Journal of Hepatocellular Carcinoma

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

The Influence of Visceral Adiposity on Overall Survival: Exploring "Obesity Paradox" Among Hepatocellular Carcinoma Patients Who Receiving Immunotherapy

Yanzhao Zhou[1,*], Jingzhong Ouyang[2–4,*], Hongcai Yang[5,*], Zhengzheng Wang[2,*], Yi Yang[3,4,*], Qingjun Li[2], Haitao Zhao[6], Jinxue Zhou[2], Qiang Li[1]

[1]Department of Hepatobiliary Cancer, Liver Cancer Research Center, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, People's Republic of China; [2]Department of Hepatobiliary and Pancreatic Surgery, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, People's Republic of China; [3]Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; [4]Key Laboratory of Gene Editing Screening and Research and Development (R&D) of Digestive System Tumor Drugs, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; [5]Department of Interventional Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; [6]Department of Liver Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Qiang Li, Department of Hepatobiliary Cancer, Liver Cancer Research Center, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, People's Republic of China, Email liqiang@tjmuch.com; Jinxue Zhou, Department of Hepatobiliary and Pancreatic Surgery, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, 450008, People's Republic of China, Email zhoujx888@126.com

Purpose: The impact of visceral adiposity on overall survival (OS) in hepatocellular carcinoma (HCC) receiving immunotherapy was unclear. We aimed to determine how visceral adiposity affected OS and explore the interrelationships between visceral adiposity, body mass index (BMI), and other body compositions.

Patients and Methods: Data from three centers were retrospectively analyzed. Skeletal muscle index (SMI), skeletal muscle density (SMD), visceral adipose tissue index (VATI), and subcutaneous adipose tissue index (SATI) were used to define each body composition. The BMI subgroups included the underweight, the normal weight, and the obesity. The Log rank test compared survival curves calculated by the Kaplan-Meier method. The relationships between body compositions and BMI with OS were examined using Cox proportional risk regression models.

Results: A total of 305 patients who met the criteria were included. Patients with low VATI had significantly worse OS ($P = 0.001$). The protections of VATI ($P = 0.011$) on OS were independent of covariates. However, after additional adjustment of SMI, the effect of VATI on OS disappeared ($P = 0.146$), but the effect of SMD on OS did not ($P = 0.021$). BMI has a significant U-shaped relationship with OS, and the effect of BMI on OS equally disappeared after additional adjustment by SMI.

Conclusion: This study first demonstrated that high VATI and mid-level BMI were protective for the survival of patients with HCC receiving immunotherapy. Skeletal muscle status (including SMI and SMD) may be the better predictor for outcomes of patients with HCC receiving immunotherapy.

Keywords: hepatocellular carcinoma, immunotherapy, body mass index, body composition, obesity paradox

Received: 18 December 2023
Accepted: 6 June 2024
Published: 24 June 2024

Introduction

Hepatocellular carcinoma (HCC) is the world's sixth most prevalent malignant tumor and the fourth leading cause of cancer-related death.[1] Approximately 70% of patients are diagnosed as advanced stages at initial diagnosis, and systemic therapy is their first choice.[2] With the presence of immune checkpoint inhibitors (ICIs), the landscape of systemic therapy has transformed from anti-angiogenic targeted monotherapy to immunotherapy-based systemic therapy.[3] However, ICI monotherapy's objective response rate (ORR) was only 14% to 20%.[4,5] Even for the combinations of anti-angiogenic agents and immunotherapies, the ORR of unresectable HCC was less than 40%.[6,7] The significant individual differences in tumor response have prompted concerns about predictable biomarkers and the explorations of advantageous groups. Bio-characteristics with great predictive effect could effectively assist oncologists in selecting the advantageous group from immunotherapy and avoid ineffective treatment.

Body mass index (BMI) was an easy index calculated by height and weight and had a specific U-shaped relationship with the mortality in HCC, in which both the underweight and the obesity had significantly worse prognosis.[8] However, some studies have demonstrated the positive impacts of obesity on the prognosis of patients with malignancies, especially those receiving immunotherapy.[9,10] This unexpected and paradoxical survival advantage of obesity has been described as the "obesity paradox". Wang et al showed that adipose tissue could induce peripheral blood programmed death-1 (PD-1) upregulation and T cell unresponsiveness by leptin and that blocking PD-1 in a mouse tumor model was validated to be more effective in the obesity.[11] In the "obesity paradox" of melanoma, Lee et al found that visceral adipose was a protector in patients receiving immunotherapy, and this protection was only adjusted by the systemic immune-inflammation index (SII).[12] According to the "portal vein theory", which describes blood circulation from the mesenteric veins returning to liver, numerous adipokines released from visceral adipose entered the liver directly through the portal vein, so we speculate that visceral adipose may also play an essential role in the immunotherapy of HCC.[13] Additionally, the "obesity paradox" may also be attributed to the vagueness of BMI in assessing body composition. Because there was study suggesting that the protective effect of obesity was related to the severity of sarcopenia.[14] However, the interaction between body compositions (including skeletal muscle, visceral adiposity) and BMI on overall survival (OS) in patients with HCC receiving immunotherapy is currently unclear.

Hence, we conducted this retrospective study in 305 patients with unresectable HCC receiving immunotherapy to explore the impacts of visceral adiposity on OS and the interaction between body compositions and BMI.

Materials and Methods

Patients

We reviewed electronic medical records of consecutive patients with unresectable HCC receiving immunotherapy at three public tertiary care hospitals in China between August 2018 and February 2022 (the Affiliated Cancer Hospital of Zhengzhou University; the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College; the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College). The inclusion criteria were as follows: 1) patients (aged 18–75 years old) with unresectable HCC confirmed by pathology or radiography;[15,16] 2) patients who received immunotherapy for at least six weeks cumulatively; 3) patients with an adequate level of hematologic and organ function, an ECOG PS score of 0 or 1, and a Child–Pugh score of 7 points; 4) patients with upper abdominal computed tomography (CT) scans within one month before treatment. The exclusion criteria were as follows: 1) patients with previous interventional therapy or radiotherapy; 2) baseline CT was not within the predefined interval or absence of baseline imaging; 3) absence of follow-up imaging; 4) uncontrollable oedema or ascites; 5) receiving immunotherapy for less than six weeks cumulatively.

Patient data were collected from the medical record system, including age, sex, height, weight, etiology, cirrhosis, modified albumin bilirubin (mALBI) classification, Eastern Cooperative Oncology Group (ECOG) performance, Barcelona Clinic Liver Cancer (BCLC) stage, tumor features, α-fetoprotein (AFP) level and albumin level. The Medical Ethics Committee of Henan Cancer Hospital approved this study, and all participating institutions were informed and agreed. This study was conducted by the Declaration of Helsinki (as revised in 2013). Because this study was retrospective, informed consent was not required.

Treatments and Follow-Up

Immunotherapy includes anti-programmed death (ligand) 1 (PD-(L)1) antibodies, and its combination with anti-angiogenic targeted therapy. Anti-programmed death (land) 1 (PD-(L)1) antibodies include pembrolizumab, nivolumab, camrelizumab, sintilimab, atezolizumab, or tislelizumab, and administered intravenously at 200 mg (atezolizumab: 1200 mg) every three weeks. The choices of immunotherapy were decided by doctors and patients in real-world practice.

Upper abdominal computed tomography (CT) scans were performed in the first month before treatment and then every 8–10 weeks for follow-up with upper abdominal CT. Immunotherapy continued to be accepted until patients reached disease progression according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), or toxicity was unacceptable Second-line systemic therapies or any other therapeutic decisions were further made through multidisciplinary discussions.

Image Evaluations

Image evaluations were completed by two independent radiologists (more than five years of experience in abdominal radiology) who had no information about clinical outcomes. In case of divergence, another senior radiologist re-evaluated.

We evaluated the cross-sectional portal phase CT images at the third lumbar vertebra level (L3) by 3DSlicer (v. 4.10.2, www.slicer.org). Abdominal wall muscles included wall muscles (rectus abdominis, transverse abdominis, internal and external obliques), paraspinal muscles (erector spinae, quadratus lumborum), and psoas. The following tissue Hounsfield unit (HU) thresholds were applied: skeletal muscle ranges from −29 to +150 HU, subcutaneous adipose from −190 to −30 HU, and visceral adipose from −150 to −50 HU.[8] Skeletal muscle, subcutaneous, and visceral adipose tissue areas were standardized for squared height (m^2) to calculate the skeletal muscle index (SMI), the subcutaneous adipose tissue index (SATI), and the visceral adipose tissue index (VATI). The mean HU of the skeletal muscle cross-section at L3 was calculated to determine the mean skeletal muscle density (SMD). The schematic images of the evaluation of body composition variables are shown in Figure 1.

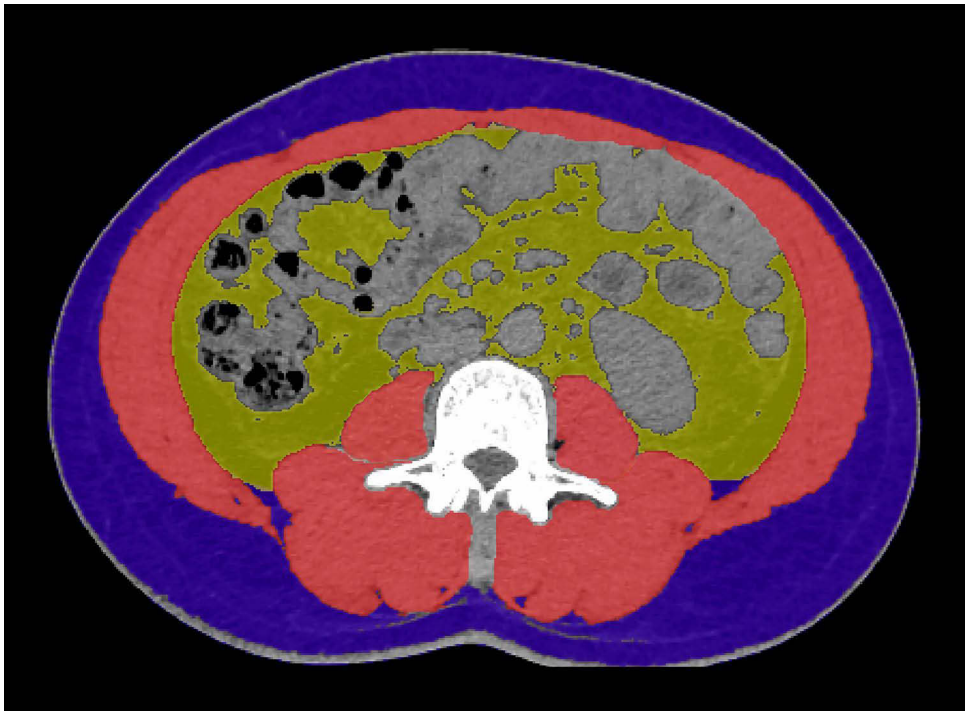

Figure 1 Axial computed tomography images at the third lumbar vertebra region. Skeletal muscle highlighted in red areas, which are evaluated and quantified using thresholds of −29 to +150 Hounsfield units (HU); visceral adipose highlighted in yellow areas, which are evaluated and quantified using thresholds of −150 to −50 HU; subcutaneous adipose highlighted in blue areas, which are evaluated and quantified using thresholds of −190 to −30 HU.

According to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), patients with at least one radiological follow-up were assessed for the best radiological tumor response. Objective response was defined as the best overall response consisting of complete response (CR), partial response (PR), and disease control was defined as the best overall response consisting of complete response (CR), partial response (PR), and stable disease (SD).

Statistical Analysis

Data are shown as frequencies (percentages) for categorical variables and as medians (interquartile ranges, IQR) or means ± standard deviations (SD) for continuous variables. OS was measured from initial therapy to death or last follow-up. Classification of BMI: < 20.0 kg/m^2 defined as underweight; 20.0–24.9 kg/m^2 defined as normal weight; and > 25.0 kg/m^2 defined as obesity.[17] The Log rank test compared survival curves calculated by the Kaplan-Meier method. SMI and VATI were adjusted for sex by Linear Regression. X-tile software (Yale University School of Medicine, New Haven, CT, USA) was applied to identify the best cut-off values for adjusted SMI and VATI that could divide patients into two groups with the greatest difference in OS. The Cox regression analyses were applied to assess the hazard rates (HRs) and 95% confidence intervals (CI) for OS associated with BMI and body composition variables. All body composition variables were processed as continuous variables (per 10 cm^2/m^2 for SMI, SATI, and VATI; per 10 HU for SMD). We first identified covariates with $P < 0.1$ by univariable analysis (Supplementary Table 1), including mALBI, BCLC Stage, major lesion diameter, macrovascular invasion, extrahepatic metastases, and AFP level. BMI and body composition variables were respectively adjusted after adjusting for covariates (Model I). Then, by additional adjustments for SMI (10 cm^2/m^2), SMD (10 HU), and VATI (10 cm^2/m^2) respectively, BMI and body composition variables were entered into Model II_{SMI}, Model III_{SMD}, and Model IV_{VATI} to explore whether the survival impact of each variable depended on skeletal muscle area, skeletal muscle density, and visceral adipose tissue area. The interaction in the Cox regression analyses was used to determine whether the associations of SMI, SMD, and VATI with OS were affected by BMI and sex. Fisher's exact or χ^2-test was used to compare the objective response rate (ORR) and disease control rate (DCR) of the two groups classified by the best cut-off values for SMI and VATI. The receiver-operating-characteristics curves (ROCs) for predicting disease control were compared by DeLong's test. All statistical analyses were processed by R version 4.2.1 (http://www.r-project.org/). A two-tailed P-value < 0.05 was deemed statistically significant.

Results

Patient Characteristics

305 patients who met the criteria were enrolled in the study (Figure 2). In the follow-up period (median follow-up period, 17.4 months; 95% CI, 16.4–19.0 months), 142 (46.6%) patients died, and the median OS was 19.0 months (95% CI, 17.0–25.7 months) (Supplementary Figure 1). The patient baselines were presented in Table 1.

The Associations of VATI and SMI with Overall Survival

The best cut-off values for sex-adjusted VATI and SMI were 30.8 cm^2/m^2 and 36.5 cm^2/m^2, respectively. Eventually, 305 patients were stratified into low VATI (≤30.8 cm^2/m^2, n=130, 42.6%) and high VATI (>30.8 cm^2/m^2, n=175, 57.4%), low SMI (≤36.5 cm^2/m^2, n=32, 10.5%) and high SMI (>36.5 cm^2/m^2, n=273, 89.5%) groups (Supplementary Figure 2). Compared to high VATI group, the OS of low VATI group was significantly worse (HR, 1.703 (95% CI 1.215–2.385); $P = 0.001$). Similar results appeared between high SMI and low SMI groups (HR, 3.794 (95% CI 1.906–7.552); $P < 0.001$; Figure 3).

In the multivariable analysis, compared with normal weight, the mortality risks of underweight (HR, 1.901 (95% CI 1.220–2.962); $P = 0.005$) and obesity (HR, 1.905 (95% CI 1.279–2.838); $P = 0.002$) were significantly increased before adjustment for SMI, SMD, and VATI. For every 10 cm^2/m^2 increase in VATI, the mortality risk was reduced by 11.1% ($P = 0.011$). For every 10 cm^2/m^2 increase in SMI, the mortality risk was reduced by 34.6% ($P < 0.001$; Table 2, Model I). After additional adjustment for SMI, the associations of VATI (HR, 0.931 (95% CI 0.847–1.025); $P = 0.146$) and BMI with OS were no longer significant (Table 2, Model II_{SMI}). The 10 cm^2/m^2 increase in VATI was significantly associated with a 16.6% reduction in the mortality risk ($P < 0.001$) after additional adjustment for SMD (Table 2, Model III_{SMD}). When VATI was additionally adjusted, BMI remained significantly associated with OS (Table 2, Model IV_{VATI}).

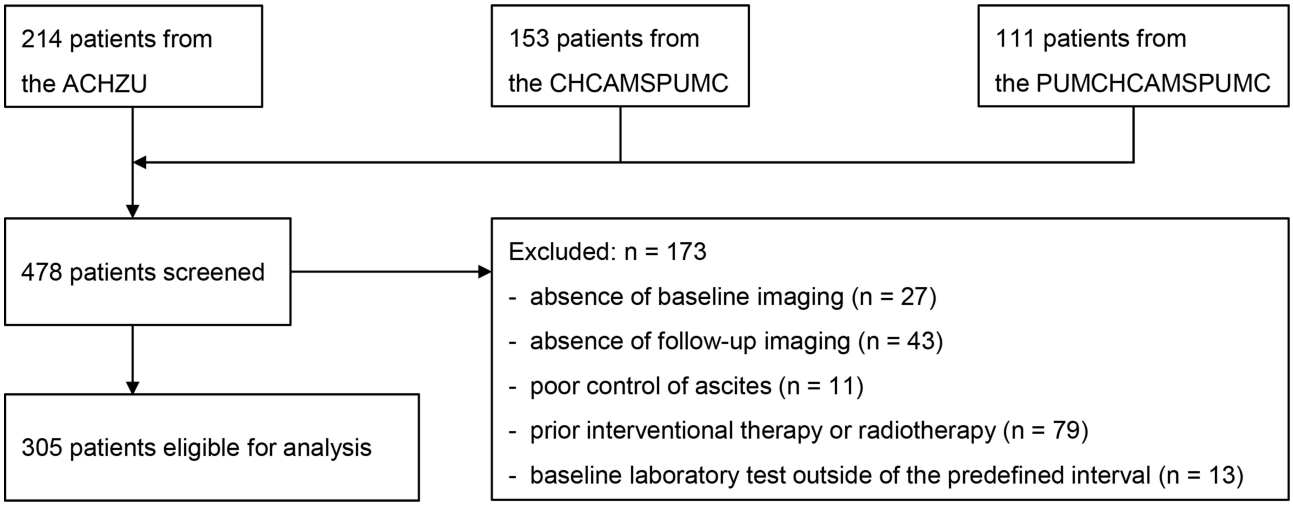

Figure 2 Flowchart of the study. The ACHZU, the Affiliated Cancer Hospital of Zhengzhou University; the CHCAMSPUMC, the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College; the PUMCHCAMSPUMC, the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Interactions for Overall Survival

The protective effect of VATI on OS in the obesity was the most prominent. For every 10 cm^2/m^2 increase in VATI, the mortality rate for the obesity, the normal weight, and the underweight decreased by 17.7%, 13.7%, and 2.9%, respectively. However, the interaction between VATI and BMI on OS was not statistically significant (*P* for interaction = 0.238). The effects of SMI and SMD on OS had no significant differences between the subgroups of BMI (*P* for interaction = 0.108; *P* for interaction = 0.466). Similarly, the effects of SMI, SMD, and VATI on OS were consistent by sex (*P* for interaction > 0.400; Table 3).

Table 1 Baseline Characteristics

Characteristics	N = 305
Age (years)[a], mean ± SD	55.6±10.0
>60, n (%)	98 (32.1)
Sex, N (%)	
Male	268 (87.9)
Female	37 (12.1)
Etiology, N (%)	
HBV	276 (90.5)
HCV	9 (3.0)
Others	20 (6.6)
Cirrhosis, N (%)	
No	55 (18.0)
Yes	250 (82.0)
ECOG performance, N (%)	
0	107 (35.1)
1	198 (64.9)
mALBI, N (%)	
Grade 1+2a	237 (77.7)
Grade 2b+3	68 (22.3)
BCLC Stage, N (%)	
A	20 (6.6)
B	64 (21.0)
C	221 (72.5)

(*Continued*)

Table 1 (Continued).

Characteristics	N = 305
Number of lesions, N (%)	
Solitary	60 (19.7)
Multiple	245 (80.3)
Major lesion diameter (cm)[b], median (IQR)	7.6 (3.5, 11.5)
Macrovascular Invasion, N (%)	
No	159 (52.1)
Yes	146 (47.9)
Extrahepatic Metastases, N (%)	
No	168 (55.1)
Yes	137 (44.9)
AFP (ng/mL), N (%)	
≤ 400	173 (56.7)
> 400	132 (43.3)
Albumin (g/dL)[b], median (IQR)	40.8 (37.3, 43.7)
Body mass index (kg/m^2)[b], median (IQR)	22.8 (20.8, 25.1)
<20.0 (Underweight), N (%)	54 (17.7)
20.0–24.9 (Normal weight), N (%)	171 (56.1)
≥25.0 (Obesity), N (%)	80 (26.2)
SMI (cm^2/m^2)[b], median (IQR)	44.1 (39.0, 49.7)
SMD (HU)[b], median (IQR)	39.8 (34.6, 44.2)
VATI (cm^2/m^2)[b], median (IQR)	35.2 (21.8, 49.8)
SATI (cm^2/m^2)[b], median (IQR)	36.8 (26.7, 49.0)

Notes: Unless indicated otherwise, data are the number of patients with percentages (%) in parentheses. [a]Data are means, with standard deviations (SD); [b]Data are medians, with interquartile ranges (IQR) in parentheses.

Abbreviations: SD, standard deviation; IQR, interquartile range; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; mALBI, modified albumin bilirubin; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein; SMI, skeletal muscle index; SMD, skeletal muscle density; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index.

Tumor Response Outcomes

Of the 305 patients, 24 (7.9%) achieved CR, 86 (28.2%) achieved PR, 138 (45.2%) achieved SD and 57 (18.7%) achieved PD. Compared to the high VATI, the ORR (28.5% vs 41.7%, $P = 0.017$) and DCR (73.8% vs 86.9%, $P = 0.004$) were significantly lower for the low VATI. Similar results showed up in the ORR (12.5% vs 38.8%, $P = 0.003$) and DCR (53.1% vs 84.6%, $P < 0.001$) for SMI (Table 4). The AUC of the VATI subgroups for predicting DCR was 0.605 (95% CI: 0.534–0.676), with 0.613 sensitivity and 0.596 specificity; the AUC of the SMI subgroups for predicting DCR was 0.654 (95% CI: 0.589–0.719), with 0.940 sensitivity and 0.368 specificity. However, the advantage of the SMI subgroups in predicting DCR was not significant compared with the VATI subgroups ($P = 0.181$; Figure 4A).

Comparison of Overall Survival for BMI Subgroups

Median OS was 25.6 months (95% CI, 19months- not evaluable (NE)) for the normal weight, 14.6 months (95% CI, 11.1months-NE) for the obesity, and 14.0 months (95% CI, 11.7months-NE) for the underweight. The OS rates at 1 and 2 years were 72.8% and 54.1% for the normal weight, 57.1% and 36.3% for the obesity, and 61.8% and 32.3% for the underweight. Both obesity (HR, 1.769 (95% CI 1.155–2.709); $P = 0.003$) and underweight (HR, 1.746 (95% CI 1.074–2.838); $P = 0.009$) were significantly associated with poorer OS (Figure 4B). This result showed that the typical U-shaped relationship between BMI and OS still existed in patients with HCC receiving immunotherapy.

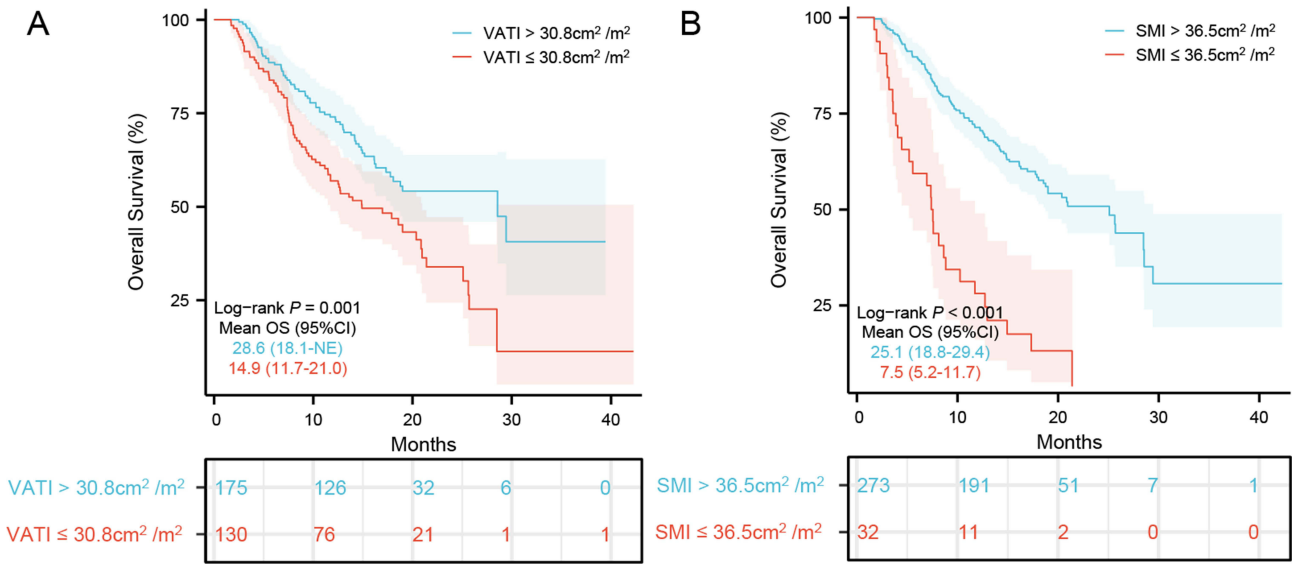

Figure 3 Kaplan-Meier curves for overall survival (OS). OS according to the best cut-off values for sex-adjusted visceral adipose tissue index (VATI, (**A**) and skeletal muscle index (SMI, (**B**).

Discussion

It is critical to screen from the limited pre-treatment data for potential biomarkers that can predict clinical outcomes to guide treatments. Body composition as a non-invasive biomarker has been proven to be significantly associated with the prognosis of several cancers.[18] Our analysis of the prognosis of patients with unresectable HCC revealed that SMI, VATI, and BMI were significant prognostic markers after immunotherapy, independent of covariates that were associated with OS ($P < 0.1$), such as mALBI grading, BCLC stage, major lesion diameter, macrovascular invasion, extrahepatic metastases, and AFP levels. Compared with Chen et al's study,[19] our study concluded that High SMI, high SMD, and high VATI were significantly associated with better OS, and there was no significant difference in these associations across BMI subgroups and sex. In addition, our results revealed a typical U-shaped relationship between BMI and OS in patients with HCC receiving immunotherapy.

Visceral adiposity consists mainly of omental and mesenteric fat depots directly drained to the portal vein. Released by visceral adipose tissue, various adipokines, such as leptin and adiponectin, and various pro-inflammatory factors, such as interleukin 1b (IL-1b), IL-6, IL-8, tumor necrosis factor-α, and monocyte chemoattractant protein-1 have been confirmed to be significantly higher in the portal vein than peripheral blood, a phenomenon known as the "portal theory".[13] It is reasonable to believe that the chronic low-grade inflammatory status created by cytokines released from visceral adiposity has a more significant impact on the tumor microenvironment (TME) in the liver than in other sites. It was the first time that our study revealed the protective effect of visceral adiposity on the prognosis of patients with HCC treated with immunotherapy. Our results showed that for every 10 cm^2/m^2 increase in VATI, the mortality risk for patients decreased by 11.1%. However, visceral obesity has been identified as an independent risk factor for OS in HCC populations receiving conventional therapy.[8] Similar contradictory conclusions were reported in lung cancer and melanoma.[12,20–22] Visceral adiposity was suspected to potentially provide an additional survival benefit for patients with cancer receiving immunotherapy. Wang et al found that leptin released from adipose tissue could promote an upregulation of PD-1 on T cells. Based on the "portal theory", it may be possible to explain why HCC patients with high VATI may benefit from anti-PD-(L)1 therapy. Moreover, the team further demonstrated that targeting PD-1 was indeed more effective in the obese murine tumor model than in the normal weight.[11] Additionally, in patients with melanoma treated with immunotherapy, the protective effect of visceral adiposity on OS has been confirmed to depend on the systemic inflammatory status.[12] In the effect of visceral adiposity on the survival of patients with HCC receiving immunotherapy, the chronic systemic inflammatory status may play an equally important role.

Table 2 Associations Between VATI, SMI and Overall Survival

Characteristics		Model I		Model II_{SMI}		Model III_{SMD}		Model IV_{VATI}	
		HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
SMI*		0.654 (0.519–0.825)	<0.001	—	—	0.711 (0.560–0.902)	0.021	0.697 (0.545–0.890)	0.004
BMI	**Normal weight**	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
	Underweight	1.901 (1.220–2.962)	0.005	1.446 (0.907–2.305)	0.121	1.828 (1.172–2.853)	0.008	1.599 (1.007–2.538)	0.047
	Obesity	1.905 (1.279–2.838)	0.002	1.417 (0.875–2.272)	0.153	1.863 (1.252–2.774)	0.002	2.076 (1.386–3.110)	<0.001
SMD†		0.665 (0.521–0.849)	0.001	0.746 (0.582–0.957)	0.021	—	—	0.572 (0.444–0.737)	<0.001
VATI *		0.889 (0.811–0.973)	0.011	0.931 (0.847–1.025)	0.146	0.834 (0.756–0.919)	<0.001	—	—
SATI *		0.956 (0.873–1.048)	0.337	0.989 (0.904–1.081)	0.804	0.594 (0.870–1.046)	0.313	1.052 (0.940–1.178)	0.379

Notes: All models were adjusted for the following covariates: mALBI (Grade 1+2a / Grade 2b+3), BCLC Stage (A/B/C), Major lesion diameter (cm), Macrovascular Invasion (No/Yes), Extrahepatic Metastases (No/Yes), and AFP (≤ 400ng/mL / > 400ng/mL). Model II_{SMI} was adjusted for covariates plus SMI in 10 cm^2/m^2. Model III_{SMD} was adjusted for covariates plus SMD in 10 HU. Model IV_{VATI} was adjusted for covariates plus VATI in 10 cm^2/m^2. *Continuous, per 10 $cm^2/m^{2.}$ †Continuous, per 10 HU.

Abbreviations: BMI, body mass index; SMI, skeletal muscle index; SMD, skeletal muscle density; VATI, visceral adipose tissue area index; SATI, subcutaneous adipose tissue area index.

Table 3 Interactions of SMI, SMD, and VATI with BMI and Sex for Overall Survival

Characteristics	BMI‡			*P*-value for Interaction	Sex§		*P*-value for interaction
	Underweight	Normal weight	Obesity		Male	Female	
	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
SMI*	0.584 (0.317–1.073)	0.687 (0.469–1.005)	0.526 (0.349–0.792)	0.108	0.557 (0.432–0.718)	0.856 (0.268–2.739)	0.683
SMD†	0.424 (0.229–0.785)	0.692 (0.490–0.987)	0.841 (0.515–1.371)	0.466	0.701 (0.528–0.931)	0.562 (0.298–1.062)	0.441
VATI*	0.971 (0.733–1.287)	0.863 (0.750–0.994)	0.823 (0.703–0.964)	0.238	0.856 (0.777–0.944)	0.967 (0.732–1.277)	0.407

Notes: Underweight was defined as BMI < 20 kg/m^2; normal weight was defined as BMI 20.0–24.9 kg/m^2; obesity was defined as BMI ≥ 25 kg/m^2. ‡Adjusted for the following covariates: mALBI (Grade 1+2a / Grade 2b+3), BCLC Stage (A/B/C), Major lesion diameter (cm), Macrovascular Invasion (No/Yes), Extrahepatic Metastases (No/Yes), and AFP (≤ 400ng/mL / > 400ng/mL). §Adjusted for the following covariates: mALBI (Grade 1+2a / Grade 2b+3), BCLC Stage (A/B/C), Major lesion diameter (cm), Macrovascular Invasion (No/Yes), Extrahepatic Metastases (No/Yes), AFP (≤ 400ng/mL / > 400ng/mL), and BMI (underweight/ normal weight/ obesity). *Continuous, per 10 cm^2/m^2. †Continuous, per 10 HU.

Abbreviations: BMI, body mass index; SMI, skeletal muscle index; SMD, skeletal muscle density; VATI, visceral adipose tissue area index.; HR, hazard ratio; CI, confidence interval.

https://doi.org/10.2147/JHC.S453262 DovePress

Table 4 Tumor Responses Stratified by VATI and SMI

Tumor Responses	Low VATI (≤30.8 cm^2/m^2) (n=130)	High VATI (>30.8 cm^2/m^2) (n=175)	*P*-value	Low SMI (≤36.5 cm^2/m^2) (n=32)	High SMI (>36.5 cm^2/m^2) (n=273)	*P*-value
ORR, N (%)	37 (28.5)	73 (41.7)	0.017	4 (12.5)	106 (38.8)	0.003
DCR, N (%)	96 (73.8)	152 (86.9)	0.004	17 (53.1)	231 (84.6)	<0.001
Best overall response						
CR, N (%)	7 (5.4)	17 (9.7)	–	0 (0.0)	24 (8.8)	–
PR, N (%)	30 (23.1)	56 (32.0)	–	4 (12.5)	82 (30.0)	–
SD, N (%)	59 (45.4)	79 (45.2)	–	13 (40.6)	125 (45.8)	–
PD, N (%)	34 (26.1)	23 (13.1)	–	15 (46.9)	42 (15.4)	–

Note: Data are the number of patients with percentages (%) in parentheses.
Abbreviations: ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; SMI, skeletal muscle index; VATI, visceral adipose tissue area index.

The association between increased BMI and increased risks of progression or death of various cancers has been widely recognized. In recent years, the obesity defined by BMI has been found to improve prognosis in a wide range of tumors, a phenomenon that contradicts conventional beliefs called the "obesity paradox". The World Cancer Research Fund has suggested that obesity possibly was associated with improved survival for breast, head, and neck cancers, non-small cell lung, renal cells, and colorectal cancers.[23] It was "possible" because the potential mechanisms of the "obesity paradox" were unclear. Skeptics argued that the hypothesis of the "obesity paradox" had some limitations for the following reasons: (1) BMI was a poor indicator to assess obesity, with excellent specificity but insufficient sensitivity; (2) The bias of studies: collider stratification bias and heterogeneity of disease bias; (3) Numerous studies used different covariates and different statistical models in their analyses; (4) Reverse causality: low BMI measured in the prediagnostic period may be caused by cachexia of patients with tumors; (5) Obesity was more likely to lead to diabetes, and drugs such as metformin used for diabetes treatment could be a potential cause of "obesity paradox".[24,25] The exciting thing was that the "obesity paradox" has been revitalized since the rise of immunotherapy. Researchers have found that the

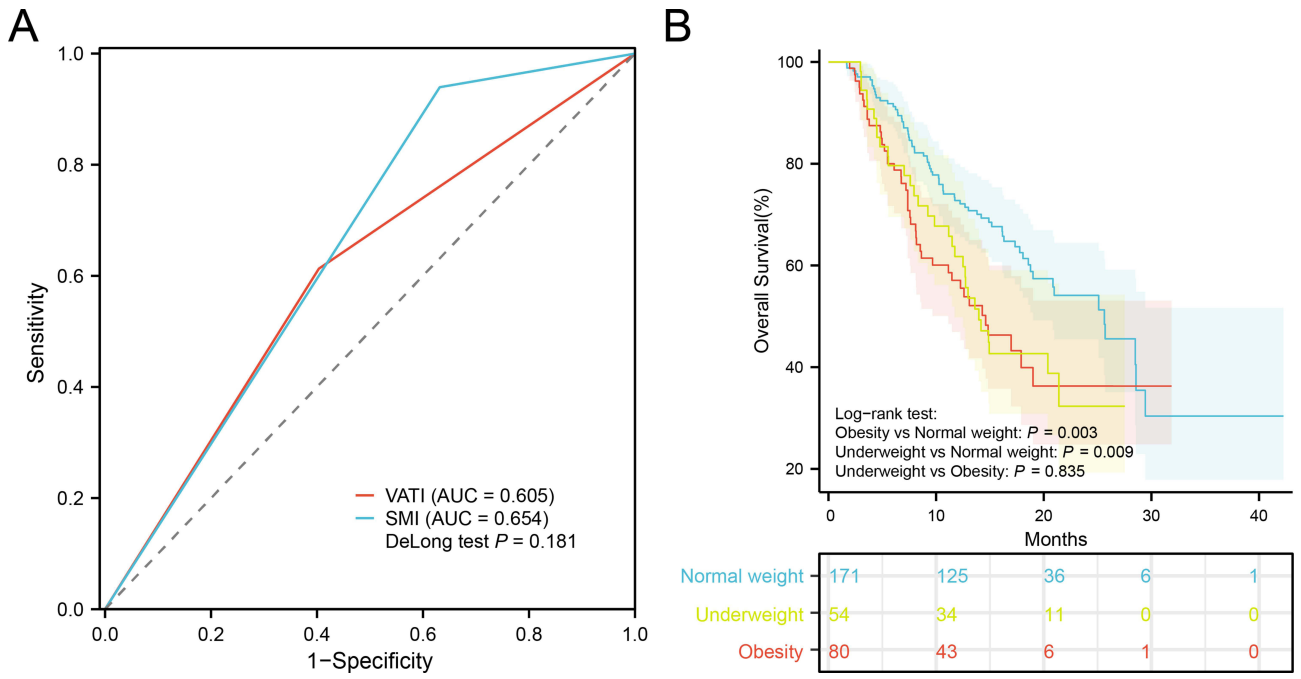

Figure 4 (**A**) The ROC curve for the visceral adipose tissue index (VATI) subgroups and the skeletal muscle index (SMI) subgroups to predict disease control rate (DCR); (**B**) Kaplan-Meier curves of overall survival (OS) for the BMI subgroups.

"obesity paradox" is better in cancer patients treated with immunotherapy. Meanwhile, with more profound mechanistic studies, researchers have discovered that cytokines released from adipose tissue do play the paradoxical roles of both cancer-promoting and cancer-resisting in cancer treatment.[11] The release of adiponectin and leptin from adipocytes promotes the release of more PD-1 proteins from T-cells, causing a reduction and dysfunction of T-cells, which promotes tumor progression.[11,26] Anti-PD-1 antibody removed this inhibition and instead made the obesity more able to benefit from immunotherapy.

We must admit that several positive results show that BMI does affect the role of immunotherapy in numerous cancer types (eg, melanoma,[27] lung cancer,[21] gastric cancer,[28] etc). However, the result that BMI increased to morbidly obese levels remained positively associated with survival benefit in some reports has raised doubts among experts.[27] It was well known that impaired nutritional status with low BMI and cardiovascular disease with high BMI could threaten cancer patients' survival.[25] Therefore, the study proposed that only some mid-level BMIs would have a protective association with cancer treatment.[9] In our results, the typical U-shaped relationship between BMI and OS validated this idea. Patients with BMI in the range of 20.0–24.9 kg/m^2 had a significantly better prognosis than BMI in the range of < 20.0 kg/m^2 and > 25.0 kg/m^2. For patients with HCC receiving atezolizumab plus bevacizumab, Mathew et al concluded that the efficacy was comparable in patients with BMI ≥25 kg/m^2 versus those with BMI < 25 kg/m^2.[29] This simple and crude binary classification masked the BMI subgroup that could significantly benefit from immunotherapy. In this era of immunotherapy, which lacks outstanding biomarkers to predict efficacy, BMI has excellent utility in clinical practice. However, enrollment-standardized large-sample studies still need to identify BMI subgroups with significant advantages during immunotherapy for different cancer types. Additionally, some researchers have proven that the effects of BMI on OS may depend on body composition.[8,12,20,28] Based on the above mechanisms, the actual manipulators (PD- 1 proteins, inflammation, or body components) behind the effect of BMI on immunotherapy need to be further explored.

In addition to visceral adiposity, we found that the skeletal muscle quantity (SMI) and skeletal muscle quality (SMD) were two other predictors for the prognosis of patients with HCC receiving immunotherapy. For every 10 cm^2/m^2 increase in SMI, the risk of death decreased by 34.6%; for every 10 HU increase in SMD, the risk of death decreased by 33.5%. As for the effects of body components on the prognosis of patients with HCC, Naoto et al revealed that skeletal muscle quantity, skeletal muscle quality, and visceral adipose distribution were independent predictors in their surgical cohort.[8] In contrast to our results, visceral adipose deposition was the risk factor for prognosis in patients with HCC in the surgical cohort. Such a difference explains the conclusion that the better survival benefit in patients with high VATI came from immunotherapy. Moreover, their results also suggested that the U-shaped relationship between BMI and OS was caused by the accumulation of three body composition variables (skeletal muscle quantity, skeletal muscle quality, and visceral adipose distribution). In our study, although BMI, VATI, SMI, and SMD were all independent predictors of OS after adjusting for covariates, the associations of VATI and BMI with OS were no longer significant after additional adjusting for SMI. Similar to our results, Chen et al found that low SMI and low SMD were the only independent risk factors for OS in patients with HCC receiving immunotherapy.[19] Moreover, our results suggest that SMI predicted tumor response better than VATI during immunotherapy. Therefore, skeletal muscle status (SMI and SMD) may be more accurate biomarkers for patients with HCC treated with anti-PD-1 antibody (monotherapy/combination therapy). In addition, skeletal muscle mass may be the potential mechanism for the "obesity paradox", which has also been recognized in melanoma treated with immunotherapy. Naik et al demonstrated that the "obesity paradox" associated with overweight/Grade I obesity only held in patients with high serum creatinine levels.[30] Compared with their methodology, in which serum creatinine levels were often influenced by renal function or meat intake, our approach to assessing skeletal muscle status in terms of cross-sectional area and density of the skeletal muscle in the third lumbar vertebrae was more objective and precise. Besides, previous studies indicated that the effects of body components on the prognosis of patients with cancer receiving immunotherapy were often regulated by the systemic inflammatory state. For example, SII could adjust for the effects of VATI and SMI on the prognosis of patients with melanoma receiving immunotherapy, as well as the effect of SATI on the prognosis of patients with gastric cancer receiving immunotherapy.[12,28] The prognosis of patients with HCC receiving immunotherapy was affected by several inflammatory markers such as platelet-to-lymphocyte ratio,[31] neutrophil-to-lymphocyte ratio,[32] and C-reactive protein.[33] Therefore, the

interrelationship between systemic inflammatory and skeletal muscle status in the prognosis of patients with HCC receiving immunotherapy deserves further exploration.

The study has several limitations that we must acknowledge. First, the retrospective nature of this study contributed to the need for further validation of our results in prospective trials with more stringent enrollment criteria. Second, the etiology of most patients we enrolled was HBV infection. The results of this study need to be further validated in HCC patients with other etiologies. Third, our patients received different immunotherapy regimens, resulting in heterogeneity of enrolled patients. Such a research approach has been reported by previous studies.[12,19,28] We believe this heterogeneity is more appropriate to the actual situation of patients. And this data from the real world is more beneficial for hepatologists and oncologists to make clinical decisions in practice.

Conclusion

In conclusion, we first illustrated that high VATI and mid-level BMI were protective for the prognosis of patients with unresectable HCC receiving immunotherapy, and the protections were adjusted by skeletal muscle quantity (SMI). Therefore, we believed that skeletal muscle status (including SMI and SMD) might be more appropriate for predicting survival outcomes in patients with HCC during immunotherapy. We should further clarify the effects of these non-invasive biomarkers on the treatment outcomes to better guide the clinical practice of immunotherapy.

Data Sharing Statement

All data will be available from the corresponding author Jinxue Zhou (zhoujx888@126.com) on reasonable request.

Ethics Approval and Informed Consent

This retrospective study was approved by the Medical Ethics Committee of Henan Cancer Hospital (No. 2023-KY-0075-002), and was conducted by the Declaration of Helsinki (as revised in 2013). All participating institutions were informed and agreed with the study. The requirement for patient consent was waived because the study was retrospective and all data was anonymized or maintained with confidentiality of patients.

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.

Funding

This work was sponsored by the Henan Provincial Medical Science and Technology Research Project (LLRGJ20220191, LHGJ20200171), the Henan Provincial Science and Technology Project (232102311080, 222102310341), the Key Scientific Research Project of Colleges and Universities in Henan Province (23A320033), the National Key Research and Development Program of China (2023YFC3403800), the National Natural Science Foundation of China (No. 81972311, 82141127), the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2021-I2M-1-066), the Non-profit Central Research Institution Fund of Chinese Academy of Medical Sciences (No. 2019PT310026).

Disclosure

All authors have no conflicts of interest to declare in this work.

References

1. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6. doi:10.1038/s41572-020-00240-3
2. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. *Lancet*. 2022;400(10360):1345–1362. doi:10.1016/S0140-6736(22)01200-4

3. Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2022;19(3):151–172. doi:10.1038/s41571-021-00573-2
4. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, Phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492–2502. doi:10.1016/S0140-6736(17)31046-2
5. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol*. 2020;38(3):193–202. doi:10.1200/JCO.19.01307
6. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
7. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. *J Clin Oncol*. 2020;38(26):2960–2970. doi:10.1200/JCO.20.00808
8. 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(1):131–140. doi:10.1016/j.jhep.2015.02.031
9. Lysaght J. The 'obesity paradox' in action with cancer immunotherapy. *Nat Rev Endocrinol*. 2019;15(3):132–133. doi:10.1038/s41574-019-0161-2
10. O'Connell F, O'Sullivan J. Help or hindrance: the obesity paradox in cancer treatment response. *Cancer Lett*. 2021;522:269–280. doi:10.1016/j.canlet.2021.09.021
11. Wang Z, Aguilar EG, Luna JI, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. *Nat Med*. 2019;25(1):141–151. doi:10.1038/s41591-018-0221-5
12. Lee JH, Hyung S, Lee J, Choi SH. Visceral adiposity and systemic inflammation in the obesity paradox in patients with unresectable or metastatic melanoma undergoing immune checkpoint inhibitor therapy: a retrospective cohort study. *J Immunother Cancer*. 2022;10(8):e005226. doi:10.1136/jitc-2022-005226
13. Item F, Konrad D. Visceral fat and metabolic inflammation: the portal theory revisited. *Obes Rev*. 2012;13(2):30–39. doi:10.1111/j.1467-789X.2012.01035.x
14. Perna S, Guido D, Grassi M, Rondanelli M. Association between muscle mass and adipo-metabolic profile: a cross-sectional study in older subjects. *Clin Interv Aging*. 2015;10:499–504. doi:10.2147/CIA.S67872
15. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67(1):358–380. doi:10.1002/hep.29086
16. Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019
17. Tan KC. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157–163. doi:10.1016/S0140-6736(03)15268-3
18. Hilmi M, Jouinot A, Burns R, et al. Body composition and sarcopenia: the next-generation of personalized oncology and pharmacology. *Pharmacol Ther*. 2019;196:135–159. doi:10.1016/j.pharmthera.2018.12.003
19. Chen BB, Liang PC, Shih TT, et al. Sarcopenia and myosteatosis are associated with survival in patients receiving immunotherapy for advanced hepatocellular carcinoma. *Eur Radiol*. 2023;33(1):512–522. doi:10.1007/s00330-022-08980-4
20. Barbi J, Patnaik SK, Pabla S, et al. Visceral obesity promotes lung cancer progression-toward resolution of the obesity paradox in lung cancer. *J Thorac Oncol*. 2021;16(8):1333–1348. doi:10.1016/j.jtho.2021.04.020
21. Kichenadasse G, Miners JO, Mangoni AA, Rowland A, Hopkins AM, Sorich MJ. Association between body mass index and overall survival with immune checkpoint inhibitor therapy for advanced non-small cell lung cancer. *JAMA Oncol*. 2020;6(4):512–518. doi:10.1001/jamaoncol.2019.5241
22. Fang S, Wang Y, Dang Y, et al. Association between body mass index, C-reactive protein levels, and melanoma patient outcomes. *J Invest Dermatol*. 2017;137(8):1792–1795. doi:10.1016/j.jid.2017.04.007
23. Shams-White MM, Brockton NT, Mitrou P, et al. Operationalizing the 2018 world cancer research fund/American Institute for cancer research (WCRF/AICR) cancer prevention recommendations: a standardized scoring system. *Nutrients*. 2019;11(7):1572. doi:10.3390/nu11071572
24. Mormile R. Metformin and lung cancer: the final blow to the obesity paradox. *J Thorac Oncol*. 2018;13(4):e65–e66. doi:10.1016/j.jtho.2017.11.114
25. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: emerging biological mechanisms and perspectives. *Metabolism*. 2019;92:121–135. doi:10.1016/j.metabol.2018.11.001
26. Boura P, Loukides S, Grapsa D, Achimastos A, Syrigos K. The diverse roles of adiponectin in non-small-cell lung cancer: current data and future perspectives. *Future Oncol*. 2015;11(15):2193–2203. doi:10.2217/fon.15.96
27. McQuade JL, Daniel CR, Hess KR, et al. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol*. 2018;19(3):310–322. doi:10.1016/S1470-2045(18)30078-0
28. He M, Chen ZF, Zhang L, et al. Associations of subcutaneous fat area and Systemic Immune-inflammation Index with survival in patients with advanced gastric cancer receiving dual PD-1 and HER2 blockade. *J Immunother Cancer*. 2023;11(6):e007054. doi:10.1136/jitc-2023-007054
29. Vithayathil M, D'Alessio A, Fulgenzi C, et al. Impact of body mass index in patients receiving atezolizumab plus bevacizumab for hepatocellular carcinoma. *Hepatol Int*. 2023;17(4):904–914. doi:10.1007/s12072-023-10491-3
30. Naik GS, Waikar SS, Johnson A, et al. Complex inter-relationship of body mass index, gender and serum creatinine on survival: exploring the obesity paradox in melanoma patients treated with checkpoint inhibition. *J Immunother Cancer*. 2019;7(1):89. doi:10.1186/s40425-019-0512-5
31. Tu X, Yang J, Zheng Y, et al. Immunotherapy combination with regorafenib for refractory hepatocellular carcinoma: a real-world study. *Int Immunopharmacol*. 2022;113(Pt B):109401. doi:10.1016/j.intimp.2022.109401
32. Jost-Brinkmann F, Demir M, Wree A, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma: results from a German real-world cohort. *Aliment Pharmacol Ther*. 2023;57(11):1313–1325. doi:10.1111/apt.17441
33. Scheiner B, Pomej K, Kirstein MM, et al. Prognosis of patients with hepatocellular carcinoma treated with immunotherapy - development and validation of the CRAFITY score. *J Hepatol*. 2022;76(2):353–363. doi:10.1016/j.jhep.2021.09.035