# Effects of In-hospital Exercise on Sarcopenia in Hepatoma Patients Who Underwent Transcatheter Arterial Chemoembolization

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**Abbreviations**: CLD; chronic liver disease, HCC; hepatocellular carcinoma, TACE; transcatheter arterial chemoembolization, METs; metabolic equivalents, TNM; tumor node metastasis, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, CT; computed tomography, PMI; psoas muscle index, SMI; skeletal muscle index, VFA; visceral fat area, L3; the third lumbar vertebra, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LD; Lactate dehydrogenase, ALP; alkaline phosphatase, GGT; gamma-glutamyl transpeptidase, BUN; blood urea nitrogen, eGFR; estimated glomerular filtration rate, HbA1c; hemoglobin A1c, IQR; interquartile range, BMI; body mass index, DXA; dual X-ray absorptiometry, BIA; bio-electric impedance analysis.

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## Abstract

**Background and Aims:** Sarcopenia is a prognostic factor in hepatocellular carcinoma (HCC) patients. HCC patients who underwent transcatheter arterial chemoembolization (TACE) are at risk for muscle atrophy. We aimed to investigate effects of in-hospital exercise on muscle mass and factors associated with prevention of muscle atrophy in HCC patients who underwent TACE.

**Methods:** We enrolled 209 HCC patients who underwent TACE. Patients were classified into the Exercise (n=102) or Control (n=107) groups. In the Exercise group, patients were treated with in-hospital exercise (median 2.5 metabolic equivalents/20-40 min/day). Effects of exercise on muscle mass were evaluated by changes in skeletal muscle index (ΔSMI) between before- and after-TACE. Factors associated with an increase in SMI were analyzed by a logistic regression and a decision-tree analyses.

**Results**: There was no significant difference in serum albumin and bilirubin levels between the two groups. ΔSMI was significantly higher in the Exercise group compared to the Control group (0.28 $cm^2/m^2$ vs. -1.11 $cm^2/m^2$, P=0.0029). In the logistic regression analysis, exercise was an independent factor for an increase in SMI (HR 2.13; 95%CI 1.215–3.846; P=0.0085). In addition, the decision-tree analysis showed that exercise was the initial divergence variable for an increase in SMI (the ratio of increased SMI: 53% in the exercise group vs. 36% in the Control group).

**Conclusions**: We demonstrated that in-hospital exercise increased muscle mass in HCC patients who underwent TACE. In addition, exercise was an

independent factor for muscle hypertrophy. Thus, in-hospital exercise may prevent sarcopenia in HCC patients who underwent TACE.

**Keywords:** skeletal muscle mass, caner rehabilitation, liver cancer, chronic liver disease

## Introduction

Sarcopenia is defined as the generalized loss of muscle mass and muscle strength [1]. Sarcopenia is frequently seen in patients with chronic liver disease (CLD) and has an adverse impact on clinical outcomes including quality of life, development of hepatocellular carcinoma (HCC), and survival [2, 3].

Transcatheter arterial chemoembolization (TACE) is a therapeutic strategy for advanced HCC and improves prognosis for HCC patients with CLD [4]. However, fever is commonly seen after TACE and TACE is also associated with transient post-embolization syndromes including hepatic insufficiency [5, 6]. Moreover, patients treated with TACE are often instructed to rest [7]. Kortebein et al. reported that there is a large loss of skeletal muscle as a result of 10 days of bed rest [8]. These findings suggest that patients who underwent TACE are at risk for loss of muscle mass. In fact, we have previously reported that skeletal muscle mass was significantly reduced after TACE in HCC patients with CLD [7, 9].

Exercise is important for preventing sarcopenia [2]. Exercise has anti-inflammatory effects, with the potential to reduce local cytokine expression and increase the expression of anti-apoptotic factors, indicating that exercise can be expected to prevent sarcopenia [10]. In addition, physical activity favorably impacts outcomes including sarcopenia and prognosis of patients with colorectal cancer, breast cancer, and prostate cancer [11-14]. Although sarcopenia is frequently seen in patients with CLD, the effects of exercise on skeletal muscle mass in HCC patients with CLD remain unclear.

The aim of this study is to evaluate the effects of exercise on skeletal muscle mass in HCC patients with CLD who underwent TACE. In addition, we performed data-mining analysis to investigate factors associated with prevention of skeletal muscle atrophy in such patients.

## Methods

*Study design*

Exercise for in-hospital patients with cancer is an approved health care service covered by the Ministry of Health, Labor and Welfare of Japanese health insurance. Therefore, intentionally using a non-exercise control group is contrary to medical ethics. Thus, we performed a retrospective case-control study to evaluate effects of exercise on skeletal muscle mass during hospitalization for HCC patients with CLD who underwent TACE.

*Ethics*

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, as reflected in the prior approval given by the institutional review board of Kurume University (approval #15072). An opt-out approach was used to obtain informed consent from patients, and personal information was protected during data collection. None of the patients were institutionalized.

*Subjects*

We enrolled 209 consecutive HCC patients with CLD from February 2013 to November 2016. Inclusion criteria were hospitalized HCC patients with CLD who were (1) 20 years of age or older, (2) a performance status of grade 0 to 2 as defined by the Eastern Cooperative Oncology Group [15], and (3) treatment with TACE. Exclusion criteria were patients with (1) risk of HCC rupture, (2) hepatic encephalopathy grade 2–4 of the West Haven Criteria [16], (3)

risk of esophageal varices rupture, (4) heart failure, or (5) respiratory failure.

Exercise was recommended to all patients from outpatient doctors and nurses. Patients who agreed to exercise were classified as the Exercise group (n = 102), and those who did not agree to exercise were classified as the Control group (n = 107).

*Exercise regimen*

To maintain physical ability and prevent sarcopenia during hospitalization for HCC treatment, enrolled patients who classified into the Exercise group were treated with exercise (median 2.5 metabolic equivalents (METs)/20–40 minutes/day), instructed by physical therapists certified in the rehabilitation of cancer patients. The exercise consisted of the following 4 types of training according to the guidelines of American College of Sports Medicine [17]. The exercise was initiated on the day following TACE, unless the patients had a fever of 38°C or greater as previously described [7]. Patients was instructed exercises which continuable after the discharge.

1) Stretching

Patients performed a series of stretches for 3–5 minutes, targeting the quadriceps femoris muscles, hamstrings, hip adductor muscles, and gastrocnemius. A static stretch was held for 10 seconds at the point of feeling tightness or slight discomfort [7, 17].

2) Strength training

Patients underwent strength training for 5–10 minutes, targeting the

bilateral quadriceps femoris muscles, gastrocnemius, and tibialis anterior muscle. Bilateral quadriceps femoris muscle and iliopsoas strength training were performed at 60% of the 1 repetition maximum (moderate to high intensity) using a hand-held dynamometer. Bilateral gastrocnemius and tibialis anterior muscles were strength trained using the patient's weight. One set consisted of 10 repetitions, and a maximum of 3 sets were performed [7, 17].

3) Balance training

Patients practiced one-leg stance and tandem stance for 5–10 minutes. Tandem stance requires standing on a straight line and maintaining posture [7, 17].

4) Endurance training

Patients were trained with either bicycle ergometers or walking for 10–15 minutes. The intensity of exercise was adjusted to maintain a subjective rating of perceived exertion of 11–13 points on the Borg scale and the target heart rate was adjusted to maintain 40% of the predicted maximum heart rate by the Karvonen Formula [7, 17].

*Nutrition and diet therapy*

HCC patients received nutritional care according to the Guidelines on nutritional management in Japanese patients with liver cirrhosis from the perspective of preventing hepatocellular carcinoma [18]. (1) Energy requirements: 25–35 kcal/kg (ideal bodyweight) per day. (2) Required protein intake: If there is no protein intolerance; 1.0–1.5 g/kg/day. (3) Required fat intake: lipid energy ratio 20–25%. (4) 200 kcal LES as a divided meal.

*Diagnosis, tumor node metastasis (TNM) staging, and treatment of HCC*

HCC was diagnosed using a tumor biopsy or a combination of tests for serum tumor makers, such as alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), and imaging procedures, such as ultrasonography, computed tomography (CT), magnetic resonance imaging, and/or angiography. The clinical stage of HCC was evaluated by TNM staging based on the Liver Cancer Study Group of Japan criteria [19]. The treatment for HCC was selected based on the evidence-based clinical practice guidelines for HCC of The Japan Society of Hepatology [20].

*Measurement of psoas muscle index (PMI), skeletal muscle index (SMI), and visceral fat area (VFA)*

PMI, SMI and VFA were evaluated using CT images obtained before- and after-TACE. The CT images were taken for HCC assessment in outpatient department. Thus, changes in SMI between before- and after-TACE were evaluated at 53 (34–84)-day intervals and 50 (35–80)-day interval in the Control and Exercise groups, respectively. The lower border of the third lumbar vertebra (L3) was used as a standard landmark for measuring psoas muscle mass and skeletal muscle mass. Slices at the umbilical level were used for evaluation of VFA. Psoas muscle mass, skeletal muscle mass, and VFA were measured by manual tracings on CT images and their sum was calculated using Image-J software [21]. Skeletal muscle mass and psoas muscle mass were normalized by the square of height and the data were expressed as PMI and SMI.

2) Biochemical tests

Blood biochemical tests performed were serum levels of AFP, DCP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LD), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), cholinesterase, total protein, albumin, total bilirubin, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), total cholesterol, creatine kinase, hemoglobin A1c (HbA1c), prothrombin activity. In addition, red blood cell count, hemoglobin level, white blood cell count, and platelet count were also measured.

*Changes in variables between before- and after-TACE*

Changes in PMI, SMI, and VFA between before- and after-TACE were evaluated by the ΔPMI, ΔSMI, and ΔVFA. Similarly, changes in each biochemical test were evaluated by the Δvariables.

In addition, the effectiveness of exercise on ΔPMI and ΔSMI was investigated by stratification analysis according to etiology of liver disease, severity of liver disease, and sex. Severity of liver disease was evaluated by using Fib-4 index. All patients were classified into the chronic hepatitis or liver cirrhosis group according to Fib-4 index (cut-off value 3.25) [22].

*Statistical analysis*

Data are expressed as the median (interquartile range [IQR]), range, or number. Differences between the Control and Exercise groups were analyzed

by using Wilcoxon rank sum tests. The level of statistical significance was set at $P<0.05$. In addition, independent factors associated with an increased in SMI and a no-increased in SMI were analyzed by using a logistic regression analysis and a decision-tree analysis, as previously described [7, 23].

## Results

*Patient characteristics*

The patient characteristics are summarized in Table 1. Patients in the Exercise group were significantly older than those in the Control group. However, there was no significant difference in female-to-male ratio, body mass index (BMI), PMI, and SMI between the Exercise and Control groups. No significant difference was seen in TNM stage and levels of AFP and DCP. There was no significant difference in Child-Pugh classification, albumin level, total bilirubin level, HbA1c value, and eGFR between the Exercise and Control groups (Table 1). No significant difference was seen in the rate of patients treated with BCAA supplementation, hospitalization period, or the evaluation period for CT imaging between the Exercise and Control groups. In the Exercise group, patients were treated with exercise as instructed by physical therapists certified in the rehabilitation of cancer patients (Table 1).

*Changes in PMI, SMI, and VFA*

Changes in PMI, SMI, and VFA were evaluated by the difference in each variable between before- and after-TACE (Fig. 1). After treatment with TACE, ΔPMI and ΔSMI were significantly higher in the Exercise group compared to the Control group. There was no significant difference in ΔVFA between the two groups after treatment with TACE.

There was no significant etiological difference of liver disease in ΔPMI and ΔSMI values among the all groups (Supplementary Figure 1). In addition, there was no significant etiological difference between the Increased PMI and

Decreased PMI groups (Supplementary Table 1). Similarly, no significant etiological difference of liver disease was seen between the Increased SMI and Decreased SMI groups (Supplementary Table 1).

Moreover, there was no significant difference in ΔPMI and ΔSMI values between patients with chronic hepatitis and patients with liver cirrhosis, and between male and female (Supplementary Figure 2 and 3). Furthermore, there was no significant difference in severity of liver disease and sex between the Increased PMI and Decreased PMI groups. Similarly, no significant difference in severity of liver disease and sex between the Increased SMI and Decreased SMI groups (Supplementary Table 1).

*Effects of the exercise on biochemical tests*

The changes of biochemical tests are summarized in Table 2. There was no significant difference in ΔAST, ΔALT, Δalbumin, Δtotal bilirubin, ΔHbA1c, and Δprothrombin activity between the Exercise and Control groups (Table 2). The Δcreatinine was significantly lower in the Exercise group compared to the Control group. In addition, ΔeGFR was significantly higher in the Exercise group compared to the Control group (Table 2).

*Logistic regression analysis for an increase in SMI*

The independent factors for an increase in SMI are summarized in Table 3. Exercise, Child-Pugh score, and TMN classification were selected by stepwise regression and exercise was identified as an independent factor for an increase in SMI (Table 3). Although Child-Pugh score was not an independent

factor, TMN classification was an independent negative factor for an increase in SMI (Table 3).

*Logistic regression analysis for a decrease in SMI in the Exercise group*

The independent factors for a decrease in SMI in the Exercise group are summarized in Supplementary Table 2. Male and non-sarcopenia were identified as independent risk factors for a decrease in SMI (Supplementary Table 2).

*Decision-tree algorithm for an increase in SMI*

To clarify the profile associated with an increase in SMI, a decision-tree algorithm was created using three divergence variables and classified the patients into four groups (Fig. 2). Exercise was the initial divergence variable. An increase in SMI was seen in 53% of patients with exercise (Group 1 in Fig. 2). On the other hand, an increase in SMI was seen in 36% of patients with no exercise (Group 2 in Fig. 2). Among patients with no exercise, sex was the variable for the second classification. An increase in SMI was seen in 41% of males. In males, eGFR was the third classification and the cut-off value was 81.7 ml/min/1.73 $m^2$. Thus, an increase in SMI was seen in 61% of patients with no exercise, male sex, and an eGFR ≥81.7 ml/min/1.73 $m^2$ (Group 3 in Fig. 2).

In this analysis, neither age, period of hospitalization, evaluation period for CT imaging, nor liver function tests were identified as a divergence variable for an increase in SMI.

## Discussion

In this study, we demonstrated that exercise during hospitalization for HCC significantly increased PMI and SMI in the Exercise group compared to the Control group. In addition, exercise was identified as the only independent factor for an increase in SMI. Moreover, decision-tree algorithm determined that exercise was the first divergence factor for an increase in SMI. Thus, exercise was important to increase skeletal muscle mass in in-hospital HCC patients with CLD who underwent TACE.

In this study, exercise during the hospitalization significantly increased PMI and SMI in HCC patients with CLD who underwent TACE. On the other hand, we previously reported that exercise did not completely prevent loss of skeletal muscle mass during hospitalization for HCC [7]. The reason for this discrepancy remains unclear. However, in the previous study, SMI was evaluated by BIA [7]. While, SMI was evaluated by CT scan images of abdominal cross-sectional area at the level of L3 in this study. Thus, the discrepancy may be account for the methodological difference for evaluation of SMI. BIA is useful for assessment of skeletal muscle mass [24]; however, the major limitation of these methods is an inability to differentiate water from muscle. Therefore, edematous tissue can falsely elevate muscle mass readings [25, 26]. In fact, BIA tends to overestimate muscle mass in cirrhotic patients [26, 27]. Measurement of abdominal cross-sectional muscle area using CT images is a useful method for diagnosing sarcopenia [28]. This CT method is recommended in The Japan Society of Hepatology guidelines for sarcopenia in liver disease[29].

Exercise is reported to increase portal pressure and might increase the risk of variceal bleeding in patients with esophageal varices [30]. In addition, high

intensity physical exercise (>7 METs) has been reported to cause a deterioration of renal function [31]. However, there was no variceal bleeding and deterioration of renal function and eGFR in the Exercise group of this study [32]. Our exercise program was consisted of moderate intensity exercise (median 2.5 METs). In addition, exercise is reported to enhance local sympathetic control mechanisms affecting the vascular function and structure of the kidney [33]. Exercise may also prevent catabolism of skeletal muscle, leading to suppression of amino acids load for kidney and the subsequent increase in eGFR in our study. Thus, possible reasons for safety and an improvement of renal function are difference in exercise intensity and exercise-caused improvement of condition in kidney, respectively. Thus, we are the first to demonstrate that moderate intensity exercise may be safe and tolerable in HCC patients with CLD who underwent TACE.

Cancer treatment and its side effects may cause muscle wasting [34]. In this study, we have demonstrated, for the first time, that exercise was the only independent factor for an increase in SMI in HCC patients with CLD who underwent TACE. Contrarily, Brustia et al. performed a meta-analysis and also reported that physical exercise has no significant effect on muscle mass in patients with end-stage liver disease [35]. Although the reason why our exercise protocol increased SMI remains unclear, the following are possible explanations: (1) Patients with end stage liver disease were enrolled in the previous studies; however, only 2% of patients in our study had Child-Pugh class C. (2) Nutritional therapy focusing on supplemental calorie and protein intake is an important therapy for sarcopenia [36]. In our study, nationally

registered dietitians managed nutritional therapy in all subjects. (3) Aerobic exercise was conducted in the most of previous studies; however, our exercise protocol consisted of both aerobic and resistance exercise. Resistance exercise is one of the most popular strategies to increase muscle mass [37]. In addition, skeletal muscle is known to be an endocrine organ releasing various cytokines, so-called “myokines”. Circulating myokine level is increased by resistance training to a greater extent than by aerobic exercise, leading to an increase in skeletal muscle mass [38, 39]. Thus, the severity of liver disease, nutritional management, and type of exercise may be possible reasons for the discrepancy between the results of previous reports and the results of our study.

There were some patients with increased SMI without exercise in this study. The profile for patients with increased SMI without exercise was consisted of “No Exercise”, “Male”, and “eGFR ≥ 81.7 ml/min/1.73 $m^2$” (Group3 in Figure 2). Physical activity in male is higher than female [40]. In addition, testosterone increases muscle mass [41]. Furthermore, eGFR is positively correlated with muscle mass in patients with chronic kidney disease [42]. Thus, sex and renal function may be associated with an increase in SMI in patients with no exercise.

In this study, 47% of patients in the Exercise group showed a decrease in SMI (Group 1 in Figure 2). We performed logistic regression analysis for a decrease in SMI of the Exercise group. Male and non-sarcopenia were identified as independent risk factors for a decrease in SMI.

Patients with non-sarcopenia tend to decrease muscle mass compared to patients with sarcopenia because muscle mass is higher in patients with non-

sarcopenia than in patients with sarcopenia. Although it remains unclear why male was an independent risk factor for a decrease in SMI, a possible reason is that male is reported to more prone to decrease in muscle mass because of apoptosis induction through activation of anabolic Akt pathway nor the ubiquitin-dependent protein degradation during aging in male but not female rats [43]. In addition, age-dependent decrease in muscle mass was reported to occur in older men than older women [44, 45].

There are limitations in this study. First, this is a retrospective study and PMI, SMI, and VFA after TACE were measured using CT images taken for HCC assessment in the outpatient department. Although the interval between before- and after-TACE was not significant different between the Exercise and the Control group; the interval was not exactly same period among all subjects. Thus, a prospective study is required to investigate effects of exercise on skeletal muscle mass precisely. Second, skeletal muscle mass was measured by manual tracing on CT image using NIH ImageJ software. Manual tracings can be subjective. However, Irving et al. reported that intra- and inter-investigator coefficients of reliability was high for measurements of skeletal muscle mass using both Slice-O-Matic (TomoVision, Magog, Canada) and NIH ImageJ [46]. Other researchers also used NIH ImageJ to measure adipose tissue and skeletal muscle cross-sectional areas [47, 48]. In our study, intraclass correlation coefficients was more than 0.9 (data not shown). Thus, manual tracing using NIH ImageJ software is thought to provide reliable information for skeletal muscle mass in this study.

## Conclusions

In conclusion, we demonstrated that exercise during hospitalization significantly increased PMI and SMI in the Exercise group compared to the Control group. In addition, exercise was identified as the only independent factor for an increase in SMI. Moreover, decision-tree algorithm determined that exercise was the first divergence factor for an increase in SMI. Thus, in-hospital exercise maybe beneficial to prevent sarcopenia in HCC patients with CLD who underwent TACE.

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Table 1. Patients' characteristics

| | Reference Value | Control | | Exercise | | |
|---|---|---|---|---|---|---|
| | | Median (IQR) | Range (min–max) | Median (IQR) | Range (min–max) | P |
| Number | N/A | 107 | | 102 | | |
| Age (years) | N/A | 74.0 (67.0–78.0) | 41.0–85.0 | 75.5 (71.0–81.3) | 60.0–91.0 | 0.0004 |
| Sex (female/male) | N/A | 36/71 | N/A | 38/64 | N/A | 0.5854 |
| Body mass index (kg/m$^2$) | 18.5–24.9 | 22.8 (20.7–24.8) | 16.0–33.1 | 23.7 (21.3–25.7) | 16.7–37.8 | 0.1267 |
| PMI (cm$^2$/m$^2$) | N/A | 4.9 (3.8–6.0) | 1.9–10.7 | 4.7 (3.7–5.8) | 1.5–8.8 | 0.4571 |
| SMI (cm$^2$/m$^2$) | N/A | 32.8 (25.1–39.6) | 13.8–60.7 | 30.7 (24.1–36.8) | 11.9–51.2 | 0.1741 |
| VFA (cm$^2$) | N/A | 46.0 (28.6–74.6) | 5.0–193.1 | 61.9 (37.7–81.2) | 4.4–244.1 | 0.0114 |
| Etiology of liver disease (AIH/ Alcohol/HBV/HCV/NASH/Others) | N/A | 1/12/6/83/3/2 | N/A | 3/11/9/67/1/11 | N/A | 0.0454 |
| TNM stage (I/II/III/IV) | N/A | 7/40/41/19 | N/A | 10/40/36/16 | N/A | 0.8031 |
| AFP (ng/mL) | ⩽10.0 | 31.7 (8.3–138.2) | 1.3–22385.0 | 29.6 (6.3–229.1) | 1.3–67036.0 | 0.9137 |

| | | | | | | |
|---|---|---|---|---|---|---|
| DCP (mAU/ml) | ⩽ 40.0 | 115.0 (27.5–2037.5) | 9.0–745283.0 | 116.0 (32.5–858.5) | 9.0–104513.0 | 0.9953 |
| Child-Pugh class (A/B/C) | N/A | 62/41/4 | N/A | 64/34/2 | N/A | 0.5723 |
| AST (IU/L) | 13–30 | 47 (34–67) | 13–177 | 42 (30–54) | 18–183 | 0.0129 |
| ALT (IU/L) | 10–30 | 34 (23–55) | 7–101 | 28 (21–38) | 7–186 | 0.0180 |
| Lactate dehydrogenase (IU/L) | 120–240 | 231 (201–276) | 118–498 | 213 (188–253) | 129–624 | 0.0159 |
| ALP (IU/L) | 115–359 | 373 (287–522) | 144–1489 | 351 (285–485) | 152–1467 | 0.4566 |
| GGT (IU/L) | 13–64 | 42 (27–90) | 12–604 | 44 (26–76) | 9–551 | 0.9787 |
| Cholinesterase (U/L) | 201–421 | 194 (95–196) | 36–418 | 159 (117–207) | 53–360 | 0.0800 |
| Total protein (g/dL) | 6.6–8.1 | 7.2 (6.8–7.6) | 5.7–9.4 | 7.2 (6.6–7.6) | 5.9–8.9 | 0.4482 |
| Albumin (g/dL) | 4.1–5.1 | 3.4 (3.0–3.7) | 2.3–4.4 | 3.4 (3.1–3.7) | 2.3–4.4 | 0.3848 |
| Total bilirubin (mg/dL) | 0.40–1.20 | 0.98 (0.70–1.28) | 0.33–4.98 | 0.86 (0.62–1.22) | 0.28–1.51 | 0.0725 |
| BUN (mg/dL) | 8.6–22.9 | 16 (13.3–19.8) | 8.8–36.9 | 17 (14–19.9) | 5.9–47.6 | 0.4621 |
| Creatinin (mg/dL) | 0.65–1.07 | 0.73 (0.60–0.92) | 0.35–8.50 | 0.76 (0.62–0.94) | 0.36–1.91 | 0.4379 |
| eGFR (mL/min/1.73 $m^2$) | > 90.0 | 74.5 (58.3–93.1) | 5.5–156.7 | 70.4 (55.0–83.2) | 20.4–128.5 | 0.0830 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Total cholesterol (mg/dL) | 150–199 | 145 (127–165) | 80–254 | 139 (126–158) | 79–233 | 0.4437 |
| Creatine kinase (U/L) | 59–248 | 121 (77–171) | 34–386 | 89 (57–132) | 10–374 | 0.0021 |
| HbA1c (%) | 4.3–5.8 | 5.7 (5.2–6.3) | 4.4–8.0 | 5.8 (5.5–6.4) | 4.3–13.4 | 0.1009 |
| Prothrombin activity (%) | 80–120 | 77 (63–88) | 15–118 | 80 (69–90) | 15–117 | 0.3499 |
| Red blood cell count ($\times 10^4/\mu L$) | 435–555 | 382 (346–418) | 186–515 | 388 (355–418) | 249–615 | 0.3588 |
| Hemoglobin (g/dL) | 13.7–16.8 | 12.0 (10.5–13.0) | 7.0–16.4 | 11.9 (10.7–12.8) | 7.3–15.6 | 0.8207 |
| White blood cell count (/μL) | 3300–8600 | 3500 (2700–4600) | 1200–9700 | 3950 (3200–5100) | 1800–21100 | 0.0524 |
| Platelet count (x $10^3/mm^3$) | 15.8–34.8 | 9.6 (6.8–14.6) | 2.8–24.4 | 10.9 (8.4–14.75) | 3.2–46.6 | 0.0761 |
| BCAA supplementation (Yes/No) | N/A | 66/41 | N/A | 55/47 | N/A | 0.2560 |
| Hospitalization (days) | N/A | 15 (13–20) | 8–38 | 15 (11–21) | 7–55 | 0.4862 |
| Evaluation period for CT imaging (days) | N/A | 53 (34–84) | 7–309 | 50 (35–80) | 7–312 | 0.8324 |
| Metabolic equivalents | N/A | N/A | N/A | 2.5 (2–3) | 2–4 | N/A |
| Energy consumption due to therapeutic exercise (kcal/hospitalization) | N/A | N/A | N/A | 509.1 (300.0–732.8) | 42.7–1718.4 | N/A |

Note. Data are expressed as median (interquartile range [IQR]), range, or number. Abbreviations: N/A; not applicable, PMI; psoas muscle index, SMI; skeletal muscle index, VFA; visceral fat area, AIH; autoimmune hepatitis, HBV; hepatitis B virus, HCV; hepatitis C virus, NASH; non-alcoholic steatohepatitis, TNM; tumor nodes metastasis, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma-glutamyl transpeptidase, BUN; blood urea nitrogen, eGFR; estimated glomerular filtration rate, HbA1c; hemoglobin A1c. BCAA; branched-chain amino acids, CT; computed tomography.

Table 2. Effects of the therapeutic exercise on biochemical tests

| | Control | | Exercise | | |
|---|---|---|---|---|---|
| | Median (IQR) | Range (min–max) | Median (IQR) | Range (min–max) | P |
| Number | 107 | | 102 | | |
| ΔAST (IU/L) | -2 (-14–9) | -62–245 | -2 (-8.5–3) | -119–61 | 0.8573 |
| ΔALT (IU/L) | 2 (-10–19) | -55–165 | 1 (-5.5–1) | -102–75 | 0.4351 |
| ΔLactate dehydrogenase (IU/L) | -35 (-60– -10) | -165–221 | -20 (-47–0) | -201–86 | 0.0501 |
| ΔALP (IU/L) | -38 (-88–31) | -657–950 | -15 (-48–32) | -505–575 | 0.0812 |
| ΔGGT (IU/L) | 0 (-9–5) | -210–125 | 0 (-5–7.25) | -210–125 | 0.2738 |
| ΔCholinesterase (U/L) | -27 (-54.5– -10.5) | -303–11 | -26 (-42– -13.5) | -127–68 | 0.4047 |
| ΔTotal protein (g/dL) | -0.63 (-0.95– -0.39) | -2.68–1.26 | -0.54 (-0.85– -0.19) | -6.49–7.69 | 0.0742 |
| ΔAlbumin (g/dL) | -0.37 (-0.61– -0.075) | -1.14–0.79 | -0.36 (-0.6– -0.185) | -1.16–0.49 | 0.8046 |
| ΔTotal bilirubin (mg/dL) | -0.09 (-0.28–0.07) | -2.10–10.03 | -0.1 (-0.27–0.03) | -0.84–1.04 | 0.4980 |
| ΔBUN (mg/dL) | -0.9 (-3.85–1.80) | -18.50–46.60 | -1.15 (-4.80–2.75) | -10.50–14.30 | 0.9704 |

| | | | | | |
|---|---|---|---|---|---|
| ΔCreatinine (mg/dL) | -0.01 (-0.07–0.05) | -2.37–0.92 | -0.05 (-0.11–0.01) | -0.59–0.36 | 0.0075 |
| ΔeGFR (mL/min/1.73 $m^2$) | 2.00 (-5.05–8.50) | -26.5–52.8 | 4.45 (-0.15–10.43) | -27.00–59.00 | 0.0242 |
| ΔTotal cholesterol (mg/dL) | -33.0 (-45.3– -20.5) | -87.0– -14.0 | -5.5 (-14.5–8.25) | -46.0–46.0 | 0.0014 |
| ΔCreatine kinase (U/L) | -73.0 (-118.0– -39.5) | -259.0–86.0 | -56.0 (-77.0– -26.0) | -299.0–121.0 | 0.0215 |
| ΔHbA1c (%) | 0.1 (0.1–0.1) | 0.1–0.1 | -0.1 (-0.3–0.1) | -0.7–0.4 | 0.2578 |
| ΔProthrombin activity (%) | -4.0 (-8.5–3.0) | -36.0–44.4 | -2.0 (-6.8–4.0) | -36.0–54.5 | 0.1603 |
| ΔRed blood cell count (×$10^4$/μL) | -25.0 (-48.0– -5.0) | -123.0–168.0 | -21.5 (-44.0– -7.3) | -110.0–69.0 | 0.6341 |
| ΔHemoglobin (g/dL) | -0.7 (-1.3–0.0) | -3.8–4.1 | -0.6 (-1.4– -0.1) | -5.4–1.1 | 0.8781 |
| ΔWhite blood cell count (/μL) | 400 (-400–900) | -4400–11400 | 350 (-300–925) | -4600–9100 | 0.8781 |
| ΔPlatelet count (x $10^3$/$mm^3$) | 0.2 (-1.1–2.2) | -6.1–14.7 | 0.8 (-0.8–2.45) | -24.3–21.3 | 0.1175 |

Note. Data are expressed as median (interquartile range [IQR]), range, or number. Abbreviations: AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma-glutamyl transpeptidase, BUN; blood urea nitrogen, eGFR; estimated glomerular filtration rate, HbA1c; hemoglobin A1c.

Table 3. Logistic regression analysis for the increase in SMI

| Factors | Unit | Hazard ratio | 95% Confidence interval | P value |
|---|---|---|---|---|
| Exercise | N/A | 2.13 | 1.215–3.846 | 0.0085 |
| Child-Pugh score | 1 | 0.50 | 0.111–1.311 | 0.1708 |
| TNM classification | N/A | 0.51 | 0.283–0.915 | 0.0238 |

Note. Abbreviations: SMI; skeletal muscle index, N/A; not applicable, TNM; tumor node metastasis.

Supplementary Table 1. Difference in etiology, severity of liver disease, and sex in the decreased PMI and increased PMI groups and in the decreased SMI and increased SMI groups of the Exercise group.

| | Decreased PMI | Increased PMI | P value | Decreased SMI | Increased SMI | P value |
|---|---|---|---|---|---|---|
| Etiology of liver disease (AIH/ Alcohol/HBV/HCV/NASH/Others) | 1/5/4/29/0/6 | 2/6/5/38/1/5 | 0.9195 | 1/4/5/33/1/4 | 2/7/4/34/0/7 | 0.7381 |
| Severity of liver disease (Chronic hepatitis/Liver cirrhosis) | 39/6 | 46/11 | 0.4222 | 39/9 | 46/8 | 0.5945 |
| Sex (Female/Male) | 14/31 | 24/33 | 0.2542 | 14/34 | 24/30 | 0.1112 |

Note. Abbreviations: PMI; psoas muscle index, SMI; skeletal muscle index, AIH; autoimmune hepatitis, HBV; hepatitis B virus, HCV; hepatitis C virus, NASH; non-alcoholic steatohepatitis.

Supplementary Table 2. Logistic regression analysis for no-increased in SMI of the Exercise group

| Factors | Unit | Hazard ratio | 95% Confidence interval | P value |
|---|---|---|---|---|
| Sex (Male) | N/A | 2.93 | 1.122–7.650 | 0.0282 |
| Etiology of liver disease (AIH/ Alcohol/HBV/HCV/NASH/Others) | N/A | 1.56 | 0.910–2.664 | 0.1061 |
| TNM stage (I/II/III/IV) | N/A | 1.40 | 0.853–2.305 | 0.1828 |
| Metabolic equivalents | 1 | 2.25 | 0.987–5.146 | 0.0538 |
| Sarcopenia according to Japan Society of Hepatology guidelines (Non-sarcopenia) | N/A | 4.12 | 1.321–12.826 | 0.0147 |
| Albumin (g/dL) | 1 | 0.44 | 0.146–1.355 | 0.1538 |

Note. Abbreviations: AIH; autoimmune hepatitis, HBV; hepatitis B virus, HCV; hepatitis C virus, NASH; non-alcoholic steatohepatitis, TNM; tumor nodes metastasis, TNM; tumor nodes metastasis.

## Figure legends

Figure 1. Difference in (A) ΔPMI, (B) ΔSMI, (C) ΔVFA between the Exercise and Control groups. Abbreviations: PMI; psoas muscle index, SMI; skeletal muscle index, N.S.; not significant.

Figure 2. Decision-tree algorithm for an increase in SMI in HCC patients who underwent TACE. The pie graphs indicate the proportion of patients with an increase in SMI (white) and patients with a decrease in SMI (black). Abbreviations: SMI; skeletal muscle index, eGFR; estimated glomerular filtration rate.

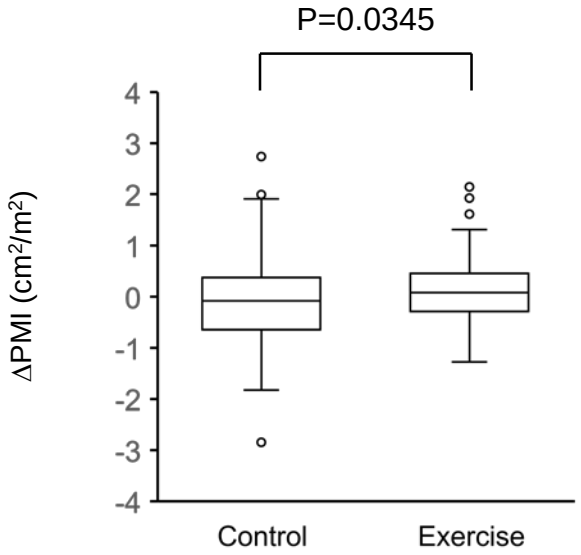
Supplementary Figure 1. Etiological differences of liver disease in (A) ΔPMI and (B) ΔSMI among all groups. Abbreviations: PMI; psoas muscle index, SMI; skeletal muscle index, AIH; autoimmune hepatitis, HBV; hepatitis B virus, HCV; hepatitis C virus, NASH; non-alcoholic steatohepatitis, N.S.; not significant.

Supplementary Figure 2. Differences in (A) ΔPMI and (B) ΔSMI between the patients with chronic hepatitis and liver cirrhosis. All patients were classified into the chronic hepatitis or liver cirrhosis group according to Fib-4 index (cut-off value 3.25). Abbreviations: PMI; psoas muscle index, SMI; skeletal muscle index.

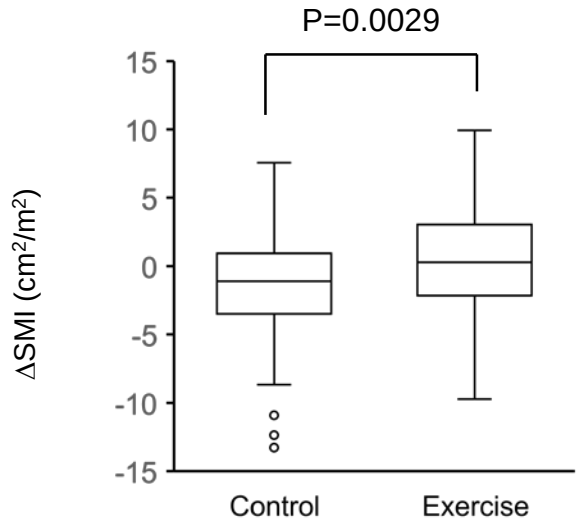
Supplementary Figure 3. Differences in (A) ΔPMI and (B) ΔSMI between the female and male groups. Abbreviations: PMI; psoas muscle index, SMI; skeletal muscle index.

Figure 1

A


P=0.0345
ΔPMI (cm²/m²)
4
3
2
1
0
-1
-2
-3
-4
Control
Exercise

B


P=0.0029
ΔSMI (cm²/m²)
15
10
5
0
-5
-10
-15
Control
Exercise

C

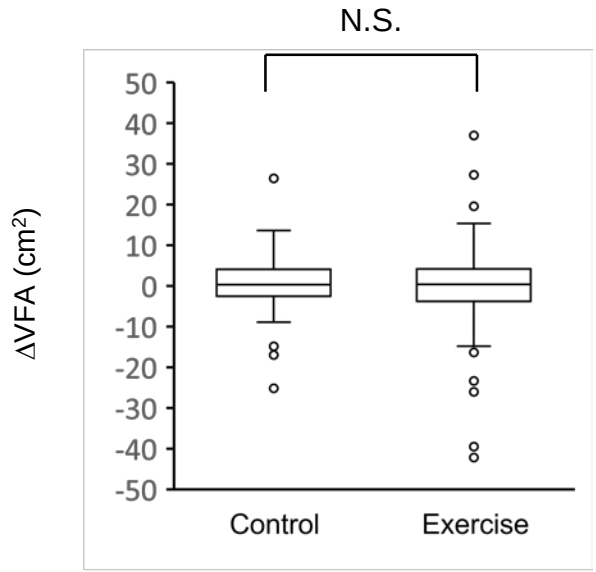

N.S.
ΔVFA (cm²)
50
40
30
20
10
0
-10
-20
-30
-40
-50
Control
Exercise

Figure 2

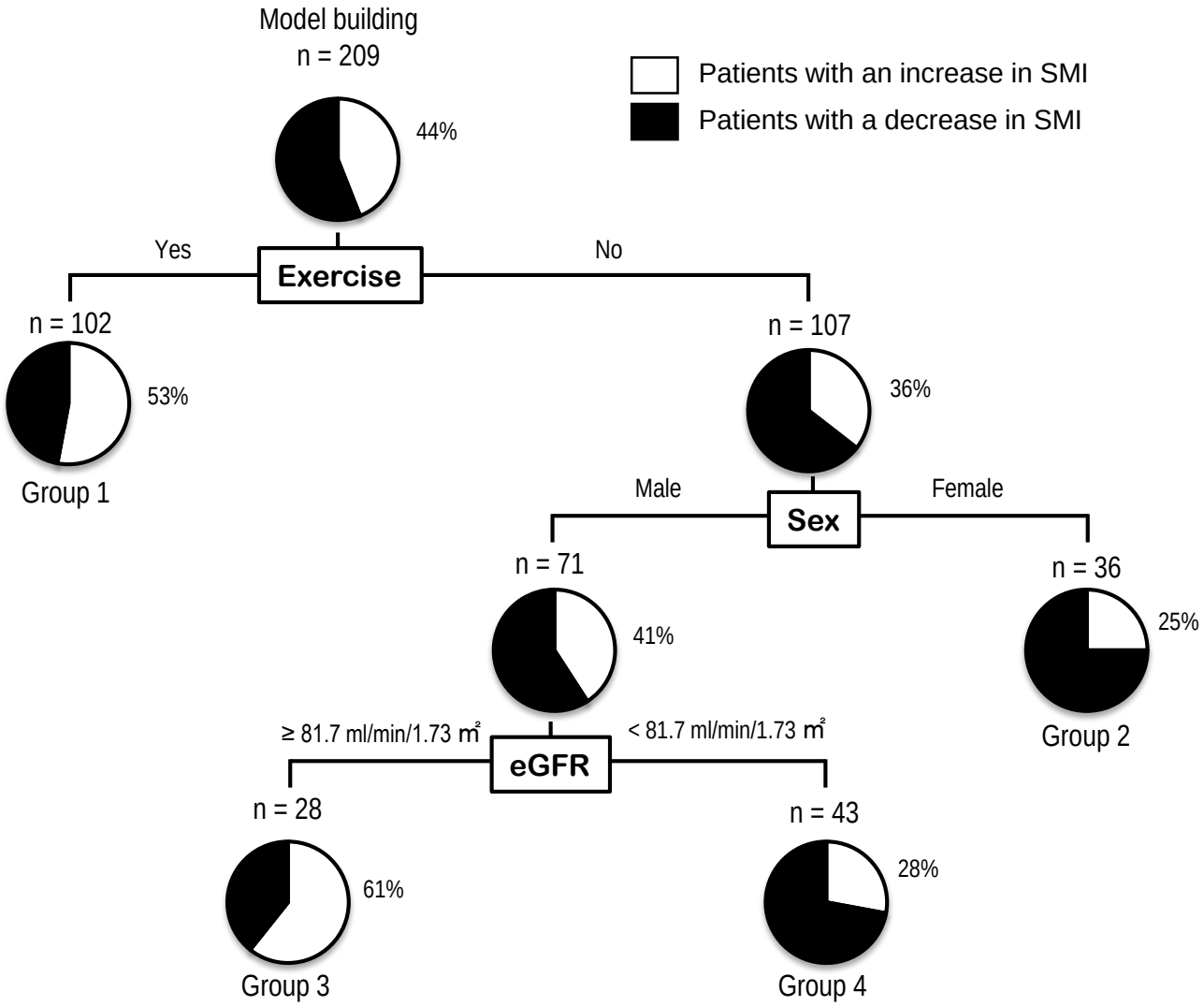

Model building
n = 209
44%
Patients with an increase in SMI
Patients with a decrease in SMI
Yes
Exercise
No
n = 102
53%
Group 1
n = 107
36%
Male
Sex
Female
n = 71
41%
n = 36
25%
Group 2
≥ 81.7 ml/min/1.73 ㎡
eGFR
< 81.7 ml/min/1.73 ㎡
n = 28
61%
Group 3
n = 43
28%
Group 4

Table 1. Patients' characteristics

| | Reference Value | Control | | Exercise | | |
|---|---|---|---|---|---|---|
| | | Median (IQR) | Range (min–max) | Median (IQR) | Range (min–max) | P |
| Number | N/A | 107 | | 102 | | |
| Age (years) | N/A | 74.0 (67.0–78.0) | 41.0–85.0 | 75.5 (71.0–81.3) | 60.0–91.0 | 0.0004 |
| Sex (female/male) | N/A | 36/71 | N/A | 38/64 | N/A | 0.5854 |
| Body mass index (kg/m$^2$) | 18.5–24.9 | 22.8 (20.7–24.8) | 16.0–33.1 | 23.7 (21.3–25.7) | 16.7–37.8 | 0.1267 |
| PMI (cm$^2$/m$^2$) | N/A | 4.9 (3.8–6.0) | 1.9–10.7 | 4.7 (3.7–5.8) | 1.5–8.8 | 0.4571 |
| SMI (cm$^2$/m$^2$) | N/A | 32.8 (25.1–39.6) | 13.8–60.7 | 30.7 (24.1–36.8) | 11.9–51.2 | 0.1741 |
| VFA (cm$^2$) | N/A | 46.0 (28.6–74.6) | 5.0–193.1 | 61.9 (37.7–81.2) | 4.4–244.1 | 0.0114 |
| Etiology of liver disease (AIH/ Alcohol/HBV/HCV/NASH/Others) | N/A | 1/12/6/83/3/2 | N/A | 3/11/9/67/1/11 | N/A | 0.0454 |
| TNM stage (I/II/III/IV) | N/A | 7/40/41/19 | N/A | 10/40/36/16 | N/A | 0.8031 |
| AFP (ng/mL) | ≤10.0 | 31.7 (8.3–138.2) | 1.3–22385.0 | 29.6 (6.3–229.1) | 1.3–67036.0 | 0.9137 |

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|---|---|---|---|---|---|---|
| DCP (mAU/ml) | ≤ 40.0 | 115.0 (27.5–2037.5) | 9.0–745283.0 | 116.0 (32.5–858.5) | 9.0–104513.0 | 0.9953 |
| Child-Pugh class (A/B/C) | N/A | 62/41/4 | N/A | 64/34/2 | N/A | 0.5723 |
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| ALT (IU/L) | 10–30 | 34 (23–55) | 7–101 | 28 (21–38) | 7–186 | 0.0180 |
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| ALP (IU/L) | 115–359 | 373 (287–522) | 144–1489 | 351 (285–485) | 152–1467 | 0.4566 |
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| Albumin (g/dL) | 4.1–5.1 | 3.4 (3.0–3.7) | 2.3–4.4 | 3.4 (3.1–3.7) | 2.3–4.4 | 0.3848 |
| Total bilirubin (mg/dL) | 0.40–1.20 | 0.98 (0.70–1.28) | 0.33–4.98 | 0.86 (0.62–1.22) | 0.28–1.51 | 0.0725 |
| BUN (mg/dL) | 8.6–22.9 | 16 (13.3–19.8) | 8.8–36.9 | 17 (14–19.9) | 5.9–47.6 | 0.4621 |
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| | | | | | | |
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| Metabolic equivalents | N/A | N/A | N/A | 2.5 (2–3) | 2–4 | N/A |
| Energy consumption due to therapeutic exercise (kcal/hospitalization) | N/A | N/A | N/A | 509.1 (300.0–732.8) | 42.7–1718.4 | N/A |

Note. Data are expressed as median (interquartile range [IQR]), range, or number. Abbreviations: N/A; not applicable, PMI; psoas muscle index, SMI; skeletal muscle index, VFA; visceral fat area, AIH; autoimmune hepatitis, HBV; hepatitis B virus, HCV; hepatitis C virus, NASH; non-alcoholic steatohepatitis, TNM; tumor nodes metastasis, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma-glutamyl transpeptidase, BUN; blood urea nitrogen, eGFR; estimated glomerular filtration rate, HbA1c; hemoglobin A1c. BCAA; branched-chain amino acids, CT; computed tomography.

Table 2. Effects of the therapeutic exercise on biochemical tests

| | Control | | Exercise | | |
|---|---|---|---|---|---|
| | Median (IQR) | Range (min–max) | Median (IQR) | Range (min–max) | P |
| Number | 107 | | 102 | | |
| ΔAST (IU/L) | -2 (-14–9) | -62–245 | -2 (-8.5–3) | -119–61 | 0.8573 |
| ΔALT (IU/L) | 2 (-10–19) | -55–165 | 1 (-5.5–1) | -102–75 | 0.4351 |
| ΔLactate dehydrogenase (IU/L) | -35 (-60– -10) | -165–221 | -20 (-47–0) | -201–86 | 0.0501 |
| ΔALP (IU/L) | -38 (-88–31) | -657–950 | -15 (-48–32) | -505–575 | 0.0812 |
| ΔGGT (IU/L) | 0 (-9–5) | -210–125 | 0 (-5–7.25) | -210–125 | 0.2738 |
| ΔCholinesterase (U/L) | -27 (-54.5– -10.5) | -303–11 | -26 (-42– -13.5) | -127–68 | 0.4047 |
| ΔTotal protein (g/dL) | -0.63 (-0.95– -0.39) | -2.68–1.26 | -0.54 (-0.85– -0.19) | -6.49–7.69 | 0.0742 |
| ΔAlbumin (g/dL) | -0.37 (-0.61– -0.075) | -1.14–0.79 | -0.36 (-0.6– -0.185) | -1.16–0.49 | 0.8046 |
| ΔTotal bilirubin (mg/dL) | -0.09 (-0.28–0.07) | -2.10–10.03 | -0.1 (-0.27–0.03) | -0.84–1.04 | 0.4980 |
| ΔBUN (mg/dL) | -0.9 (-3.85–1.80) | -18.50–46.60 | -1.15 (-4.80–2.75) | -10.50–14.30 | 0.9704 |

| | | | | | |
|---|---|---|---|---|---|
| ΔCreatinine (mg/dL) | -0.01 (-0.07–0.05) | -2.37–0.92 | -0.05 (-0.11–0.01) | -0.59–0.36 | 0.0075 |
| ΔeGFR (mL/min/1.73 $m^2$) | 2.00 (-5.05–8.50) | -26.5–52.8 | 4.45 (-0.15–10.43) | -27.00–59.00 | 0.0242 |
| ΔTotal cholesterol (mg/dL) | -33.0 (-45.3– -20.5) | -87.0– -14.0 | -5.5 (-14.5–8.25) | -46.0–46.0 | 0.0014 |
| ΔCreatine kinase (U/L) | -73.0 (-118.0– -39.5) | -259.0–86.0 | -56.0 (-77.0– -26.0) | -299.0–121.0 | 0.0215 |
| ΔHbA1c (%) | 0.1 (0.1–0.1) | 0.1–0.1 | -0.1 (-0.3–0.1) | -0.7–0.4 | 0.2578 |
| ΔProthrombin activity (%) | -4.0 (-8.5–3.0) | -36.0–44.4 | -2.0 (-6.8–4.0) | -36.0–54.5 | 0.1603 |
| ΔRed blood cell count (×$10^4$/μL) | -25.0 (-48.0– -5.0) | -123.0–168.0 | -21.5 (-44.0– -7.3) | -110.0–69.0 | 0.6341 |
| ΔHemoglobin (g/dL) | -0.7 (-1.3–0.0) | -3.8–4.1 | -0.6 (-1.4– -0.1) | -5.4–1.1 | 0.8781 |
| ΔWhite blood cell count (/μL) | 400 (-400–900) | -4400–11400 | 350 (-300–925) | -4600–9100 | 0.8781 |
| ΔPlatelet count (x $10^3$/$mm^3$) | 0.2 (-1.1–2.2) | -6.1–14.7 | 0.8 (-0.8–2.45) | -24.3–21.3 | 0.1175 |

Note. Data are expressed as median (interquartile range [IQR]), range, or number. Abbreviations: AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma-glutamyl transpeptidase, BUN; blood urea nitrogen, eGFR; estimated glomerular filtration rate, HbA1c; hemoglobin A1c.

Table 3. Logistic regression analysis for the increase in SMI

| Factors | Unit | Hazard ratio | 95% Confidence interval | P value |
|---|---|---|---|---|
| Exercise | N/A | 2.13 | 1.215–3.846 | 0.0085 |
| Child-Pugh score | 1 | 0.50 | 0.111–1.311 | 0.1708 |
| TNM classification | N/A | 0.51 | 0.283–0.915 | 0.0238 |

Note. Abbreviations: SMI; skeletal muscle index, N/A; not applicable, TNM; tumor node metastasis.

**Figure legends**

Figure 1. Difference in (A) ΔPMI, (B) ΔSMI, (C) ΔVFA between the Exercise and Control groups. Abbreviations: PMI; psoas muscle index, SMI; skeletal muscle index, N.S.; not significant.

Figure 2. Decision-tree algorithm for an increase in SMI in HCC patients who underwent TACE. The pie graphs indicate the proportion of patients with an increase in SMI (white) and patients with a decrease in SMI (black). Abbreviations: SMI; skeletal muscle index, eGFR; estimated glomerular filtration rate.