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ORIGINAL RESEARCH

Increment of Skeletal Muscle Mass Predicts Survival Benefit for Hepatocellular Carcinoma Treated with Transarterial Chemoembolization Combining Molecular Targeted Agents and Immune Checkpoint Inhibitors

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Purpose: To assess the relationship between clinical prognosis and changes of skeletal muscle mass for unresectable hepatocellular carcinoma (uHCC) patients who received transarterial chemoembolization (TACE) with molecular-targeted agents and immune checkpoint inhibitors (TACE-MTAs-ICIs).

Methods: From June 2019 to June 2023, a total of 92 uHCC patients who received TACE-MTAs-ICIs therapy were included. Skeletal muscle mass was assessed before and 6 months after treatment. Skeletal muscle index (SMI) is calculated as skeletal muscle area at the L3 vertebra divided by the square of height, then the change rate of SMI (ΔSMI) is calculated. Patients were stratified based on ΔSMI as muscle gain and non-muscle gain groups. Overall survival (OS) was compared between groups and prognostic factors for OS were analyzed. Progression-free survival (PFS) was also recorded.

Results: The median OS in the muscle gain group was significantly longer than that in the non-muscle gain group (Not reach vs 25.2 months, $P < 0.001$). The median PFS did not reach significant between two groups (16.2 vs 9.1 months, $P = 0.101$). Multivariate analyses revealed that skeletal muscle gain (HR = 0.20; 95% CI, 0.06–0.68; $P = 0.010$) and Barcelona Clinic Liver Cancer stage (HR = 1.94; 95% CI, 1.02–3.69; $P = 0.044$) were independent prognostic factors for OS.

Conclusion: SMI increment appeared as a favorable predictor for these uHCC patients who received TACE-MTAs-ICIs therapy.

Keywords: hepatocellular carcinoma, immune checkpoint inhibitors, molecular targeted therapy, sarcopenia, transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies.[1] Major HCC patients are initially diagnosed at an intermediate or advanced stage, which means that they lost the best opportunity for curative treatment (unresectable HCC, uHCC).[2] Previous studies had proved that there was considerable theoretical for the combination of TACE with MTAs plus ICIs (TACE-MTAs-ICIs) for uHCC treatment.[3,4] And the retrospective studies had demonstrated survival benefits brought by this triple therapy modality.[4,5]

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Notably, the judgment of clinical prognosis of these patients was mainly depended on tumor stage and liver function, and often overlooked the performance status.[6] Sarcopenia, as a measure of performance and nutritional status, has attracted attention due to its possible predictive value.[7,8] Sarcopenia is characterized by the depletion of skeletal muscle mass, strength, and functionality, and is generally associated with severe malnutrition.[8,9] The skeletal muscle index (SMI) and subcutaneous fat area (SFA) have been acknowledged as significantly correlated variables associated with the occurrence and development of HCC.[10,11] In addition, the negative impact of sarcopenia on the prognosis of HCC patients who received TACE or systemic treatment, including Lenvatinib, Sorafenib, or Atezolizumab plus Bevacizumab, had also been reported.[12–14] Despite that there is a consensus on the definition of sarcopenia, the diagnosis of sarcopenia remains ambiguous due to the utilization of numerous distinct cutoff values, leading to unclear implications.[8,15] So, thought-provoking triggered by this was whether the dynamic changes in SMI could reflect the clinical outcomes of different treatment strategies. Thereafter, some studies investigated that a declining SMI was accelerated with dismal outcomes hardly.[13,16] However, it is not yet to known whether effective results of the triple therapy could be reflected on the SMI reversal. In fact, tumor cells promote muscle atrophy by secreting inflammatory factors, such as IL-6 and TNF-α,[17,18] while skeletal muscle cells can secrete cytokines like CHI3L1 to protect themselves from TNF-α-induced inflammatory damage.[19] Besides, previous study demonstrated that muscle atrophy was associated with immune cells in the tumor microenvironment, which may provide a theoretical basis for the potential of triple therapy to modulate the tumor microenvironment and subsequently influence muscle atrophy.[20] These connections potentially reminded that the relationship and crosstalk between the changes in SMI and treatment effectiveness of HCC was thought-provoking and deserved further exploration.

Therefore, we conducted this retrospective study to evaluate changes in SMI after the TACE-MTAs-ICIs treatment, and to analyze the association of reversal of SMI with prognosis in these HCC patients.

Methods

This is a retrospective, cross-sectional study conducted in a single-center. The study was conducted in accordance with the World Medical Association Declaration of Helsinki. The study protocol was also approved by the Ethics Committee of our institution. This study was approved by the local institutional ethics review board of the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (ethical review no. 2024-SR-518). Written informed consent was not required for this retrospective study. The data of this study are available from the author upon rational request.

Patients

Between June 2019 and June 2023, the medical records of 131 patients treated with TACE-MTAs-ICIs were reviewed. HCC was confirmed pathologically or clinically based on the Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China.[21] Patients who underwent non-contrast and contrast enhanced abdomen CT scan within 1 month prior to treatment and approximately 6 months (range 5–7 months) after treatment were included in the study. The exclusion criteria were as follows: (1) incomplete CT imaging; (2) patients who received MTAs less than 4 weeks or ICIs less than two cycles; (3) patients with other malignant tumors; and (4) patients with incomplete data or who were lost to follow-up. A total of 92 patients were ultimately enrolled in this study (Figure 1).

Baseline data about patients were collected, including age, sex, etiology, Barcelona Clinic Liver Cancer (BCLC) stage, Child–Pugh class, albumin-bilirubin (ALBI) grade, Eastern Cooperative Oncology Group (ECOG) performance status, laboratory parameters, and body composition variable.

Skeletal Muscle Mass and Adipose Tissue Assessment

Data at CT were obtained at baseline (1 month prior to treatment), 6 months after treatment (5–7 months). Quantifying skeletal muscle and subcutaneous fat at the L3 vertebra was based on CT images obtained for each patient. Skeletal muscle area (SMA) and subcutaneous fat area (SFA) were delineated by density thresholds ranging from −29 to 150 hounsfield Unit (HU) and −190 to −30 hU, respectively.[22] Additionally, the regions of interest were manually corrected as needed. Images were analyzed by two trained observers (each over 5 years of clinical experience in CT scanning and image postprocessing) by using software (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany). SMI is defined as SMA at the L3 level normalized by the square of height. Representative images are shown in Figure 2a-d.

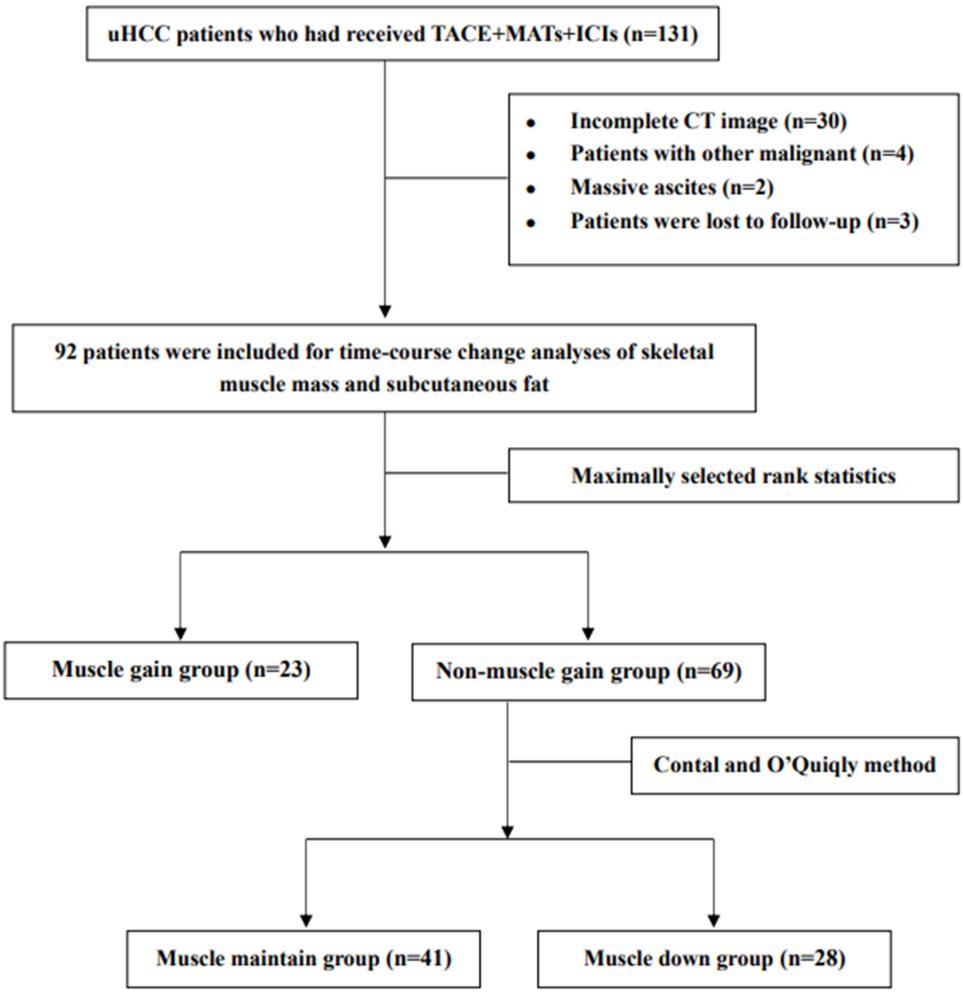

Figure 1 Patient enrollment flowchart.
Abbreviations: uHCC, unresectable hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; MTAs, molecular targeted agents; ICIs, immune checkpoint inhibitors.

TACE Procedure

TACE procedure was performed initially. Usually, under local anesthesia, a 5-F catheter was introduced. Programmed angiography was used to identify the blood supply of tumor. Then, a microcatheter was inserted into the feeding artery. Emulsion of epirubicin (5–10 mg) and iodized oil (5–20 mL) was infused, followed by embolization of gelatin sponges particles or microsphere until basically cessation of the blood flow.

Systematic Therapy

About 5–7 days after TACE procedure, systematic therapy was prescribed. For ICIs, Atezolizumab (1200 mg), sintilimab (200 mg) or camrelizumab (200 mg) was injected intravenously approximately every 3 weeks. For MTAs, bevacizumab was injected intravenously at 15 mg/kg or 7.5 mg/kg, lenvatinib was administered orally at a dose of 8 mg daily for patients <60 kg or 12 mg daily for patients ≥60 kg. MTAs or ICIs were suspended during TACE and resumed after TACE. Discontinuation or changes in treatment regimen were considered based on disease progression, unacceptable adverse events (AEs), patient refusal or clinician decision.

Follow-up and Assessments

Overall survival (OS) was defined as the time from initiation of therapy to death from any cause; progression-free survival (PFS) was defined as the time from initiation of therapy to progression. Contrast-enhanced CT or MRI was

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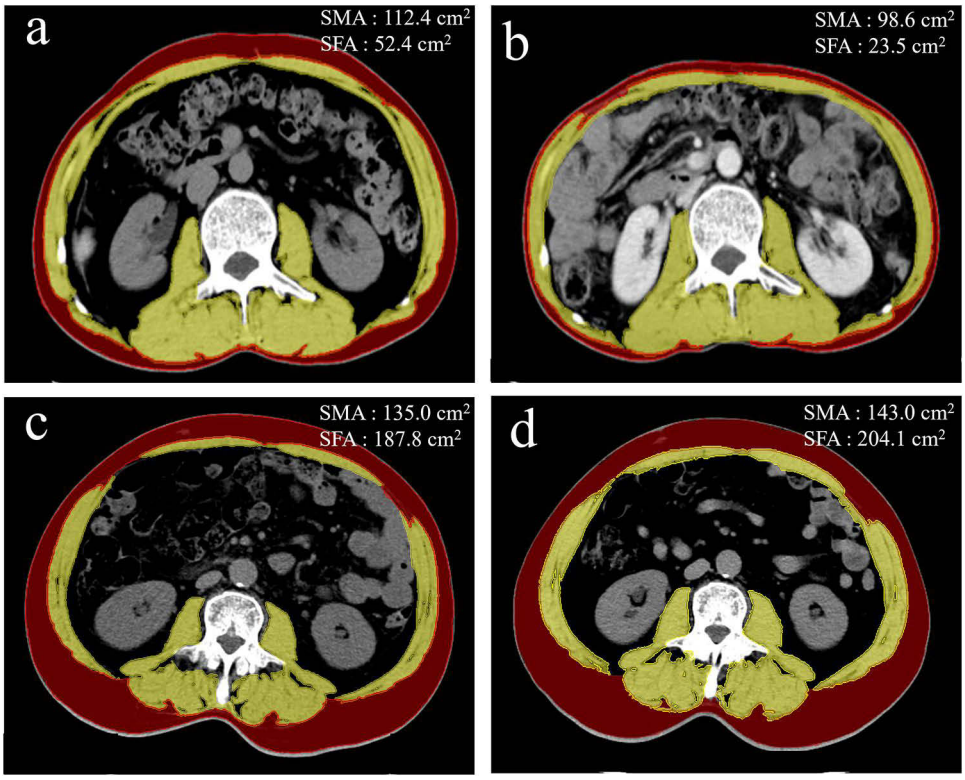

Figure 2 Representative CT images show the changes in skeletal muscle and fat mass. (**a**) and (**b**) are baseline and six-month post-treatment CT images of a 58-year-old male patient with HCC (non-muscle gain); (**c**) and (**d**) are baseline and six-month after triple therapy CT images of a 54-year-old male patient with HCC (muscle gain). **Abbreviations**: SMA, skeletal muscle area; SFA, subcutaneous fat area.

implemented at 1.5–2-month intervals. Treatment-related toxicity was observed and recorded according to the National Cancer Institute Common Toxicity Criteria Adverse Events (CTCAE) version 5.0. Liver and kidney function, thyroid function, and myocardial enzyme profiles were monitored before every circle of ICI injection. For grade 3–4 adverse events, under the premise of providing symptomatic treatment and supportive care, discontinuation or changes in treatment regimen were considered. The end date of follow-up was December 31, 2023. Tumor response was evaluated about 3 months after triple therapy, based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[23] It focuses on changes in viable tumor size, emphasizing the presence of arterial enhancement as an indicator of viable tumor tissue. Identify up to two target lesions per organ (liver) and a maximum of five target lesions in total. The response include: (1) Complete Response (CR): Disappearance of all arterial enhancement in target lesions, indicating the absence of viable tumor tissue. (2) Partial Response (PR): At least a 30% reduction in the sum of the diameters of the enhancing target lesions. (3) Stable Disease (SD): A change that does not meet the criteria for either PR or progressive disease (PD). (4) Progressive Disease (PD): An increase of at least 20% in the sum of the diameters of the enhancing target lesions, or the appearance of new lesions. Objective response rate (ORR) was defined as the proportion of patients with CR or PR. Disease control rate (DCR) was defined as the rates of CR, PR, and SD.

Statistical Analysis

OS and PFS were estimated by the Kaplan–Meier method, and the differences were assessed for significance using the Log rank test. Sarcopenia cutoffs were determined based on the European Association for the Study of the Liver's clinical guidelines (L3 SMI<50 cm^2 /m^2 for men and <39 cm^2 /m^2 for women).[24] The rate of change in skeletal muscle mass (ΔSMI) over 6 months was calculated (ΔSMI= ($SMI_{post\text{-}treatment}$ − $SMI_{pre\text{-}treatment}$) / $SMI_{pre\text{-}treatment}$) × 100%). "Maximally selected log-rank statistic" was used to stratify the patients, based on ΔSMI. Subsequently, based on the results of "Contal and O'Quiqly method", we established a cutoff value to further categorize patients in the non-muscle gain group into muscle maintain and muscle down groups.

The Cox proportional hazards regression model was used to determine the factors associated with survival. Categorical data were compared between the two groups using the $\chi 2$ test or Fisher's exact test as appropriate. For continuous variables, group differences were assessed using either Student's *t*-test or the Mann–Whitney test. A two-tailed P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Version 25.0, Chicago, IL), GraphPad Software (Prism 8.0.1, San Diego, California), and R software (version 4.2.1).

Results

Patient Characteristics and Cutoff Values for ΔSMI

The clinical characteristics of all the patients (n = 92) are list in Table 1. The study cohort contained 79 male patients (85.9%), with mean age of 57.0 years old. Thirty-six patients (39.1%) were classified as BCLC C, 57 patients (62.0%) with ECOG 0, and 49 patients (53.3%) with sarcopenia. The cutoff value for ΔSMI was set at 0.03% (minimum positive value) over 6 months, according to maximally selected rank statistics (Supplementary Figure 1). This cut-off value divided the study population into a muscle gain group (ΔSMI ≥ 0.03%, n = 23) and non-muscle gain group (ΔSMI < 0.03%, n = 69). Apart from the ECOG score, no significant difference was observed between the two groups in the other clinical variables. Then, by using the Contal and O'Quiqly method, a cut-off value of −10.2% was used to further divide the non-muscle gain cohort into muscle maintain group (ΔSMI ≥ −10.2%, n = 41) and muscle down group (ΔSMI < −10.2%, n = 28).

Table 1 Patient Characteristics

Characteristics	All Patients	Muscle Gain	Non Muscle Gain	*P*
No. of patients	92	23	69	
Age (y)	57.0 ± 10.7	55.5 ± 8.3	57.5 ± 11.4	0.488
Sex				
Male	79 (85.9%)	21 (91.3%)	58 (84.1%)	0.506
Female	13 (14.1%)	2 (8.7%)	11 (15.9%)	
BCLC stage				0.205
B	56 (60.9%)	17 (73.9%)	39 (56.5%)	
C	36 (39.1%)	6 (26.1%)	30 (43.5%)	
Child-Pugh Class				
A	75 (81.5%)	20 (87.0%)	55 (79.7%)	0.643
B	17 (18.5%)	3 (13.0%)	14 (20.3%)	
ALBI				0.357
1	22 (23.9%)	7 (30.4%)	15 (21.7%)	
2	68 (73.9%)	15 (65.2%)	53 (76.8%)	
3	2 (2.2%)	1 (4.3%)	1 (1.4%)	
ECOG score				0.025
0	57 (62.0%)	19 (82.6%)	38 (55.1%)	
1	35 (38.0%)	4 (17.4%)	31 (44.9%)	
Etiology				0.173
HBV	79 (85.9%)	22 (95.7%)	57 (82.6%)	
Others	13 (14.1%)	1 (4.3%)	12 (17.4%)	
Laboratory parameters				
AFP (ng/mL)				0.224
< 400	52 (56.5%)	16 (69.6%)	36 (52.2%)	
≥ 400	40 (43.5%)	7 (30.4%)	33 (47.8%)	
Neutrophil ($\times 10^9$/L)	3.1 (2.0–4.2)	3.2 (2.4–3.8)	3.0 (2.0–4.3)	0.808
Lymphocyte ($\times 10^9$/L)	1.1 (0.8–1.5)	1.2 (0.9–1.6)	1.1 (0.8–1.5)	0.473
Platelet ($\times 10^9$/L)	129.0 (87.5–188.0)	142.0 (98.0–179.5)	122.0 (84.5–188.0)	0.598
Albumin	37.2 (33.4–39.7)	38.2 (34.8–40.7)	36.7 (32.8–36.7)	0.337
Total bilirubin (μmol/L)	17.7 (12.9–24.0)	18.3 (12.8–26.4)	17.1 (12.7–24.0)	0.543

(*Continued*)

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Table 1 (Continued).

Characteristics	All Patients	Muscle Gain	Non Muscle Gain	*P*
Body composition variable				
Sarcopenia (n)	49	13	36	0.811
SMA (cm^2)	136.7 ± 24.6	132.8 ± 23.6	137.9 ± 25.2	0.386
SMI (cm^2/m^2)	47.7 ± 8.1	46.4 ± 8.9	48.1 ± 7.9	0.397
SFA (cm^2)	121.7 (89.7–155.8)	108.6 (70.5–134.4)	128.5 (102.0–155.8)	0.082
Weight (kg)	68.5 ± 9.8	69.4 ± 9.9	68.2 ± 9.8	0.622
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.806
BMI (kg/m^2)	23.9 ± 3.0	24.1 ± 2.8	23.7 ± 3.1	0.728

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin-bilirubin; MELD, model for end-stage liver disease; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; AFP, α-fetoprotein; SMA, skeletal muscle area; SMI, skeletal muscle index; SFA, subcutaneous fat area.

Changes in Skeletal Muscle and Fat Mass After TACE-MTAs-ICIs

For both muscle gain group and non-muscle gain group, the changes in SAM and SMI from baseline to 6 months are statistically significant (Figure 3a, 3b, 3d, and 3e). However, the changes of SFA are not statistically significant in muscle gain group (Figure 3c), but it is significant in non-muscle gain group (Figure 3f). Changes in SAM, SMI and SFA are all statistically significant in both the muscle maintain group and muscle down group (Supplementary Figure 2a-f).

Survival Analysis

The median follow-up was 28.7 months. After the last follow-up visit, 40 patients (43.5%) died. The median OS was not reached (NR) in the muscle gain group and 25.2 months in the non-muscle gain group ($P < 0.001$) (Figure 4a), and the corresponding median PFS was 16.2 and 9.1 months, respectively ($P = 0.101$) (Figure 4b). The median OS was 29.3 in the muscle maintain group and 11.7 months in the muscle down group ($P = 0.009$) (Figure 5a), and the corresponding median PFS was 12.3 and 6.6 months, respectively ($P = 0.013$) (Figure 5b).

For OS, the multivariate analysis indicated that BCLC C stage [hazard ratios (HR) = 1.94; 95% CI, 1.02–3.69; $P = 0.044$] and muscle gain (HR = 0.20; 95% CI, 0.06–0.68; $P = 0.010$) were independent predictive factors (Table 2). For muscle maintain group and muscle down group, the multivariate analysis showed that muscle maintain (HR = 0.31; 95% CI, 0.14–0.66; $P = 0.002$), SFA (HR = 0.99; 95% CI, 0.99–1.00; $P = 0.019$) were independent predictive factors for OS (Supplementary Table 1).

Tumor Response

Tumor responses in the different groups are shown in Supplementary Table 2. For muscle gain group and non-muscle group, the ORR (69.6% vs 58.0%, $P = 0.460$) and DCR (78.3% vs 69.6%, $P = 0.594$) were not reach significantly difference. Additionally, similar negative results were observed between muscle maintain group and muscle down group.

AEs (Grade 3 and 4)

Treatment-related AEs are shown in Table 3. The incidence rates of grade 3 and 4 AEs were slight lower in the muscle gain group than the non-muscle group (39.1% vs 53.6%, $P = 0.229$). These AEs were resolved or eliminated after conservative treatment. No treatment-related deaths occurred. Additionally, dose reduction and treatment interruption of MTAs were observed in 16.3% (15 of 92) of patients.

Discussion

Sarcopenia is highly prevalent among patients with cirrhosis and HCC and leads to adverse prognoses, including higher mortality rates.[22,25] A systematic review revealed that sarcopenia was a strong prognostic factor for HCC in OS, exhibiting HR point estimates ranging between 1.57 and 3.19.[15] However, the diagnosis of sarcopenia remains uncertain due to the application of various different cutoff values, contributing to ambiguity. In contrast, by using the changes in

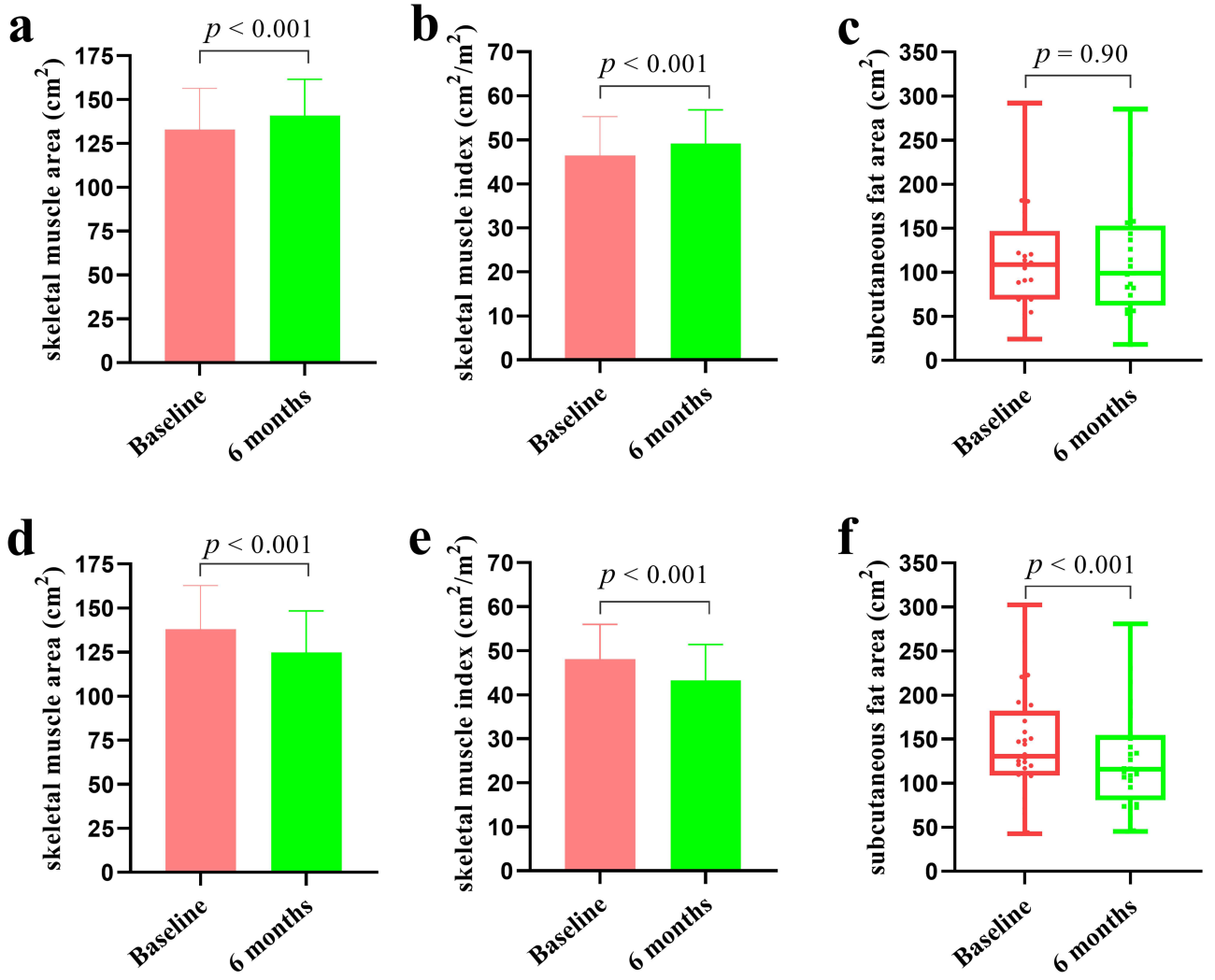

Figure 3 Graphs after triple therapy in patients with muscle gain group show time-course changes of (**a**) skeletal muscle area (SMA), (**b**) skeletal muscle index (SMI), (**c**) subcutaneous fat area (SFA). Graphs after triple therapy in patients with non-muscle gain group show time-course changes of (**d**) mean skeletal muscle area (SMA), (**e**) skeletal muscle index (SMI), (**f**) subcutaneous fat area (SFA).

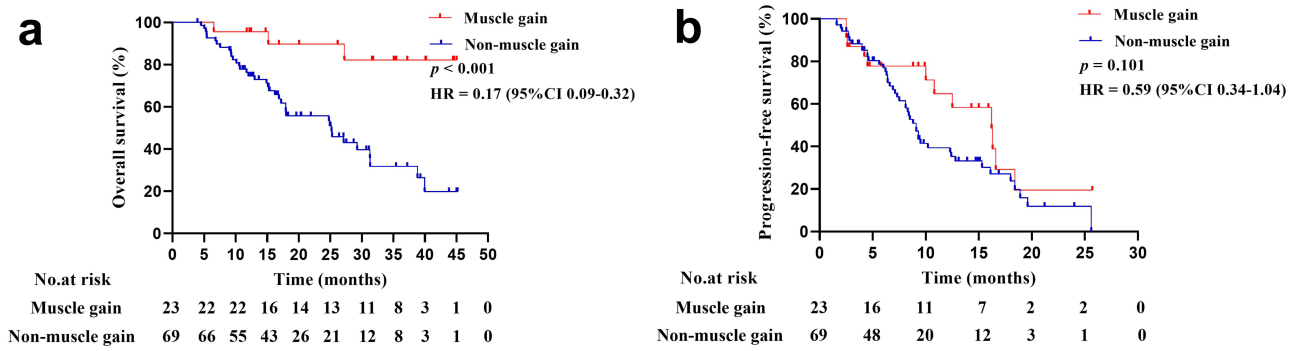

Figure 4 Kaplan-Meier survival for overall survival (**a**); Kaplan-Meier survival for progression-free survival (**b**).

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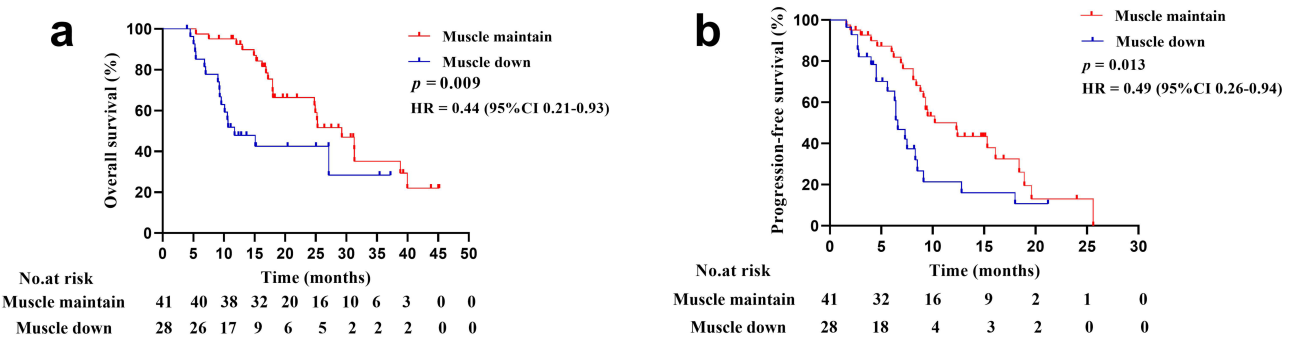

Figure 5 Kaplan-Meier survival for overall survival (**a**); Kaplan-Meier survival for progression-free survival (**b**).

skeletal muscle mass, which may eliminate the impact of solo SMI evaluation on different populations, could be accurately reflect on treatment effectiveness. In this study, the results confirmed that after TACE-MTAs-ICIs treatment, the median OS in the muscle gain group was significantly longer than that in the non-muscle gain group (NR vs 25.2 months, $P < 0.001$). And multivariate analyses also revealed that skeletal muscle gain was an independent favorable predictor for OS (HR = 0.20; 95% CI, 0.06–0.68; $P = 0.010$).

Table 2 Predictive Factor Analysis for Overall Survival in Muscle Gain Group and Non-Muscle Gain Group

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.00 (0.98–1.02)	0.656		
BCLC (C)	2.57 (1.37–4.82)	0.003	1.94 (1.02–3.69)	0.044
Child-Pugh Class (B)	1.55 (0.71–3.38)	0.270		
ECOG score (1)	1.61 (0.86–3.02)	0.137		
AFP (≥ 400 ng/mL)	2.20 (1.16–4.18)	0.015	1.74 (0.91–3.35)	0.097
Albumin	0.97 (0.91–1.03)	0.342		
SMI	1.01 (0.97–1.04)	0.678		
SFA	1.00 (0.99–1.00)	0.485		
Muscle gain	0.16 (0.05–0.52)	0.002	0.20 (0.06–0.68)	0.010

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein. SMI, skeletal muscle index; SFA, subcutaneous fat area.

Table 3 Treatment-Related Adverse Events (Grade 3 or 4)

Adverse Events	Muscle gain (n = 23)	Non muscle gain (n = 69)	*P* Value
All	9 (39.1%)	37 (53.6%)	0.229
Hypertension	1 (4.3%)	3 (4.3%)	
Elevated AST	2 (8.7%)	8 (11.6%)	
Elevated ALT	3 (13.0%)	11 (15.9%)	
Hand-foot-skin reactions	0 (0.0%)	3 (4.3%)	
Abdominal pain	2 (8.7%)	5 (7.2%)	
Fever	1 (4.3%)	3 (4.3%)	
Hypothyroidism	0 (0%)	2 (2.9%)	
Elevated bilirubin	0 (0%)	2 (2.9%)	

Abbreviations: AST, alanine; AST, aspartate aminotransferase.

TACE, MTAs, and ICIs have been recommended as the primary treatment for patients with HCC at an intermediate or advance stage.[6] However, just by locoregional therapy or systemic therapy, achieving satisfactory clinical benefits remains challenging.[26] The combination of atezolizumab and bevacizumab increased the patient's survival period to 19.2 months with an ORR of 33.2% in the IMbrave 150 study.[27] The CHANCE series and other studies further optimized the triple modality results, with about 60% of ORRs and 19.2–24.1 months of median OS, in contrast of 32.0–37.4% ORR and 15.7 months of median OS by TACE monotherapy.[4,5,28] In this study, the ORR was 60.9% and median OS was over 25.2 months for all patients, while treatment-related adverse events occurred in 50% patients but reversible, which indicated a comparable and acceptance effectiveness and safety profiles.

Given the stable survival outcomes brought about by the triple therapy, we need to rethink what may predict prognosis and further optimize it. Among them, the initial state sarcopenia could reflect the nutritional status of patients, definitely contributing to poor prognosis.[12–14,16,29] However, one obvious limitation of sarcopenia was the cutoff values defined by different research populations or race, which could lead to uncertain results. It was worth learning from scholars had observed the impact of dynamic changes in skeletal muscle mass on prognosis. Kobayashi T. et al demonstrated that a rapid decline in skeletal muscle mass approximately 6 months following the initial transcatheter intraarterial therapy was linked to an unfavorable prognosis in patients with HCC (HR =1.68; 95% CI, 1.03–2.72; P = 0.037).[16] And Matsumoto H. et al assessed that the impact of muscle volume depletion on the prognosis of HCC patients treated with the atezolizumab plus bevacizumab, also showed that PFS was significantly different in patients with or without SMI decreases (5.6 vs 8.7 months, $P = 0.017$), and SMI decreases was a significant factor associated with PFS (HR 5.1; 95% CI, 1.0–21.4; $P = 0.025$).[30] However, it was not yet known whether priority results could be reflected on the SMI reversal, especially in the situation of local and systemic combination treatment modality. Here, we set a six-month duration to access the dynamic change of SMI. In our cohort, patients who harvested muscle gain showed significant longer OS (NR vs 25.2 months, P < 0.001), compared to those who did not. For patients of non-muscle gain group, ΔSMI with a cutoff value of < −10.2% could further classify patients into two categories, which also brought significant difference in OS and PFS (median OS: 29.3 vs11.7 months, P = 0.009; median PFS: 12.3 vs 6.6 months, P = 0.013). These results also reverse demonstrated that the ΔSMI could reflect the sensitivity and accuracy on prognostic evaluation better. Since that's the case, what is worth further exploration is, for these HCC patients, the complex and potentially bidirectional relationship between changes in skeletal muscle mass and the outcomes after TACE-MTAs-ICIs. The presence or absence of muscle gain may be affected by patients' liver function.[31] The reduction in SMI coincided with the worsening of liver function for HCC patients (the decrease in SMI accompanied by elevation of ALBI, $P < 0.01$),[16] which may indicate a stable or delayed-declining in SMI may be accompanied by maintenance in liver function and physical condition. As the primary organ of metabolism, the liver's functional maintenance and the downregulation of inflammatory cytokines provide potential conditions for the increase or preservation of SMI.[32] However, the change of SMI during treatment was the result of complex interactions between patient baseline characteristics, aggressive tumor, biology, and treatment response.[30] The potential mechanisms and influencing factors still require further investigation. Prior studies indicate that supplementation of branched-chain amino acids and exercise was linked to reduced skeletal muscle atrophy in patients with HCC, ΔSMI was higher in the exercise group (0.28 cm^2/m^2 vs −1.11 cm^2/m^2, $P = 0.0029$).[33,34] It was reported that alterations in skeletal muscle mass were accompanied by changes in the secretion of inflammatory cytokines (such as IL-6), which modulated the tumor immune microenvironment by enhancing the recruitment and activation of NK cells and $CD8^+$ T cells, then may strengthen antitumor immune responses.[35,36] Therefore, it is warranted to explore whether nutritional support and exercise for these patients could achieve a comprehensive synergistic effect and extended survival with the triple therapy.

In this study, the changes of SFA were different between the muscle gain group and the non-muscle gain group. There was a significant decrease in SFA in the non-muscle gain group ($P < 0.001$), suggesting concurrent SFA consumption alongside skeletal muscle depletion. Besides, no doubt existed that the BCLC staging was closely correlated with the survival time,[6] and the multivariate analysis also confirmed again that BCLC stage was independent predictive factor for OS in our study. Here, it could be seen that muscle gain demonstrating independent predictability with BCLC staging simultaneously, which further suggested the stability and predictive value of the SMI changes across intermediate and advanced HCC stages. Currently, the molecular mechanisms underlying how tumors promote muscle depletion remain

unclear, but certain signaling pathways had been proven to play crucial roles in muscle atrophy.[18,37,38] In addition to appropriate exercise and protein supplementation, effective drugs targeting these signaling pathways to reverse muscle atrophy also expect to be identified to further promote the prognosis of triple therapy. So, elaboration on how these findings could be translated into clinical practice is warranted.

This study also had several natural limitations. First, assessment of skeletal muscle changes was limited to six months period, and we did not explore the relationship between tumor response and SMI changes. Second, the cutoff value of ΔSMI was generated from our study cohort, which needs further validation in prospective studies. Third, limited number of patients, selection bias, and some variables (eg, nutritional support or physical therapy) may not directly impact skeletal muscle changes but could be correlated, which could not be ignored although considering its retrospective design nature.

Conclusion

In conclusion, SMI increment appeared as a favorable predictor for these uHCC patients who received TACE-MTAs-ICIs therapy.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional (Ethical review no. 2024-SR-518) and with the 1964 helsinki declaration and its later amendments or comparable ethical standards. For this retrospective study, formal consent was not required. The collection, storage, and analysis of all patient-related data were strictly conducted in accordance with established principles of confidentiality and privacy protection.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Wen Chen, Hai-Tao Yan, Jin-Xing Zhang, Xiao Shen, Jin Liu, Sheng Liu, Hai-Bin Shi, Ye Ding, and Qing-Quan Zu have no conflicts of interest or financial ties to disclose.

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