard ratios (HR) and 95% confidence intervals (95% CIs) were calculated. After univariate analysis, variables with a p-value < 0.1, along with age and sex, were incorporated into a multivariate analysis framework (utilizing backward selection methodology). All statistical evaluations were conducted using Stata Version 15.1 (StataCorp LLC, College Station, TX, USA), with a predetermined alpha level of 0.05 denoting statistical significance.

Ethical approval

Ethical approval was obtained from the Ethics Committee of Hatyai Hospital (HYH EC 019–65-01). The need for obtaining informed consent was waived due to the nature of the study.

Results

Patient characteristics

One hundred patients diagnosed with HCC fulfilled the inclusion criteria and were enrolled in the study. The cohort's mean age was 58.8 ± 11.2 years, with females constituting 25% (n = 25) of the population. BCLC staging revealed 4% (n = 4) at stage 0, 22% (n = 22) at stage A, 69% (n = 69) at stage B, and 5% (n = 5) at stage C. Regarding baseline liver functionality, 57% (n = 57) of patients were classified as CTP grade A, whereas 43% (n = 43) were classified as grade B. Pre-sarcopenia was identified in 39 (39%) patients.

Tables 1 and 2 show the demographic data, tumor characteristics, and treatment outcomes of the entire cohort, along with a comparative analysis between patients with and without pre-sarcopenia. Notably, significant differences in BMI and serum albumin levels were observed between patients with and without pre-sarcopenia. Specifically, BMI was significantly lower in the pre-sarcopenia (mean ± SD = 22.0 ± 4.8 kg/m^2) than in the non-pre-sarcopenia group (mean ± SD = 25.5 ± 4.0 kg/m^2, $P < 0.001$). Similarly, serum albumin levels were lower in the pre-sarcopenia group (mean ± SD = 3.2 ± 0.7 g/dL) than in their non-sarcopenia counterpart (mean ± SD = 3.5 ± 0.6 g/dL, P = 0.049). Other baseline characteristics, including sex, age, laboratory results, HCC status, serum biomarkers, and the number of TACE sessions, did not differ significantly between the groups.

Post-treatment tumor response and factors for achieving CR

Additionally, the analysis revealed that the proportion of patients who achieved CR after treatment did not differ significantly between the pre-sarcopenia and non-pre-sarcopenia groups. Furthermore, the presence of pre-sarcopenia was not associated with CR achievement after treatment in multivariate logistic regression analysis (Table S1 in Supplementary Information).

Relationship between pre-sarcopenia before TACE and survival

Based on the Kaplan–Meier method, the median OS in the pre-sarcopenia group was significantly lower at 18 months when compared to the 30 months in the non-pre-sarcopenia group (log-rank $P = 0.039$). (Fig. 1). Table 3 shows the prognostic factors for OS in the univariate and multivariate analyses. The multivariate analysis revealed that only the MELD score was significantly associated with decreased survival (adjusted hazard ratio [HR] per 1-unit increase 1.117; $P = 0.001$).

Impact of pre-sarcopenia before TACE on OS after stratification by tumor burden

Analyses were also conducted on subgroups of patients stratified by the tumor burden, using serum AFP levels at a diagnostic cutoff value of 200 ng/mL. Among the 29 patients with serum AFP levels ≥ 200 ng/mL, the presence of pre-sarcopenia did not significantly correlate with an increased risk of death (log-rank $P = 0.069$) (Figure S1 in Supplementary Information). Conversely, in the subgroup of 71 patients with serum AFP levels < 200 ng/mL, the median OS was notably worse for the pre-sarcopenia group (16 months) than that for the non-pre-sarcopenia group (34 months; log-rank $P < 0.001$) (Fig. 2). The multivariate Cox proportional hazards analysis identified increased AFP level (adjusted HR per 10-unit increase 1.142; $P < 0.001$), higher MELD score (adjusted HR per 1-unit increase 1.176; $P < 0.001$), and the presence of pre-sarcopenia (adjusted HR 2.965; $P < 0.001$) as significant predictors of shorter OS (Table 4).

Variables	Overall (n = 100)	Pre-sarcopenia group (n = 39)	Non-pre-sarcopenia group (n = 61)	*P*-value
Female sex, N (%)	25 (25.0%)	12 (30.8%)	13 (21.3%)	0.346
Age (years), mean ± SD	58.8 ± 11.2	59.2 ± 12.1	58.6 ± 10.6	0.788
Body mass index (kg/m^2), mean ± SD	24.2 ± 4.6	22.0 ± 4.8	25.5 ± 4.0	< 0.001
Underlying disease, N (%)				
Diabetic mellitus	26 (26.0%)	12 (30.8%)	14 (23.0%)	0.484
Hypertension	25 (25.0%)	10 (25.6%)	15 (24.6%)	1.000
Dyslipidemia	8 (8.0%)	3 (7.7%)	5 (8.2%)	1.000
Hepatitis B virus infection	34 (34.0%)	14 (35.9%)	20 (32.8%)	0.830
Hepatitis C virus infection	35 (35.0%)	15 (38.5%)	20 (32.8%)	0.668
Hepatitis B and C virus coinfection	2 (2.0%)	1 (2.6%)	1 (1.6%)	1.000
Alcohol-related liver disease	33 (33.0%)	19 (31.1%)	14 (35.9%)	0.667
Cirrhosis	94 (94.0%)	37 (94.9%)	57 (93.4%)	1.000
Child–Turcotte–Pugh classification, N (%)				0.099
A	57 (57.0%)	18 (46.2%)	39 (63.9%)	
B	43 (43.0%)	21 (53.8%)	22 (36.1%)	
Laboratory data				
Hemoglobin (g/dL), mean ± SD	11.8 ± 2.0	11.7 ± 2.0	11.9 ± 2.0	0.615
Platelet median (×10^3/μL), median [IQR]	127 [72–208]	112 [70–192]	128 [73–225]	0.484
Serum creatinine (mg/dL), mean ± SD	0.9 ± 0.3	0.8 ± 0.3	0.9 ± 0.3	0.168
Serum albumin (g/dL), mean ± SD	3.4 ± 0.6	3.2 ± 0.7	3.5 ± 0.6	0.049
Total bilirubin (mg/dL), median [IQR]	1.2 [0.7–2.1]	1.6 [0.9–2.5]	1.2 [0.7–1.9]	0.072
Aspartate aminotransferase (mg/dL), median [IQR]	64 [44–90]	64 [44–90]	63 [46–90]	0.854
Alanine aminotransferase (mg/dL), median [IQR]	39 [26–57]	39 [22–57]	39 [26–57]	0.849
International normalized ratio, mean ± SD	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	0.152
Alpha-fetoprotein (ng/mL), median [IQR]	18.1 [6.3–312.5]	24.0 [7.1–418]	17.5 [5.7–280]	0.654
ALBI grade, N (%)				0.446
1	20 (20.0%)	7 (17.9%)	13 (21.3%)	
2	63 (63.0%)	23 (59.0%)	40 (65.6%)	
3	17 (17.0%)	9 (23.1%)	8 (13.1%)	
MELD: mean ± SD	10.8 ± 3.7	11.4 ± 3.6	10.4 ± 3.7	0.182
ECOG score, N (%)				0.372
0	70 (70.0%)	25 (64.1%)	45 (73.8%)	
1	30 (30.0%)	14 (35.9%)	16 (26.2%)	
BCLC staging, N (%)				0.640
0	4 (4.0%)	1 (2.6%)	3 (4.9%)	
A	22 (22.0%)	7 (17.9%)	15 (24.6%)	
B	69 (69.0%)	28 (71.8%)	41 (67.2%)	
C	5 (5%)	3 (3.7%)	2 (3.3%)	

Table 1. Overall baseline characteristics and comparison between patients with and without pre-sarcopenia. SD, standard deviation; IQR, interquartile range; ALBI, albumin-bilirubin; MELD, model for end-stage liver disease; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer.

Discussion

In recent years, the focus on predicting outcomes in patients with HCC undergoing TACE has expanded to include the role of muscle mass, in terms of sarcopenia[23]. Here, we explored the significance of pre-sarcopenia in patients with unresectable HCC who underwent TACE and found that pre-sarcopenia did not predict post-treatment tumor response. Patients with pre-sarcopenia had markedly poorer OS when compared to those without pre-sarcopenia. This effect was particularly pronounced in patients with serum AFP levels below 200 ng/mL, in whom pre-sarcopenia significantly predicted a worse prognosis.

Variables	Overall (n = 100)	Pre-sarcopenia group (n = 39)	Non-pre-sarcopenia group (n = 61)	*P*-value
Number of tumors, median [IQR]	2 [1–3]	2 [1–3]	2 [1–3]	0.095
Multinodular (> 1 lesion), N (%)	65 (65.0%)	28 (71.8%)	37 (60.7%)	0.289
Largest tumor size (cm), median [IQR]	4 [3–7]	4 [3–8]	4 [3–7]	0.748
Largest tumor size > 5 cm, N (%)	42 (42.0%)	17 (43.6%)	25 (41.0%)	0.837
Number of TACE sessions, median [IQR]	2 [2–3]	2 [1–4]	2 [2–3]	0.837
Achievement of complete response, N (%)	21 (21.0%)	5 (12.8%)	16 (26.2%)	0.135

Table 2. Overall tumor characteristics and post-TACE tumor response and comparison between patients with and without pre-sarcopenia. IQR, interquartile range; TACE, transarterial chemoembolization.

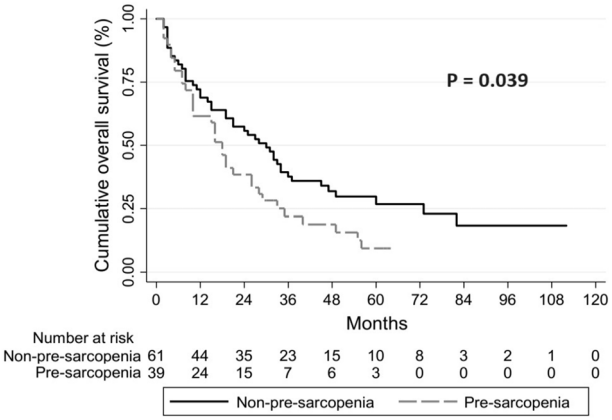

Figure 1. Kaplan–Meier curves of cumulative overall survival rates after transarterial chemoembolization in patients with unresectable hepatocellular carcinoma with pre-sarcopenia compared with those without pre-sarcopenia.

Most patients (94%) in this study had cirrhosis, which aligns with the understanding that cirrhosis, present in over 80% of HCC patients, is the strongest risk factor for developing HCC[30]. Further, both HCC and cirrhosis are closely associated with impaired muscle mass[8]. The prevalence of pre-sarcopenia in our cohort was 39%, higher than in patients with chronic liver disease (15–24%)[31] and early-stage HCC (16%)[17]. This is contrast to a recent Japanese study reporting a higher prevalence of pre-sarcopenia among advanced HCC patients (57%)[16]. Our cohort, primarily at the intermediate stage of HCC, shows a prevalence rate lying between these two previously reported rates. This variation underscores the complex interplay between cirrhosis, tumor progression, and muscle mass reduction, emphasizing that the presence of pre-sarcopenia is linked to both tumor staging and baseline hepatic function.

Recent studies have investigated the role of muscle mass in determining both procedural outcomes and tumor responses after TACE for HCC. Notably, investigations by Loosen et al.[32] and Roth et al.[33] have demonstrated that sarcopenia present prior to interventions does not significantly influence the rate of tumor response or progression post-TACE. These findings are consistent with those of our study, which identified no significant correlation between pre-treatment pre-sarcopenia and tumor response to TACE. This suggests that tumor-specific characteristics and hepatic reserves may play a more pivotal role than does nutritional status in influencing post-treatment tumor dynamics, which warrants further exploration.

The prevalence of protein–energy malnutrition in HCC, often under-assessed by conventional laboratory tests, highlights the need for more accurate nutritional status indicators. The advent of noninvasive techniques for skeletal muscle evaluation has led to the inclusion of sarcopenia as a prognostic factor across various medical domains, including liver disease management[34]. Prior investigations have demonstrated the prognostic utility of reduced muscle mass, highlighting it as a surrogate marker for functional capacity and nutritional status. Additionally, skeletal muscle depletion is linked to poor survival, partly due to endocrine changes affecting muscle synthesis and catabolism[35]. Lower insulin-like growth factor (IGF)-1 levels in HCC patients correlate with reduced muscle mass and poor survival, indicating that severe sarcopenia and low IGF-1 levels may reflect poor liver function and higher mortality[17]. However, although sarcopenia has been reported to be a strong prognostic factor for overall survival in cancer patients, including those with HCC[15,36,37], the effects of pre-sarcopenia remain poorly studied. Thus, the identification of pre-sarcopenia as a critical factor influencing post-TACE outcomes underscores the importance of early recognition of and intervention targeting muscle mass preservation in HCC management.

Although the prognostic value of pre-sarcopenia in surgical resection[38–40], liver transplantation[41,42], and sorafenib treatment[16,43] for HCC has been documented, its effect on outcomes following TACE in unresectable

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p*-value
Female sex	1.083	0.653–1.795	0.757			
Age, every 1-year increase	1.006	0.986–1.026	0.563			
Body mass index < 18 kg/m^2	1.497	0.807–2.778	0.201			
Pre-sarcopenia	1.596	1.014–2.510	0.043			
Hepatitis B infection	0.947	0.591–1.517	0.820			
Hepatitis C infection	1.562	0.951–2.343	0.103			
Alcohol-related liver disease	1.424	0.897–2.262	0.134			
Portal hypertension	1.578	0.967–2.575	0.068			
Child–Pugh score			0.019			
A	1	Ref				
B	1.709	1.092–2.675				
MELD score, every 1 unit increased	1.120	1.059–1.185	< 0.001	1.098	1.033–1.167	0.003
ALBI grade > 1	1.700	0.934–3.095	0.082			
Alpha-fetoprotein level, every 10 ng/mL increased	1.000	1.000–1.000	0.599			
Multinodular (> 1 lesion)	2.026	1.236–3.322	0.005	1.645	0.977–2.770	0.061
Tumor size > 5 cm	1.118	0.711–1.757	0.630			
BCLC			0.935			
0	1	Ref				
A	0.737	0.244–2.233				
B	0.769	0.277–2.138				
C	0.929	0.231–3.742				
ECOG			0.985			
0	1	Ref				
1	1.005	0.614–1.644				

Table 3. Univariate and multivariate Cox proportional-hazards model of predictive factors of overall survival after transarterial chemoembolization in individuals with unresectable hepatocellular carcinoma. MELD, Model for End-Stage Liver Disease; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group.

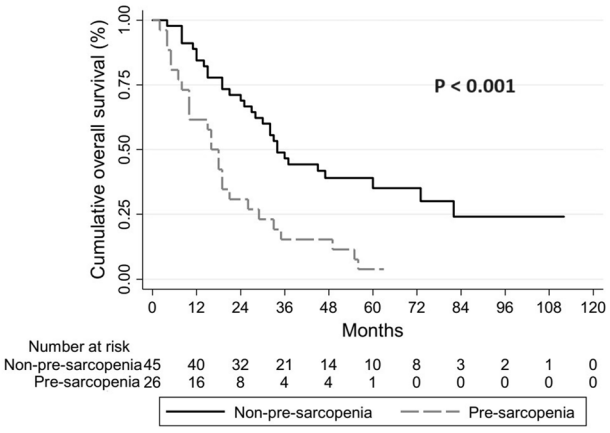

Figure 2. Kaplan–Meier curves of cumulative overall survival rates of unresectable hepatocellular carcinoma after transarterial chemoembolization among patients who had serum alpha-fetoprotein level < 200 ng/dL, compared between patients with pre-sarcopenia and those who without pre-sarcopenia.

HCC remains underexplored. Our analysis revealed that, although OS was reduced in patients with pre-sarcopenia, it was not a statistically significant prognostic factor across the cohort. This discrepancy might be attributed to the overarching influence of HCC itself, as demonstrated by Kobayashi et al., who found that AFP levels were a more potent predictor of survival than muscle mass reduction[44]. In dissecting the impact of pre-sarcopenia, our study stratified patients based on tumor burden, as defined by AFP levels at diagnosis. Interestingly, in the subset of patients with AFP levels > 200 ng/mL, pre-sarcopenia did not significantly affect prognosis. Conversely, pre-sarcopenia significantly predicted worse outcomes in patients with lower AFP levels, highlighting it as a

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p*-value
Female sex	1.484	0.818–2.694	0.194			
Age, every 1-year increase	1.014	0.988–1.040	0.290			
Body mass index < 18 kg/m^2	1.798	0.874–3.695	0.111			
Pre-sarcopenia	2.743	1.585–4.745	< 0.001	2.965	1.691–5.199	< 0.001
Hepatitis B infection	0.781	0.431–1.417	0.416			
Hepatitis C infection	1.547	0.900–2.660	0.115			
Alcohol-related liver disease	1.385	0.798–2.404	0.246			
Portal hypertension	1.719	0.944–3.130	0.076			
Child–Pugh score			0.001			
A	1	Ref				
B	2.420	1.408–4.159				
MELD score, every 1 unit increased	1.170	1.093–1.251	< 0.001	1.176	1.090–1.268	< 0.001
ALBI grade > 1	2.470	1.111–5.491	0.027			
Alpha-fetoprotein level, every 10 ng/mL increased	1.114	1.044–1.189	0.001	1.142	1.063–1.227	< 0.001
Multinodular (> 1 lesion)	1.582	0.906–2.764	0.107			
Tumor size > 5 cm	0.859	0.489–1.510	0.598			
BCLC			0.090			
0	1	Ref				
A	0.559	0.175–1.782				
B	0.605	0.212–1.728				
C	2.166	0.536–8.759				
ECOG			0.830			
0	1	Ref				
1	1.066	0.595–1.909				

Table 4. Univariate and multivariate Cox proportional-hazards model of predictive factors of overall survival after transarterial chemoembolization in individuals with unresectable hepatocellular carcinoma among the patient with AFP < 200. MELD, Model for End-Stage Liver Disease; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group.

potential independent risk factor for mortality (HR = 2.965). These observations imply that, in the context of a high tumor burden where survival prospects are inherently limited, the impact of pre-sarcopenia on survival might be mitigated. Given these insights, muscle volume is a plausible prognostic indicator in HCC management, particularly in patients with a lower tumor burden.

Our results have practical clinical implications for treatment strategies for patients with unresectable HCC. Early identification of patients at an increased mortality risk is critical and significantly shapes clinical management strategies for HCC. Prompt recognition of skeletal muscle depletion, combined with targeted nutritional support and physical therapy, is essential in sarcopenia management and may improve prognosis in HCC patients[45,46]. Recent guidelines recommend specific nutritional strategies[2], including supplementation with branched-chain amino acids and L-carnitine, to protect liver function and enhance muscle protein synthesis[32]. Additionally, pre-treatment leucine/creatine supplementation can boost muscle synthesis and maintain strength[47]. Physical exercise also plays a critical role in reducing muscle atrophy and weight loss in HCC patients[48]. Furthermore, the prognostic implications of sarcopenia can inform deliberations over the timing and necessity of subsequent TACE procedures, helping identify individuals who may benefit from accelerated retreatment schedules. Additionally, in cases where TACE is deemed unsuitable, early recognition of a potentially poor prognosis may facilitate the transition to early systemic therapeutic options[46]. Consequently, we advocate the integration of muscle status evaluations within the clinical decision-making framework for TACE eligibility to facilitate the initiation of tailored nutritional interventions for patients with diminished muscle mass.

The widespread use of TACE has led to the development of several scoring systems to predict patient survival, such as the HAP score, six-and-twelve score, ALBI-TAE model, and FAIL-T model, which combine tumor-specific and patient-specific factors[49,50]. However, these systems do not include muscle wasting as a factor. Recently, Wang et al. developed a novel prognostic nomogram incorporating the neutrophil-to-lymphocyte ratio and sarcopenia, which demonstrated strong predictive performance and outperformed other currently available models[51]. This innovative approach highlights the importance of including muscle mass evaluation in future risk stratification models to improve prognostic accuracy and patient management.

To the best of our knowledge, no previous study has evaluated the effect of pre-sarcopenia in patients with HCC who underwent TACE. However, this study also had some limitations. First, the retrospective nature of this cohort study introduced inherent constraints, notably the lack of systematically recorded data on subjective factors, such as appetite loss or anorexia, as well as objective measures of muscular strength, including grip strength and walking speed, usually regarded as diagnostic criteria for sarcopenia. Additionally, the absence of CT data for

a subset of patients may have introduced a selection bias. Second, while providing valuable insights, the sample size of 100 patients may be considered limited for the complex analysis of endpoints, such as OS. This could have affected the robustness and statistical power of the findings, particularly in the subgroup analysis. Third, this single-center study conducted exclusively in Thai patients introduces the possibility of center-specific biases, thereby limiting the generalizability of the results to broader populations. Despite these constraints, this study offered significant real-world insights into managing HCC in a community-based hospital setting in Thailand, a region with constrained medical resources. Fourth, the absence of key datapoints, such as baseline clinical status parameters including accurate BMI (which may be affected by ascites or edema), and the occurrence of new extrahepatic metastasis during treatment may have influenced survival outcomes and potentially impacted the study results. Finally, the inclusion criteria spanned an extended period during which the methodologies applied for TACE evolved. This temporal variation might have influenced the consistency and applicability of our findings across the entire study cohort.

Conclusion

Pre-sarcopenia significantly predicts increased mortality in patients with unresectable HCC undergoing TACE, particularly in those with serum AFP levels < 200 ng/mL, and could be an intervention target among such patients.

Data availability

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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Author contributions

Author contributions: Attapon Rattanasupar was the main contributor to manuscript writing and collected and analyzed the data. Tanaporn Prateepchaiboon, Keerati Akarapatima, Apiradee Songjamrat, and Songklod Pakdeejit collected information on patients with hepatocellular carcinoma. Arunchai Chang provided ideas for this study and critically revised the manuscript for important intellectual content. All the authors have read and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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