ORIGINAL RESEARCH

Short running header: Prognostic value of subcutaneous adipose tissue in HCC patients

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Manuscript title:

Prognostic Value of Subcutaneous Adipose Tissue Volume in Hepatocellular Carcinoma Treated with Transcatheter Intra-arterial Therapy

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Abstract

Background: Prognosis of patients with hepatocellular carcinoma (HCC) who undergo transcatheter intra-arterial therapies including transcatheter arterial chemoembolization and transcatheter arterial infusion chemotherapy is affected by many clinical factors including liver function and tumor progression. However, the effect of body composition such as skeletal muscle and visceral and subcutaneous adipose tissues (VAT and SAT, respectively) on the prognosis of these patients remains unclear. We investigated the prognostic value of body composition in HCC patients treated with transcatheter intra-arterial therapies.

Patients and Methods: This study retrospectively evaluated 100 HCC patients treated with transcatheter intra-arterial therapies between 2005 and 2015. Areas of skeletal muscle, VAT, and SAT were measured on computed tomography images at third lumbar vertebra level and normalized by the height squared to calculate the skeletal muscle index, VAT index, and SAT index (SATI). Visceral to subcutaneous adipose tissue area ratio was also calculated. Overall survival (OS) was compared between high- and low-index groups for each body composition. Furthermore, prognostic significance was assessed by univariate and multivariate analyses using Cox proportional hazards models.

Results: Among the body composition indexes, only SATI could significantly differentiate OS (*P* = .012). Multivariate analysis showed that SATI (low- vs. high-SATI; hazard ratio [HR], 2.065; 95% confidence interval [CI], 1.187-3.593; *P* = .010), serum albumin (<3.5 vs. ≥3.5 g/dL; HR, 2.007; 95% CI, 1.037-3.886; *P* = .039), serum alpha-fetoprotein (<20 vs. ≥20 ng/mL; HR, 0.311; 95% CI, 0.179-0.540; *P* < .001), and mRECIST assessment (complete response + partial response + stable disease vs. progressive disease; HR, 0.392; 95% CI, 0.221-0.696; *P* = .001) were indicated as independent prognostic factors for OS.

Conclusions: High SAT volume is associated with better survival outcomes in HCC patients treated with transcatheter intra-arterial therapies. Elucidation of the mechanisms regulating SAT volume may offer new therapeutic strategy in these patients.

Key words: hepatocellular carcinoma, subcutaneous adipose tissue, transcatheter arterial chemoembolization, transcatheter arterial infusion chemotherapy, prognosis

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world and a leading cause of cancer death.[1] Transcatheter intra-arterial therapies, including transcatheter arterial chemoembolization (TACE) and transcatheter arterial infusion chemotherapy (TAI) are endorsed in practice guidelines as major treatment options for patients with unresectable HCC.[2-6] However, it is often difficult to exactly predict the prognosis of HCC patients treated with transcatheter intra-arterial therapies in clinical practice, because outcomes are affected by various factors, including the etiology of underlying liver disease, hepatic reserve function, tumor-specific factors, such as number, diameter, and distribution in the liver, and the efficacy of treatment.[7-10] Furthermore, a close association between sarcopenia and clinical outcomes of HCC has been shown in recent studies, and thus, body composition changes related to skeletal muscle loss may also affect prognosis.[11,12] It is important to identify all contributors to the prognosis for precise prediction.

Body mass index (BMI) is a widely used anthropometric index to assess the degree of obesity and is associated with clinical outcomes of malignancies including HCC.[13] In addition, recent studies have revealed that quantification of

several body compositions, such as skeletal muscle mass and visceral and subcutaneous adipose tissue (VAT and SAT, respectively) volumes, is also useful to predict the prognosis of HCC patients treated with various methods, including surgical resection, radiofrequency ablation, and tyrosine kinase inhibitors.[14-17] However, there has been no study that specifically focused on the association between body composition and outcomes of HCC patients treated with transcatheter intra-arterial therapies.

In this study, we retrospectively measured the area of skeletal muscle, VAT, and SAT using cross-sectional computed tomography (CT) images in HCC patients treated with transcatheter intra-arterial therapies. We statistically analyzed the association between these body compositions and outcomes and evaluated the prognostic value of the body compositions.

Patients and methods

Patients

We retrospectively analyzed consecutive HCC patients who underwent transcatheter intra-arterial therapies as initial treatment at Niigata University Medical and Dental Hospital between January 2005 and December 2015. The

diagnosis of HCC was confirmed on the basis of typical enhancement patterns on dynamic CT or dynamic magnetic resonance imaging, i.e., contrast enhancement in the arterial phase and subsequent wash-out in the equilibrium phase.[18] When the typical enhancement patterns of HCC were not depicted, the diagnosis of HCC depended on histopathological analyses by tumor biopsy. Exclusion criteria were as follows: (I) presence of massive ascites or subcutaneous edema; (II) undergoing initial treatment other than TACE or TAI; and (III) achievement of complete response (CR) by additional radical treatment with surgical resection or local ablation therapies such as radiofrequency ablation following transcatheter intra-arterial therapies.

This retrospective study was approved by the ethics committee of Niigata University School of Medicine and carried out in accordance with the 1975 Helsinki Declaration (approval number 2442). Because of the anonymous nature of the data, the requirement for additional informed consent to participate in this study was waived.

Treatment procedure

TACE and/or TAI were performed according to the clinical practice guidelines for

HCC of the Japan Society of Hepatology.[6] Briefly, TACE or TAI is recommended for patients with multiple tumors and liver damage of Child-Pugh class A or B. The TAI procedure consists of injecting cisplatin (IA-call; Nippon Kayaku, Tokyo, Japan), miriplatin (Miripla; Dainippon Sumitomo Pharma, Osaka, Japan), or an emulsion of epirubicin (Farmorubicin; Pfizer, Tokyo, Japan) in lipiodol into hepatic arteries including tumor nourishing arteries. TACE includes subsequent embolization of the feeding arteries with gelatin sponge particles (Gelpart; Nihonkayaku, Tokyo, Japan) after TAI. TAI, which was devoid of embolization, was implemented when multiple tumors were extensively distributed in bilateral lobes of the liver, the arterial anatomy precluded a super selective injection, or significant arteriovenous fistulas or tumor thrombi in the main trunk of portal vein existed.

Body composition quantification

The body composition variables were quantified by the acquisition of a CT scan slice image at the third lumbar vertebra (L3) level undertaken prior to treatment for the purpose of the clinical workup for HCC. The skeletal muscle area was measured by using sliceOmatic software (version 5.0; Tomovision, Montreal,

Canada; Fig. 1A), and adipose tissue area was determined by using Ziostation2 (version 2.1; Ziosoft, Tokyo, Japan; Fig. 1B). As previously described, thresholds of tissue Hounsfield units (HU) for delineation of the regions were adopted as follows: −29 to +150 HU for skeletal muscle, −150 to −50 for VAT, and −190 to −30 for SAT.[19,20] These cross-sectional areas (cm^2) were normalized by the height squared (m^2) to determine the skeletal muscle index (SMI), VAT index (VATI), and SAT index (SATI). The visceral to subcutaneous adipose tissue area ratio (VSR) was also calculated. The cut-off values for the classification of SMI into low-SMI or high-SMI groups were defined as SMI <42 cm^2/m^2 for men and <38 cm^2/m^2 for women according to the Japanese Society of Hepatology guideline for sarcopenia in liver disease.[21] The cut-off values of VATI, SATI, and VSR were set for each sex by using optimal stratification to find the most significant *P* value by means of a log-rank test as previously described.[22,23]

Clinical data

The following clinical data were retrospectively collected from medical records and used for analysis: age; sex; BMI; hepatitis virus infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), or non-B non-C (NBNC); serum alanine

transaminase (ALT) level; serum total bilirubin level; serum albumin level; platelet count; Child-Pugh classification; serum alpha-fetoprotein (AFP) level; the tumor-node-metastasis (TNM) stage;[24] maximal tumor size; number of tumors classified into solitary or multiple; branched-chain amino acid (BCAA) supplementation; and treatment response of transcatheter intra-arterial therapies. The treatment response was assessed according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST), and classified as follows: CR, partial response (PR), stable disease (SD), and progressive disease (PD).[25]

Overall survival (OS) was calculated based on the days between the date of CT examination prior to treatment and the date of death or December 2015 for surviving patients.

Statistical analyses

Continuous variables were expressed as median (interquartile range: IQR), and categorical variables were expressed as numbers of patients. The Mann-Whitney U-test was used to compare differences in median values. Either Fisher's exact test or the chi-squared test was used to compare differences in categorical variables between groups. The correlations between each body composition

index and BMI were analyzed using Spearman's correlation analysis by sex. OS rates were calculated using the Kaplan-Meier method and compared between groups using a log-rank test. Univariate and multivariate analyses with Cox proportional hazards model were used to analyze prognostic variables for OS, expressed as hazard ratios (HR) and 95% confidence intervals (CI). All variables were dichotomized, and significant variables in univariate analysis were included in multivariate models. All statistical analyses were conducted using SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). All tests of significance were two-sided and *P* values < .05 were considered statistically significant.

Results

Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics of the patients are shown in Table 1. A total of 100 patients, including 69 male and 31 female patients, were enrolled in this study. HCC was diagnosed according to histopathological findings in only 4 patients and imaging features in other 96 patients. Sixty-five patients died during the median observation period of 746 days. The median age of all patients was 71 years, and female patients were significantly older than male

patients in the cohort. SMI and VSR were significantly higher in male than in female patients, whereas BMI, VATI, and SATI did not significantly differ between men and women. Seventy-two patients were classified into Child-Pugh class A, 28 into class B, and 0 into class C. Fifty-nine patients had advanced HCC which was classified into TNM stage III and IV. Fifty-three patients were treated with the combination of TACE and TAI, and the treatment response of transcatheter intra-arterial therapies was PD in more than half of patients. No difference was observed in TNM stages and treatment response between men and women.

Correlation analyses of body composition indexes and BMI

The correlations between each body composition index and BMI were analyzed (Table 2). In men, the BMI was significantly correlated with SMI, VATI, and SATI, but not with VSR. SATI showed a significantly negative correlation with VSR. In contrast, in women, there was no significant correlation between BMI and VSR or SMI. The correlation between SATI and VSR was also not significant in women.

Survival analysis

Sex-specific cut-off values for VATI, SATI, and VSR determined by optimal

stratification were as follows: VATI <44.0 cm^2/m^2 for men and <35.0 cm^2/m^2 for women, SATI <40.0 cm^2/m^2 for men and <30.0 cm^2/m^2 for women, and VSR <1.08 for men and <0.86 for women. The patients were classified by the cut-off values into low- or high-index groups for each body composition (Table 3) and incorporated into the survival analysis.

The results of univariate and multivariate analyses of Cox proportional hazards model are shown in Table 4. Of the body composition indexes, only SATI was significantly associated with OS in univariate analysis. In addition to SATI, serum albumin level, Child-Pugh classification, serum AFP level, TNM stages, maximal tumor size, and mRECIST assessment were also statistically significant predictors for OS in univariate analysis. Of these variables, SATI (low- vs. high-SATI; HR, 2.065; 95% CI, 1.187-3.593; *P* = .010), serum albumin level (<3.5 vs. ≥3.5 g/dL; HR, 2.007; 95% CI, 1.037-3.886; *P* = .039), serum AFP level (<20 vs. ≥20 ng/mL; HR, 0.311; 95% CI, 0.179-0.540; *P* < .001), and mRECIST assessment (CR+PR+SD vs. PD; HR, 0.392; 95% CI, 0.221-0.696; *P* = .001) were indicated as independent prognostic factors for OS in multivariate analysis.

Kaplan-Meier survival curves of the patients stratified by BMI and body composition indexes are shown in Fig. 2. The log-rank test showed a significant

difference in OS stratified only by SATI (*P* = .012; Fig. 2D), but not by BMI (*P* = .126; Fig. 2A), SMI (*P* = .701; Fig. 2B), and VATI (*P* = .566; Fig. 2C). Although not statistically significant, the OS of the high-VSR group tended to be lower than that of the low-VSR group (*P* = .067; Fig. 2E).

Cross-sectional areas of SAT and VAT measured on CT images in typical cases with high and low SATI are demonstrated in Fig. 3. The CT image of the patient no. 1 with high SATI is shown in Fig. 3A. The patient was 68-years man and had HBV infection, TNM stage III, Child-Pugh grade B, 59.5 in SATI, and 56.0 in VATI. The patient was alive for 1800 days at the observation end time. The patient no. 2 was 73-years man with low SATI (Fig. 3B). The patient had HCV infection, TNM stage II, Child-Pugh grade A, 19.5 in SATI, and 57.3 in VATI. The patient died in 751 days,

Comparison of demographic and clinical characteristics between low- and high-SATI groups

The comparison of baseline demographic and clinical characteristics between patients in the low- and high-SATI groups is shown in Table 5. The low-SATI group consisted of 38 men and 7 women, which were a significantly lower proportion of

women than in the high-SATI group. BMI, SMI, and VATI were significantly higher in the high-SATI group; however, VSR was not. Regarding etiology, NBNC were also significantly more frequent in the high-SATI group. No other variables, including laboratory data, tumor-specific factors, or course of treatment, differed significantly between the two groups.

Discussion

In this study, we retrospectively quantified the volume of skeletal muscle, VAT, and SAT using cross-sectional CT images and investigated the association with the survival outcome of HCC patients treated with transcatheter intra-arterial therapies. It was revealed that a low SATI was an independent prognostic factor of poor OS in these patients, whereas no other body composition index affected the OS.

In cancer patients, adipose tissue lipolysis is augmented, whereas adipogenesis is weakened with cancer progression.[26-30] One of the major biological functions of white adipose tissue is energy storage, and it can protect cancer patients against increased energy exhaustion induced by the cachectic state.[31-33] In previous studies, SAT has been reported to be beneficial for lipid and

glucose metabolism.[34,35] Thus, these functions of SAT may contribute to the improvement of outcomes of patients with advanced HCC in this study.

Whether VAT accumulation is beneficial or harmful for the survival of HCC patients is currently controversial.[14-17] In contrast, a high VSR was revealed as an adverse prognostic factor for various malignancies, including HCC, in previous studies.[12,36-38] Contrary to the favorable effects of SAT, the detrimental effects of VAT have frequently been observed in cancer patients. Although VAT is also a component of white adipose tissues, it has functions distinct from SAT.[34] VAT is a metabolically active endocrine organ, and its excess accumulation induces the alteration of expression levels of various adipokines, such as interleukin-6, tumor necrosis factor, and leptin, leading to carcinogenesis and tumor progression.[39-41] Furthermore, many studies have demonstrated that low skeletal muscle volume was also associated with poor clinical outcomes in HCC patients.[11,12,42-46]

Contrary to the significantly detrimental impacts of high VAT volume, high VSR, and low skeletal muscle volume reported previously, other than SATI, the body composition indexes examined in this study were not significant prognosticators. We have considered that this discrepancy may be attributed to the more advanced tumor stages and less curative treatment undergone in most

of our patients compared to subjects in previous studies, because, in general, tumor progression and treatment methods affect prognosis more profoundly than body composition changes in cancer patients.

To our knowledge, this is the first study that demonstrated the association between high SAT volume and improved survival outcomes of HCC patients treated with transcatheter intra-arterial therapies. The results of our study are consistent with those of previous studies on subjects with prostate cancer and multiple myeloma.[47,48] The study that investigated multiple myeloma additionally showed that fluorodeoxyglucose (FDG) uptake as assessed by positron emission tomography CT (PET/CT) was significantly increased in patients with lower SAT volumes.[48] This finding suggests that a more active tumor metabolism indicated by a higher FDG uptake may lead to hypercatabolism, which is responsible for a decrease in SAT volume. Although we were unable to assess FDG uptake because PET/CT is not performed as the routine workup for HCC, a similar mechanism may also be at work in our patients.

Several limitations of this study should be acknowledged. First, this was a single-institution study with a relatively small number of patients which was not sufficient to determine optimal cut-off values of SATI to predict the outcomes of

HCC patients. Besides, there were differences in sex and etiology between low- and high-SATI groups which may become confounding factors of the prognosis. Further study including larger number of patients is needed to confirm our results. Second, the design of this study was retrospective, and we were unable to reveal the mechanism underlying the relationship between lower SAT volume and worse survival. A comprehensive investigation, including a biological analysis of SAT in patients with HCC, is required.

Conclusion

This study found that high SAT volume is associated with better survival outcomes in HCC patients treated with transcatheter intra-arterial therapies. Further investigation to elucidate the mechanisms regulating SAT volume in cancer patients may lead to an improvement in clinical outcomes through early therapeutic interventions.

Acknowledgements

Not applicable.

Author contributions

All authors contributed to the study design as well as collection and analysis of the data. TK, HK, and ON developed the study concept, performed statistical analysis, and drafted the manuscript. SA, HK, AS, KK, AT, MT, and SY were involved in data assembly and interpretation. ST supervised the study design and critically revised the manuscript. All authors approved the final version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

2. Llovet JM, Real MI, Montaña X, et al; Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734-1739.

3. Takayasu K, Arii S, Ikai I, et al; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006;131:461-469.

4. Okusaka T, Kasugai H, Shioyama Y, et al. Transarterial chemotherapy alone versus transarterial chemoembolization for hepatocellular carcinoma: a randomized phase III trial. J Hepatol 2009;51:1030-1036.

5. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.

6. Kokudo N, Hasegawa K, Akahane M, et al. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res. 2015; doi: 10.1111/hepr.12464.

7. Ogasawara S, Chiba T, Ooka Y, et al. A prognostic score for patients with intermediate-stage hepatocellular carcinoma treated with transarterial chemoembolization. PLoS One. 2015;10:e0125244.

8. Barman PM, Sharma P, Krishnamurthy V, et al. Predictors of mortality in patients with hepatocellular carcinoma undergoing transarterial chemoembolization. Dig Dis Sci. 2014;59:2821-2825.

9. Hu HT, Kim JH, Lee LS, et al. Chemoembolization for hepatocellular carcinoma: multivariate analysis of predicting factors for tumor response and survival in a 362-patient cohort. J Vasc Interv Radiol. 2011;22:917-923.

10. Ikeda M, Maeda S, Ashihara H, Nagahama H, Tanaka M, Sasaki Y. Transcatheter arterial infusion chemotherapy with cisplatin-lipiodol suspension in patients with hepatocellular carcinoma. J Gastroenterol. 2010;45:60-67.

11. Iritani S, Imai K, Takai K, et al. Skeletal muscle depletion is an independent prognostic factor for hepatocellular carcinoma. J Gastroenterol. 2015;50:323-332.

12. Fujiwara N, Nakagawa H, Kudo Y, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol. 2015;63:131-140.

13. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity,

and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-1638.

14. Ohki T, Tateishi R, Shiina S, et al. Visceral fat accumulation is an independent risk factor for hepatocellular carcinoma recurrence after curative treatment in patients with suspected NASH. Gut 2009;58:839-844.

15. Itoh S, Shirabe K, Matsumoto Y, et al. Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma. Ann Surg Oncol 2014;21:3063-3068.

16. Higashi T, Hayashi H, Kaida T, et al. Prognostic Impact of Visceral Fat Amount and Branched-Chain Amino Acids (BCAA) in Hepatocellular Carcinoma. Ann Surg Oncol 2015;22 Suppl 3:S1041-1047.

17. Nault JC, Pigneur F, Nelson AC, et al. Visceral fat area predicts survival in patients with advanced hepatocellular carcinoma treated with tyrosine kinase inhibitors. Dig Liver Dis 2015;47:869-876.

18. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.

19. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, et al. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized

tomography. J Appl Physiol (1985). 1998;85:115-122.

20. Miller KD, Jones E, Yanovski JA, et al. Visceral abdominal-fat accumulation associated with use of indinavir. Lancet 1998;351:871-875.

21. Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K, Nishiguchi S. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol Res. 2016;46:951-963.

22. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629-635.

23. van Vledder MG, Levolger S, Ayez N, et al. Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg 2012;99:550-557

24. Liver Cancer Study Group of Japan. General Rules for the Clinical and Pathological Study of Primary Liver Cancer, 3rd English ed. Tokyo: KANEHARA & CO., LTD.; 2010. p. 26-27.

25. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for

hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.

26. Tsoli M, Swarbrick MM, Robertson GR. Lipolytic and thermogenic depletion of adipose tissue in cancer cachexia. Semin Cell Dev Biol 2016;54:68-81.

27. Batista ML Jr, Neves RX, Peres SB, et al. Heterogeneous time-dependent response of adipose tissue during the development of cancer cachexia. J Endocrinol 2012;215:363-373.

28. Dahlman I, Mejhert N, Linder K, et al. Adipose tissue pathways involved in weight loss of cancer cachexia. Br J Cancer 2010;102:1541-1548.

29. Bing C, Russell S, Becket E, et al. Adipose atrophy in cancer cachexia: morphologic and molecular analysis of adipose tissue in tumour-bearing mice. Br J Cancer 2006;95:1028-1037.

30. Zuijdgeest-van Leeuwen SD, van den Berg JW, Wattimena JL, et al. Lipolysis and lipid oxidation in weight-losing cancer patients and healthy subjects. Metabolism 2000;49:931-936.

31. Murphy RA, Wilke MS, Perrine M, et al. Loss of adipose tissue and plasma phospholipids: relationship to survival in advanced cancer patients. Clin Nutr 2010;29:482-487.

32. Camus V, Lanic H, Kraut J, et al. Prognostic impact of fat tissue loss and

cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Eur J Haematol 2014;93:9-18.

33. Cooper AB, Slack R, Fogelman D, et al. Characterization of Anthropometric Changes that Occur During Neoadjuvant Therapy for Potentially Resectable Pancreatic Cancer. Ann Surg Oncol 2015;22:2416-2423.

34. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev 2010;11:11-18.

35. Tran TT, Yamamoto Y, Gesta S, et al. Beneficial effects of subcutaneous fat transplantation on metabolism. Cell Metab 2008;7:410-420.

36. Wu W, Liu X, Chaftari P, et al. Association of body composition with outcome of docetaxel chemotherapy in metastatic prostate cancer: a retrospective review. PLoS One 2015 Mar 30;10:e0122047. doi: 10.1371/journal.pone.0122047. eCollection 2015.

37. Grignol VP, Smith AD, Shlapak D, et al. Increased visceral to subcutaneous fat ratio is associated with decreased overall survival in patients with metastatic melanoma receiving anti-angiogenic therapy. Surg Oncol 2015;24:353-358.

38. Okamura A, Watanabe M, Mine S, et al. Clinical Impact of Abdominal Fat

Distribution on Prognosis After Esophagectomy for Esophageal Squamous Cell Carcinoma. Ann Surg Oncol 2016;23:1387-1394.

39. Cabia B, Andrade S, Carreira MC, et al. A role for novel adipose tissue-secreted factors in obesity-related carcinogenesis. Obes Rev 2016;17:361-376.

40. Park EJ, Lee JH, Yu GY, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 2010;140:197-208.

41. Sharma D, Wang J, Fu PP, et al. Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. Hepatology 2010;52:1713-1722.

42. Harimoto N, Shirabe K, Yamashita YI, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg 2013;100:1523-1530.

43. Levolger S, van Vledder MG, Muslem R, et al. Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. J Surg Oncol 2015;112:208-213.

44. Kamachi S, Mizuta T, Otsuka T, et al. Sarcopenia is a risk factor for the recurrence of hepatocellular carcinoma after curative treatment. Hepatol Res

2016;46:201-208.

45. Yabusaki N, Fujii T, Yamada S, et al. Adverse impact of low skeletal muscle index on the prognosis of hepatocellular carcinoma after hepatic resection. Int J Surg 2016;30:136-142.

46. Harimoto N, Yoshizumi T, Shimokawa M, et al. Sarcopenia is a poor prognostic factor following hepatic resection in patients 70 years of age and older with hepatocellular carcinoma. Hepatol Res 2016;46:1247-1255.

47. Antoun S, Bayar A, Ileana E, et al. High subcutaneous adipose tissue predicts the prognosis in metastatic castration-resistant prostate cancer patients in post chemotherapy setting. Eur J Cancer 2015;51:2570-2577.

48. Takeoka Y, Sakatoku K, Miura A, et al. Prognostic Effect of Low Subcutaneous Adipose Tissue on Survival Outcome in Patients With Multiple Myeloma. Clin Lymphoma Myeloma Leuk 2016;16:434-441.

Figure legends

Figure 1. Cross-sectional computed tomography images at the third lumbar vertebra level to measure body composition areas. The green area indicates skeletal muscle (A). The red and blue areas indicate visceral adipose and subcutaneous adipose tissues, respectively (B).

Figure 2. Overall survival rate stratified by body mass index (BMI, A), skeletal muscle index (SMI, B), visceral adipose tissue index (VATI, C), subcutaneous adipose tissue index (SATI, D), and visceral to subcutaneous adipose tissue area ratio (VSR, E).

Figure 3. Cross-sectional computed tomography images of typical cases with high and low subcutaneous adipose tissue index (A and B, respectively).

Figure 1

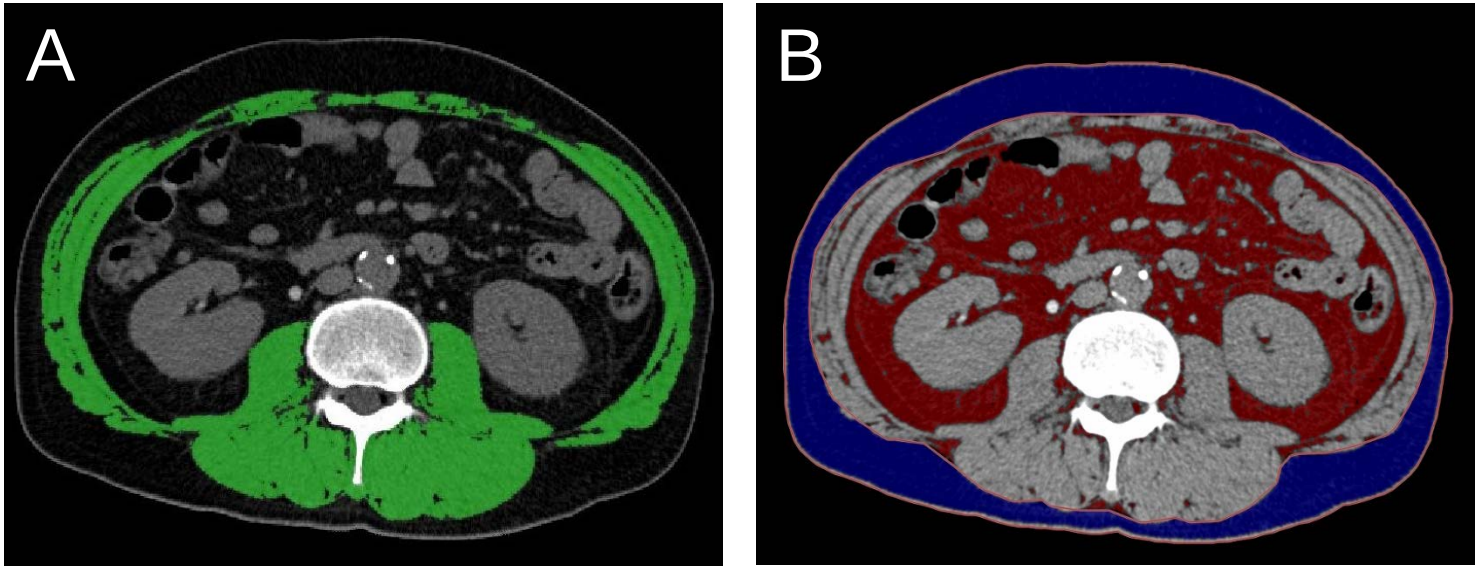

Figure 2

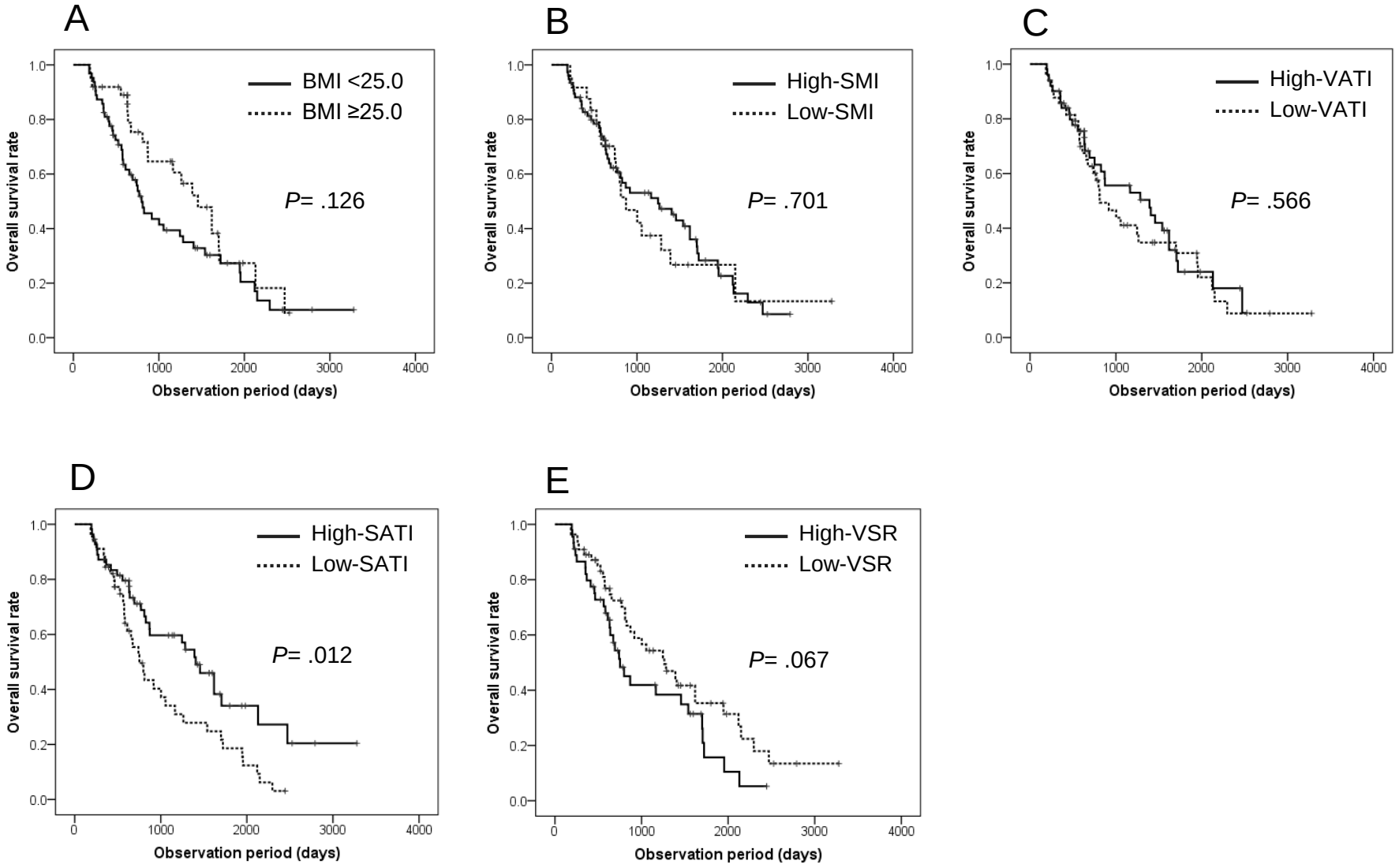
A
BMI <25.0
BMI ≥25.0
P= .126
B
High-SMI
Low-SMI
P= .701
C
High-VATI
Low-VATI
P= .566
D
High-SATI
Low-SATI
P= .012
E
High-VSR
Low-VSR
P= .067
Overall survival rate
Observation period (days)
0.0
0.2
0.4
0.6
0.8
1.0
0
1000
2000
3000
4000

Figure 3

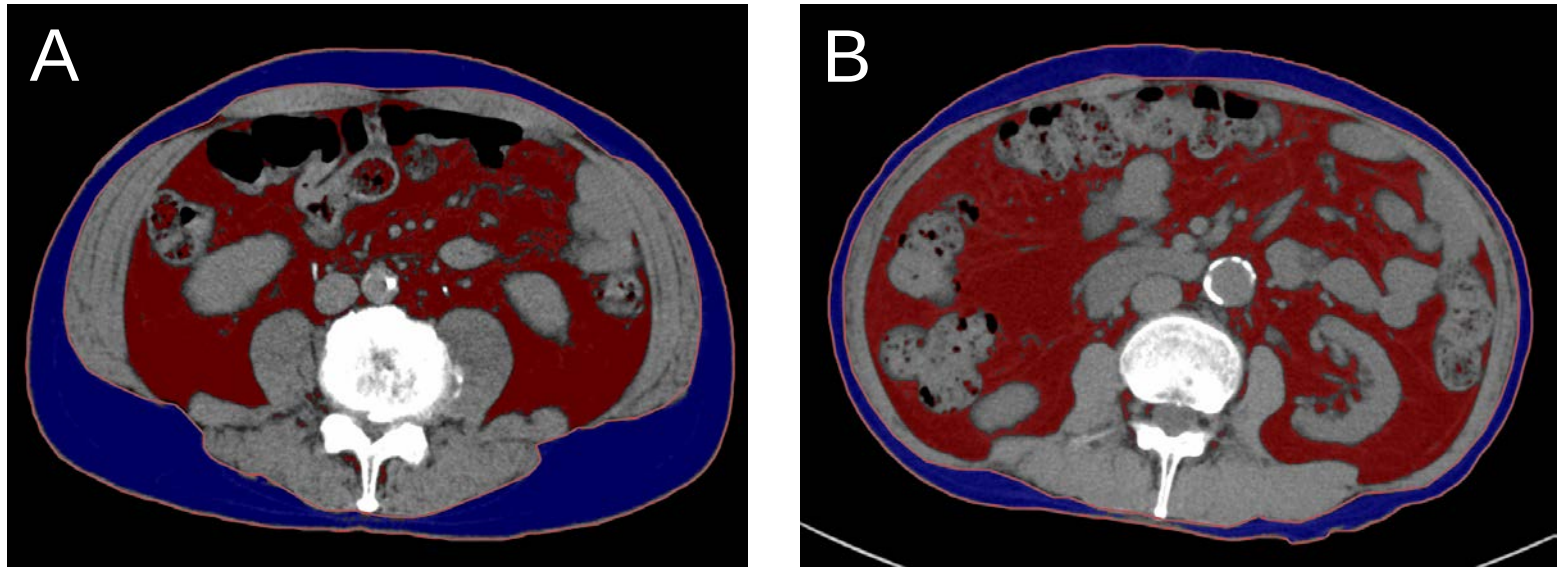

Table 1. Baseline demographic and clinical characteristics.

Variables	Total (n=100)	Men (n=69)	Women (n=31)	*P* value
Observation period, days, median [IQR]	746 [466-1455]	673 [460-1473]	826 [563-1456]	.348
Age, years, median [IQR]	71 [60-77]	66 [59-74]	75 [73-80]	.001
BMI, kg/m^2, median [IQR]	23.6 [21.4-26.4]	24.0[22.0-26.4]	22.7 [20.8-26.7]	.206
SMI, cm^2/m^2, median [IQR]	45.2 [40.0-49.5]	47.2 [44.5-53.3]	39.0 [35.3-42.0]	< .001
VATI, cm^2/m^2, median [IQR]	42.2 [23.9-58.6]	47.8 [29.8-58.5]	30.3 [15.4-60.6]	.126
SATI, cm^2/m^2, median [IQR]	41.3 [25.5-55.6]	37.0 [24.4-49.8]	46.6 [30.3-62.3]	.059
VSR, median [IQR]	0.97 [0.69-1.28]	1.07 [0.83-1.78]	0.75 [0.45-0.93]	< .001
Etiology (HBV/HCV/NBNC), n	11/49/40	11/28/30	0/21/10	.012
ALT, U/L, median [IQR]	37 [23-59]	42 [25-69]	27 [21-41]	.016
Total bilirubin, mg/dL, median [IQR]	1.0 [0.7-1.4]	1.0 [0.7-1.5]	0.9 [0.7-1.2]	.348
Albumin, g/dL, median [IQR]	3.7 [3.2-4.0]	3.7 [3.2-4.1]	3.7 [3.2-4.0]	.794
Platelet count, $\times 10^4/\mu L$, median [IQR]	12.2 [7.4-17.3]	12.2 [7.4-18.1]	12.0 [7.4-15.9]	.835
Child-Pugh classification (A/B), n	72/28	47/22	25/6	.235
AFP, ng/mL, median [IQR]	21.4 [7.0-313.8]	14.0 [7.0-224.5]	29.8 [7.0-808.0]	.461
TNM stage (I/II vs III/IV), n	11/30 vs 37/22	8/18 vs 26/17	3/12 vs 11/5	.381
Maximal tumor size, mm, median [IQR]	32 [20-65]	36 [20-72]	26 [21-51]	.304
Number of lesions (solitary/multiple), n	30/70	19/50	11/20	.482
Treatment modality (TACE/TAI/TACE+TAI)	26/21/53	16/15/38	10/6/15	.633
mRECIST (CR/PR/SD vs PD), n	19/17/8 vs 56	13/10/7 vs 39	6/7/1 vs 17	1.000
BCAA supplementation (yes/no)	66/34	46/23	20/11	.824

Table 1 (continued). Baseline demographic and clinical characteristics.

Abbreviations: IQR, interquartile range; BMI, body mass index; SMI, skeletal muscle index; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, none of HBV or HCV; ALT, alanine transaminase; AFP, alpha-fetoprotein; TNM, tumor node metastasis; TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BCAA, branched chain amino acids

Table 2. Spearman’s correlation analysis among body composition indexes

	Men (n=69)				Women (n=31)			
	SMI	VATI	SATI	VSR	SMI	VATI	SATI	VSR
BMI	r = .670 *P* < .001	r = .555 *P* < .001	r = .758 *P* < .001	r = -.019 *P* = .875	r = .310 *P* = .090	r = .840 *P* < .001	r = .867 *P* < .001	r = .333 *P* = .067
SMI	–	r = .201 *P* = .098	r = .456 *P* < .001	r = -.135 *P* = .270	–	r = .252 *P* = .171	r = .379 *P* = .036	r = -.061 *P* = .743
VATI	–	–	r = .553 *P* < .001	r = .584 *P* < .001	–	–	r = .806 *P* < .001	r = .655 *P* < .001
SATI	–	–	–	r = -.270 *P* = .025	–	–	–	r = .136 *P* = .465

Abbreviations: BMI, body mass index; SMI, skeletal muscle index; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

Table 3. Sex-specific cut-off values of body composition indexes

Variables		Cut-off values	Low, n	High, n
VATI, cm^2/m^2	Men	44.0	32	37
	Women	35.0	17	14
SATI, cm^2/m^2	Men	40.0	38	31
	Women	30.0	7	24
VSR	Men	1.08	35	34
	Women	0.86	20	11

Abbreviations: VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio

Table 4. Univariate and multivariate analysis of clinical characteristics for overall survival using Cox proportional hazards model

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years, <70 vs ≥70	1.420 (0.868-2.323)	.162		
Sex, Men vs Women	1.327 (0.773-2.278)	.305		
BMI, kg/m^2, <25.0 vs ≥25.0	1.498 (0.889-2.525)	.129		
SMI, Low SMI vs High SMI	1.115 (0.640-1.943)	.701		
VATI, Low VATI vs High VATI	1.153 (0.708-1.880)	.567		
SATI, Low SATI vs High SATI	1.863 (1.135-3.057)	.014	2.065 (1.187-3.593)	.010
VSR, Low VSR vs High VSR	0.631 (0.384-1.037)	.069		
ALT, U/L, <30 vs ≥30	0.935 (0.571-1.530)	.788		
Total bilirubin, mg/dL, <1.5 vs ≥1.5	0.651 (0.374-1.133)	.129		
Albumin, g/dL, <3.5 vs ≥3.5	1.749 (1.037-2.951)	.036	2.007 (1.037-3.886)	.039
Platelet count, $\times 10^4/\mu L$, <10.0 vs ≥10.0	1.030 (0.627-1.693)	.907		
Child-Pugh classification, A vs B	0.543 (0.316-0.933)	.027	0.630 (0.321-1.237)	.180
AFP, ng/mL, <20 vs ≥20	0.375 (0.226-0.621)	< .001	0.311 (0.179-0.540)	< .001
TNM stage, I/II vs III/IV	0.558 (0.335-0.927)	.024	0.707 (0.381-1.313)	.273
Maximal tumor size, mm, <30 vs ≥30	0.464 (0.281-0.764)	.003	0.711 (0.377-1.343)	.293
Number of tumor, solitary vs multiple	0.737 (0.427-1.272)	.273		
mRECIST assessment, CR+PR+SD vs PD	0.379 (0.220-0.655)	< .001	0.392 (0.221-0.696)	.001
BCAA supplementation, yes vs no	1.421 (0.807-2.501)	.224		

Table 4 (continued). Univariate and multivariate analysis of clinical characteristics for overall survival using Cox proportional hazards model

Abbreviations: BMI, body mass index; SMI, skeletal muscle index; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio; ALT, alanine transaminase; AFP, alpha-fetoprotein; TNM, tumor node metastasis; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BCAA, branched chain amino acids

Table 5. Comparison of demographic and clinical characteristics between low- and high-SATI group.

Variables	Low SATI (n=45)	High SATI (n=55)	*P* value
Observation period, days, median [IQR]	611 [450-1110]	869 [556-1563]	.089
Age, years, median [IQR]	71 [62-78]	70 [59-76]	.822
Sex (men/women), n	38/7	31/24	.004
BMI and body composition indexes in men			
BMI, kg/m^2, median [IQR]	22.3 [20.4-23.6]	26.2 [24.9-28.3]	< .001
SMI, cm^2/m^2, median [IQR]	46.1 [43.8-47.9]	51.5 [46.0-55.7]	.002
VATI, cm^2/m^2, median [IQR]	32.8 [19.7-51.0]	56.0 [47.8-70.1]	< .001
SATI, cm^2/m^2, median [IQR]	26.2 [19.9-33.1]	51.1 [45.5-64.0]	< .001
VSR, median [IQR]	1.14 [0.92-2.04]	1.00 [0.73-1.29]	.103
BMI and body composition indexes in women			
BMI, kg/m^2, median [IQR]	17.6 [17.1-20.8]	23.5 [21.6-28.8]	.001
SMI, cm^2/m^2, median [IQR]	33.7 [33.6-36.0]	40.2 [35.9-42.5]	.014
VATI, cm^2/m^2, median [IQR]	9.5 [8.1-14.6]	41.7 [23.9-74.7]	< .001
SATI, cm^2/m^2, median [IQR]	16.6 [12.1-20.6]	53.9 [43.9-82.3]	< .001
VSR, median [IQR]	0.68 [0.43-0.88]	0.81 [0.46-1.00]	.369
Etiology (HBV/HCV/NBNC), n	9/22/14	2/27/26	.022
ALT, U/L, median [IQR]	41 [23-79]	32 [23-50]	.216
Total bilirubin, mg/dL, median [IQR]	1.0 [0.7-1.5]	0.9 [0.8-1.3]	.911
Albumin, g/dL, median [IQR]	3.7 [3.2-4.1]	3.7 [3.2-4.0]	.821

Table 5 (continued). Comparison of demographic and clinical characteristics between low- and high-SATI group.

Variables	Low SATI (n=45)	High SATI (n=55)	*P* value
Platelet count, $\times 10^4/\mu L$, median [IQR]	12.1 [7.6-17.6]	12.2 [7.3-16.1]	.854
Child-Pugh classification (A/B), n	29/16	43/12	.179
AFP, ng/mL, median [IQR]	25.8 [5.3-539.0]	17.0 [7.3-330.0]	.808
TNM stage (I/II vs III/IV), n	6/14 vs 16/9	5/16 vs 21/13	.547
Maximal tumor size, mm, median [IQR]	42 [20-88]	28 [20-50]	.243
Number of lesions (solitary/multiple), n	17/28	13/42	.133
Treatment modality (TACE/TAI/TACE+TAI)	10/9/26	16/12/27	.657
mRECIST (CR+PR+SD vs PD), n	21 vs 24	23 vs 32	.688
BCAA supplementation (yes/no)	30/15	36/19	1.000

Abbreviations: IQR, interquartile range; BMI, body mass index; SMI, skeletal muscle index; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, none of HBV or HCV was infected; ALT, alanine transaminase; AFP, alpha-fetoprotein; TNM, tumor node metastasis; TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BCAA, branched chain amino acids