Journal for ImmunoTherapy of Cancer

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

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To cite: Lee JH, Hyung S, Lee J, *et al*. 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. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e005226. doi:10.1136/jitc-2022-005226

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jitc-2022-005226).

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Accepted 15 July 2022

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ABSTRACT

Background The obesity paradox is a topic of increasing interest in oncology and epidemiology research. Although this phenomenon has been observed in melanoma patients receiving immune checkpoint inhibitors, little is known about its mechanism. We aim to investigate the prognostic value of obesity and its association with adiposity and systemic inflammation.

Methods This retrospective study evaluates the data of patients who received pembrolizumab or nivolumab for unresectable or metastatic melanoma between June 2015 and April 2021. The skeletal muscle index (SMI) and visceral fat index (VFI) (cm^2/m^2) were calculated by dividing the cross-sectional areas of skeletal muscle and visceral fat by height squared. The systemic immune-inflammation index (SII) was defined as the total peripheral platelet count×neutrophil/lymphocyte ratio. Cox proportional hazard regression analysis was conducted to determine the association with overall survival.

Results We analyzed 266 patients with a median age of 60 years (IQR 51–69 years; 135 men and 131 women). The protective effect of obesity was independent of covariates (HR 0.60; 95% CI 0.37 to 0.99; p=0.048), but disappeared after adjusting for VFI (HR 0.76; 95% CI 0.41 to 1.40; p=0.380) or SII (HR 0.71; 95% CI 0.42 to 1.18; p=0.186). An increase of 10 cm^2/m^2 in VFI was associated with longer overall survival after adjusting for covariates (HR 0.88; 95% CI 0.79 to 0.99; p=0.029). The prognostic value of VFI remained and predicted favorable overall survival after additional adjustment for SMI (HR 0.86; 95% CI 0.76 to 0.98; p=0.025), but disappeared with adjustment for SII (HR 0.92; 95% CI 0.82 to 1.03; p=0.142). An increase of 100×10^9/L in SII was associated with poor overall survival when adjusted for covariates (HR 1.08; 95% CI 1.05 to 1.11; p<0.001) or when additionally adjusted for VFI (HR 1.07; 95% CI 1.04 to 1.10; p<0.001).

Conclusions Visceral adiposity and systemic inflammation are significant prognostic factors in patients with unresectable or metastatic melanoma receiving immune checkpoint inhibitors. The prognostic impact of visceral adiposity is dependent on systemic inflammation status.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A positive association between body mass index and survival was noted in some cancers, including melanoma, and has been labeled as the 'obesity paradox'; however, the mechanism of action of this phenomenon remains poorly understood.

WHAT THIS STUDY ADDS

⇒ In patients with unresectable or metastatic melanoma undergoing immune checkpoint inhibitor therapy, we observed that visceral adiposity, rather than skeletal muscle mass, and systemic inflammation drive the obesity paradox.

⇒ In addition, the prognostic impact of visceral adiposity seems to be influenced by systemic inflammation, raising the suspicion that systemic inflammation may be a confounding factor in this phenomenon.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future research is needed to investigate the causal relationship between visceral adiposity and systemic inflammation and the mechanisms by which they affect survival in patients with unresectable or metastatic melanoma, to unravel the underlying biology of the obesity paradox further.

BACKGROUND

Melanoma is a cancer arising from melanocytes that produce pigment in the skin, and its incidence has increased rapidly in developed countries since the 1950s.[1] Although surgical excision is an effective treatment in the early stages, the survival of patients with unresectable or metastatic melanoma remains low historically, as treatment options are limited.[2] Despite using immune checkpoint inhibitors (ICI) that have substantially improved the survival in such patients, many patients do not respond or develop resistance to this treatment, resulting in a poor prognosis.[3] Given that little is known about which prognostic marker can predict treatment outcomes after ICI therapy, it would be desirable to find a prognostic marker to determine which patients are likely to achieve a survival benefit.[4]

Obesity is recognized as a major preventable cause of cancer mortality[5]; however, several observational studies have reported conflicting results concluding that obesity is associated with better clinical outcomes in chronic diseases and various types of cancers.[6] This unexpected and paradoxical benefit to obesity, termed the 'obesity paradox', has also been described in patients with melanoma.[7] Notably, this phenomenon was evident in patients receiving ICI therapy as reported in a recent meta-analysis study, which suggested that body mass index (BMI) may be a prognostic factor in these patients.[4] Since BMI does not distinguish between skeletal muscle and adipose tissue, which are biologically different, cross-sectional imaging that provides accurate and quantitative body composition analysis may play a crucial role in understanding the obesity paradox.

While the mechanism of the obesity paradox remains poorly understood and is yet to be elucidated, substantial evidence of its underlying biology has been suggested. Obesity upregulates the programmed death-1 (PD-1) receptor, which may partly explain the improved outcomes in patients with obesity receiving ICI therapy.[8] As increased leptin secretion from adipose tissues is linked to boosting this signaling cascade, it might be reasonable to assume that adiposity, rather than skeletal muscle, may affect this phenomenon. On the other hand, the association between obesity and 'meta-inflammation', characterized by a low-grade chronic inflammatory state with a dysregulated immune response,[9] implies that the inflammatory perspective could be another underlying mechanism. Among several biomarkers, the systemic immune-inflammation index (SII) based on neutrophil, platelet, and lymphocyte counts is suggested to be a novel systemic inflammatory index that reflects the balance between host inflammation and immune response in patients with cancer.[10]

We hypothesized that adiposity and systemic inflammation could explain the obesity paradox and that they are significant prognostic factors in patients with unresectable or metastatic melanoma. Thus, we conducted this study to investigate the impact of adiposity and systemic inflammation, determined using cross-sectional imaging and SII, respectively, on the association between BMI and survival in patients with unresectable or metastatic melanoma after ICI therapy.

METHODS

Patients

We reviewed the electronic medical records of 288 consecutive patients aged >18 years who started receiving ICI therapy between June 2015 and April 2021 for unresectable or metastatic melanoma at a single tertiary hospital. Patients who had no available baseline abdominal cross-sectional imaging (n=16), who were lost to follow-up immediately after treatment initiation (n=4), or who had a history of instrumentation in the lumbar spine (n=2) were excluded.

All patients received one of the following treatments: (1) pembrolizumab (intravenous infusion over 30 min, 200 mg flat dose, mixed with 50 mL of normal saline, every 3 weeks) and (2) nivolumab (intravenous infusion over 1 hour, 3 mg/kg body weight, mixed with 100 mL of normal saline, every 2 weeks). Patients continued to receive treatment until disease progression according to the Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria[11] was reached, or toxicity was unacceptable. Radiological assessments were performed every 6 weeks using abdominal and chest CT or by the same tests that were used for initial tumor staging.

Image analysis

Baseline abdominal cross-sectional imaging (CT, n=163; or positron emission tomography-CT, n=103) before treatment initiation was analyzed using a commercially available deep learning-based software (DeepCatch V.1.0.0.0; MedicalIP, Seoul, Korea). The level of the third lumbar vertebrae[12] was automatically selected, followed by segmenting of the cross-sectional areas of skeletal muscle (including the rectus, transverse and oblique abdominal muscles, psoas muscles, paraspinal muscles), subcutaneous fat, and visceral fat. A board-certified radiologist with 7 years of experience in musculoskeletal imaging confirmed the appropriateness of the level selection and segmentation while being blinded to patient information. The patients' body composition areas (cm^2) were normalized by dividing by the square of the height (m^2) of the patient to calculate the skeletal muscle index (SMI),[13] subcutaneous fat index (SFI), and visceral fat index (VFI). CT-determined sarcopenia was defined as an SMI of $\leq 52.4\,cm^2/m^2$ in men and $\leq 38.5\,cm^2/m^2$ in women, as proposed by a CT-based sarcopenia study of patients with cancer.[14]

Clinical data collection and end points

Electronic medical records were reviewed to collect the baseline demographics on the day of treatment initiation as follows: age, sex, body weight, height, stage according to the eighth edition of the American Joint Committee on Cancer staging system,[15] primary site and subtype of melanoma, line of treatment, Eastern Cooperative Oncology Group performance status, and serum blood counts including neutrophils, lymphocytes, and platelets. BMI was calculated as the weight divided by height squared (kg/m^2) and categorized according to criteria for Asia-Pacific classification of underweight ($<18.5\,kg/m^2$), normal (18.5–$22.9\,kg/m^2$), overweight (23.0–$24.9\,kg/m^2$), or obese ($\geq 25\,kg/m^2$).[16] SII was calculated as total peripheral platelets count×neutrophil/lymphocyte ratio.

We also recorded the date of treatment initiation, date of death, or date of the last follow-up to calculate overall survival (OS) as the primary end point of this study, which was defined as the time from treatment initiation to death from any cause. The secondary end points included progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). PFS was defined as the time from treatment initiation to disease progression or death from any cause, whichever occurred first. Patients without any of the two events were censored at the last follow-up visit. As efficacy outcomes, ORR was defined as the proportion of patients who achieved complete response (CR) or partial response (PR), and DCR was defined as the proportion of patients who achieved CR, PR, or stable disease (SD). Tumor response was assessed according to the RECIST 1.1 criteria.[11] *BRAF* mutational status was examined by next-generation sequencing (online supplemental material).

Statistical analysis

Data are presented as absolute frequencies and percentages for categorical variables and as medians and IQRs for continuous variables. The Kaplan-Meier method with the log-rank test was used to characterize event-time distributions and evaluate OS and PFS according to BMI, body composition features, and SII. The optimal cut-off values to dichotomize SFI, VFI, and SII were determined at the point that maximized the difference between OS in the two groups identified using the minimum log-rank p-value approach.[17] We used the Cox proportional hazards model to estimate the HRs and corresponding 95% CIs for OS and PFS associated with BMI, body composition features, and SII; BMI was treated both categorically (underweight/normal/overweight/obese) and continuously (per 3 kg/m^2). Other variables, except for CT-determined sarcopenia and obesity, were treated continuously (per 10 cm^2/m^2 for SMI, SFI, and VFI; per 100×10^9/L for SII). Adjustments for covariates were performed with and without adjustment for body composition features and SII. We first adjusted for age (>65 years/≤65 years), sex (male/female), treatment agent (pembrolizumab/nivolumab), stage (III/IV), line of treatment (first-line/non-first-line), and *BRAF* mutational status (mutated/wild-type) (model I). Thereafter, variables with p<0.20 in model I were entered into models II_{Muscle}, II_{Fat}, and II_{SII} by additional adjustment for SMI (continuous, per 10 cm^2/m^2), VFI (continuous, per 10 cm^2/m^2), and SII (continuous, per 100×10^9/L), respectively, to explore whether their prognostic value depended on skeletal muscle mass, visceral adiposity, and inflammatory status. Variables relevant to adjusting covariates (eg, SMI and CT-determined sarcopenia in model II_{Muscle}; VFI and SFI in model II_{Fat}; SII in model II_{SII}) or variables with p≥0.20 in model I were not included in models II_{Muscle}, II_{Fat}, or II_{SII}. The interaction term in the Cox proportional hazard regression model was used to determine whether the association between obesity, adiposity, SII, and survival differed according to stage and sex.

The ORR and DCR according to subgroups stratified by VFI and SII were compared by using the χ^2 test. The relationships between BMI, body composition features, and SII were assessed using Spearman's correlation analysis. All statistical analyses were performed using SPSS Statistics (V.27.0; IBM, Armonk, New York, USA) and MedCalc Statistical Software V.20.023 (MedCalc Software, Ostend, Belgium). Statistical significance was set at p<0.05.

RESULTS

A total of 266 patients (224 treated with pembrolizumab and 42 with nivolumab) with a median age of 60 years (IQR 51–69 years; 135 men and 131 women) were finally included in the analysis. The most common subtype was acral melanoma (103 patients, 38.7%), 81 patients (30.5%) had cutaneous melanoma, 55 patients (20.7%) had mucosal melanoma, and 7 patients (2.6%) had uveal melanoma. The lower extremity was the most common location of primary melanoma (n=111, 41.7%), followed by the craniofacial region (n=49, 18.4%), trunk (n=34, 12.8%), upper extremities (n=24, 9.0%), gastrointestinal tracts (n=19, 7.1%), and genital organs (n=9, 3.4%). Subtype could not be classified in 20 patients (7.5%) with nodal and/or visceral metastases from unknown primary sites. The median interval between abdominal cross-sectional imaging and treatment initiation was 10 days (IQR 5–20 days). Our cohort comprised 8 underweight patients (3.0%), 92 patients (34.6%) with a normal BMI, 63 overweight patients (23.7%), and 103 patients (38.7%) with obesity, 13 (4.9%) of whom had a BMI ≥30 kg/m^2. According to the cut-off value, CT-determined sarcopenia was present in 105 patients (39.5%). Of all patients for whom next-generation sequencing data were available (n=178), 36 patients (20.2%) had *BRAF* mutations (all missense mutations; V600E, 30 cases; V600K, 3 cases; V600M, 1 case; G469A, 1 case; L597Q, 1 case). During the follow-up period, with a median of 13.9 months (IQR 6.2–26.1 months), 75 patients (28.2%) died, and disease progression occurred in 184 patients (69.2%). The baseline patient characteristics are shown in table 1.

The optimal cut-off values for the SFI, VFI, and SII were 46 cm^2/m^2, 25 cm^2/m^2, and 850×10^9/L, respectively. Consequently, patients were stratified into high (≥46 cm^2/m^2, n=157, 59.0%) and low SFI (<46 cm^2/m^2, n=109, 41.0%) groups, high (≥25 cm^2/m^2, n=158, 59.4%) and low VFI (<25 cm^2/m^2, n=108, 40.6%) groups, and high (≥850×10^9/L, n=61, 22.9%) and low SII (<850×10^9/L, n=202, 75.9%) groups.

Overall survival

Because mortality was <50%, the median OS was undefined, and the mean OS was 45.0 months (95% CI 40.7 to 49.3 months). OS did not differ significantly according to BMI categories when BMI was categorized into four subgroups: underweight, normal, overweight, or obese (log-rank p=0.274), or into two subgroups of obese and others (log-rank p=0.058), or according to CT-determined sarcopenic status (log-rank p=0.367). The OS was

Table 1 Baseline patient characteristics (n=266)

Characteristic	Patients
Age (years)*	60 (51–69)
>65, n (%)	90 (33.8%)
Sex	
Male	135 (50.8%)
Female	131 (49.2%)
Treatment agent	
Pembrolizumab	224 (84.2%)
Nivolumab	42 (15.8%)
Stage	
<M1 (III)	97 (36.5%)
≥M1 (IV)	169 (63.5%)
M1a	31 (11.7%)
M1b	49 (18.4%)
M1c and M1d	89 (33.5%)
ECOG PS	
1	266 (100%)
Line of treatment	
First-line	203 (76.3%)
Non-first-line	63 (23.7%)
BMI (kg/m^2)*	24.3 (21.6–26.2)
Underweight (<18.5)	8 (3.0%)
Normal (18.5–22.9)	92 (34.6%)
Overweight (23.0–24.9)	63 (23.7%)
Obese (≥25)	103 (38.7%)
SMI (cm^2/m^2)*	47.2 (41.3–54.0)
CT-determined sarcopenia, n (%)	105 (39.5%)
SFI (cm^2/m^2)*	51.4 (37.6–69.2)
VFI (cm^2/m^2)*	35.0 (17.0–52.8)
SII (10^9/L)*	500.0 (328.0–791.5)
NA	3 (1.1%)

Except where indicated, data are presented as numbers of patients with percentages in parentheses.
*Numbers are medians, with IQRs in parentheses.
BMI, body mass index; NA, not available; ECOG PS, Eastern Cooperative Oncology Group performance status; SFI, subcutaneous fat index; SII, systemic immune-inflammation index; SMI, skeletal muscle index; VFI, visceral fat index.

significantly longer in patients with high VFI (mean OS 49.1 months; 95% CI 44.4 to 53.8 months), compared with patients with low VFI (mean OS 38.0 months; 95% CI 31.1 to 44.8 months) (log-rank p<0.001). Patients with high SII (mean OS 20.7 months; 95% CI 15.2 to 26.2 months) had shorter OS than patients with low SII (mean OS 49.0 months; 95% CI 44.3 to 53.6 months) (log-rank p<0.001) (figure 1). However, the OS did not significantly differ between patients with high SFI (mean OS 46.9 months; 95% CI 42.1 to 51.7 months) and patients with low SFI

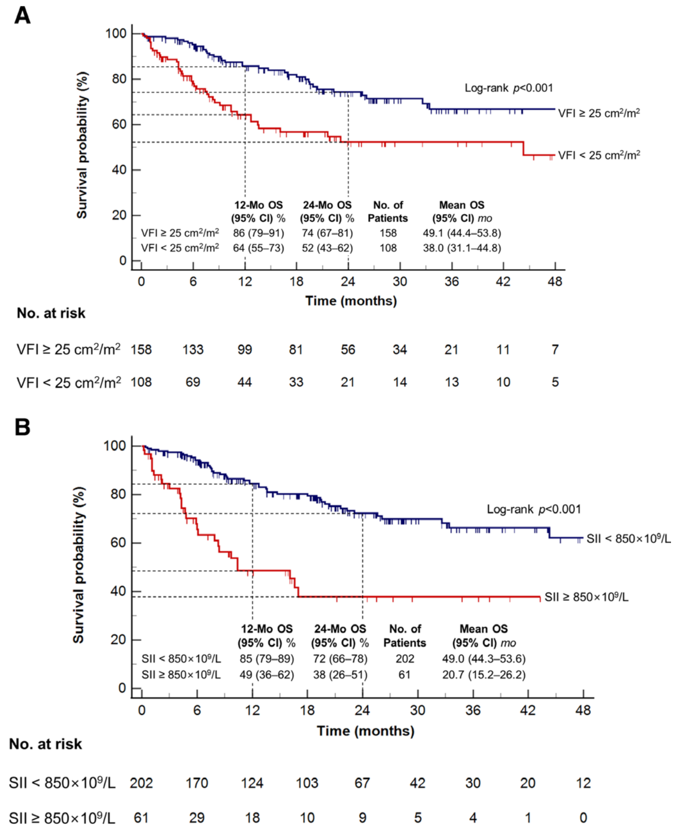

Figure 1 Kaplan-Meier estimates of overall survival, according to VFI (A) and SII (B). OS, overall survival; SII, systemic immune-inflammation index; VFI, visceral fat index.

(mean OS 40.5 months; 95% CI 32.8 to 48.3 months) (log-rank p=0.073).

In multivariable Cox proportional hazard regression models, before adjusting for body composition features or SII, a high BMI was associated with a favorable prognosis, demonstrating a 21% decreased risk of death as BMI increased by 3 kg/m^2. Likewise, patients with obesity had a 40% decreased risk of death compared with patients without obesity. An increase of 10 cm^2/m^2 in the VFI was associated with a 12% decrease in the risk of death (table 2; model I). The association observed in BMI (continuous), obesity, and VFI remained significant after additional adjustment for SMI (table 2; model II$_{Muscle}$), whereas the association observed in BMI and obesity disappeared on adjustment for VFI (table 2; model II$_{Fat}$). An increase of 100×10^9/L in SII was associated with an 8% increased risk of death, with a significant association remaining after additional adjustment for SMI or VFI. None of the body composition features was significantly associated with OS when additionally adjusted for SII (table 2; model II$_{SII}$).

Progression-free survival

The median PFS was 6.3 months (95% CI 4.2 to 7.5 months). When applying the same cut-off values as the OS, Kaplan-Meier curves and log-rank tests showed that PFS was not significantly different between the BMI categories or subgroups stratified by SFI or VFI (log-rank

Table 2 Association between BMI, body composition features, SII, and overall survival

	Model I		Model II_{Muscle}*		Model II_{Fat}†		Model II_{SII}‡	
Characteristic	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
CT-determined sarcopenia								
Absent	1 (reference)		–	–	–	–	–	–
Present	1.03 (0.63 to 1.69)	0.894	–	–	–	–	–	–
BMI								
Underweight (<18.5 kg/m^2)	1.51 (1.35 to 6.45)	0.576	1.69 (0.39 to 7.34)	0.486	1.43 (0.34 to 6.11)	0.629	1.36 (0.31 to 5.87)	0.681
Normal (18.5–22.9 kg/m^2)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Overweight (23.0–24.9 kg/m^2)	1.00 (0.56 to 1.79)	1.000	0.92 (0.50 to 1.70)	0.799	1.27 (0.65 to 2.46)	0.489	1.35 (0.73 to 2.51)	0.341
Obese (≥25 kg/m^2)	0.61 (0.35 to 1.07)	0.086	0.51 (0.25 to 1.03)	0.060	0.90 (0.42 to 1.93)	0.781	0.82 (0.45 to 1.49)	0.508
Continuous, per 3 kg/m^2	0.79 (0.63 to 0.98)	0.038	0.68 (0.50 to 0.93)	0.015	0.89 (0.65 to 1.22)	0.463	0.88 (0.70 to 1.10)	0.270
Obesity								
Non-obese (BMI <25 kg/m^2)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Obese (BMI ≥25 kg/m^2)	0.60 (0.37 to 0.99)	0.048	0.54 (0.30 to 0.98)	0.041	0.76 (0.41 to 1.40)	0.380	0.71 (0.42 to 1.18)	0.186
SFI§	0.90 (0.80 to 1.02)	0.102	0.89 (0.78 to 1.02)	0.105	–	–	0.94 (0.84 to 1.06)	0.306
VFI§	0.88 (0.79 to 0.99)	0.029	0.86 (0.76 to 0.98)	0.025	–	–	0.92 (0.82 to 1.03)	0.142
SII¶	1.08 (1.05 to 1.11)	<0.001	1.08 (1.05 to 1.11)	<0.001	1.07 (1.04 to 1.10)	<0.001	–	–

All models were adjusted for the following covariates: age (>65 years/≤65 years), sex (male/female), treatment agent (pembrolizumab/nivolumab), stage (III/IV), line of treatment (first line/non-first line), and *BRAF* mutational status (mutated/wild-type).
*Model II_{Muscle} was adjusted for covariates plus SMI in cm^2/m^2 (continuous).
†Model II_{Fat} was adjusted for covariates plus VFI in cm^2/m^2 (continuous).
‡Model II_{SII} was adjusted for covariates plus SII in 10^9/L (continuous).
§Continuous, per 10 cm^2/m^2.
¶Continuous, per 100×10^9/L.
BMI, body mass index; SFI, subcutaneous fat index; SII, systemic immune-inflammation index; SMI, skeletal muscle index; VFI, visceral fat index.

p>0.05). In contrast, patients with high SII (median PFS 2.4 months; 95% CI 1.4 to 3.4 months) had shorter PFS than patients with low SII (median PFS 7.8 months; 95% CI 6.3 to 10.2 months) (log-rank p<0.001) (figure 2).

Before adjusting for body composition features or SII, a high BMI was associated with a favorable prognosis, demonstrating a 12% decreased risk of progression as BMI increased by 3 kg/m^2. However, this association did not remain significant after adjustment for SMI, VFI, or SII. None of the other BMI or body composition features were associated with PFS in the multivariable Cox proportional hazard regression model, with or without additional adjustment for SMI, VFI, or SII. SII was independently associated with PFS, with an increase of 100×10^9/L in SII being associated with a 6% increased risk of progression, which remained significant after additional adjustment for SMI or VFI (table 3).

Interaction tests for survival outcomes

The effects of VFI on OS and PFS were numerically more evident in stage IV disease than in stage III disease, with a 15% reduction in the risk of death and a 9% reduction in the risk of progression as VFI increased by 10 cm^2/m^2 in stage IV disease. However, the test for statistical interaction between VFI and stage did not reach statistical significance for OS (p for interaction=0.058) and PFS (p for interaction=0.140). The association of obesity, SFI, and SII with OS and PFS did not differ significantly between stage III and stage IV disease (p for interaction >0.05). Likewise, the associations of obesity, SFI, VFI, and SII with OS and PFS were consistent for men and women (p for interaction >0.05) (table 4).

Efficacy outcomes

Among the 266 patients, the treatment response was evaluable in 248 patients. CR was achieved in 52 (19.5%) patients, PR in 55 (20.7%) patients, and SD in 64 (24.1%) patients, resulting in overall ORR and DCR of 40.2% (95% CI 34.3% to 46.4%) and 64.3% (95% CI 58.2% to 70.0%), respectively. Patients with high VFI had significantly higher DCR when compared with patients with low VFI (69.6% vs 56.5%, p=0.028). Patients with high SII had significantly lower ORR (23.0% vs 45.5%, p=0.002) and DCR (37.7% vs 72.8%, p<0.001) when compared with patients with low SII. However, ORR was not significantly different between patients with low VFI and patients with high VFI (38.0% vs 41.8%, p=0.535) (table 5).

Associations between BMI, body composition features, and SII

Among the BMI and body composition features, BMI (ρ=−0.122, p=0.048) and VFI (ρ=−0.153, p=0.013) were significantly correlated with SII, showing a weak inverse correlation. However, SMI (ρ=−0.064, p=0.298) and SFI (ρ=0.004, p=0.944) were not significantly correlated with SII.

DISCUSSION

Our analyses of patients with melanoma showed that BMI was a significant prognostic marker after ICI therapy,

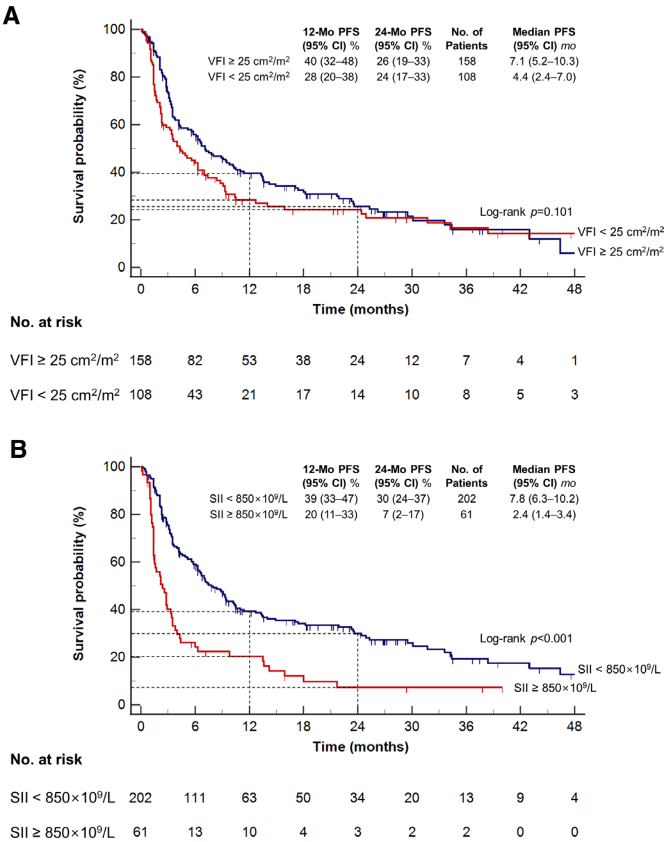

Figure 2 Kaplan-Meier estimates of progression-free survival, according to VFI (A) and SII (B). PFS, progression-free survival; SII, systemic immune-inflammation index; VFI, visceral fat index.

with patients with obesity being associated with improved OS, independent of covariates, including age, sex, treatment agent, stage, line of treatment, and *BRAF* mutational status. Although this survival advantage of obesity was comparable to that reported in a previous study by McQuade *et al*,[7] it was unclear whether skeletal muscle mass, adiposity, or other factors drive this phenomenon. In contrast, the strength of our study lies in the fact that we were able to conclude that among body composition, visceral adiposity, rather than skeletal muscle mass, could explain the obesity paradox. Furthermore, in addition to showing the potential of SII as a prognostic factor associated with OS, PFS, and response rate, our results imply that systemic immune-inflammatory status determined by SII may also influence the impact of obesity and visceral adiposity on patient survival, as the significant association between obesity, VFI, and OS disappeared after additional adjustment for SII.

Given that BMI misclassifies body fat status,[18] some researchers have pointed out the crudeness of BMI in explaining the obesity paradox. It was concluded that being overweight or having excessive fat mass was only protective in the absence of low skeletal muscle mass,[19 20] presuming that the beneficial influence of adiposity is attributed to its protectiveness with respect to muscle loss.[21] These hypotheses seem convincing since skeletal muscle mass has been widely recognized as a prognostic factor[22 23]; however, studies with contrasting results have also been reported recently, showing that the prognostic impact of visceral adiposity and/or BMI was independent

Table 3 Association between BMI, body composition features, SII, and progression-free survival

	Model I		Model II$_{Muscle}$*		Model II$_{Fat}$†		Model II$_{SII}$‡	
Characteristic	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
CT-determined sarcopenia								
Absent	1 (reference)		–	–	1 (reference)		1 (reference)	
Present	1.23 (0.91 to 1.66)	0.184	–	–	1.14 (0.82 to 1.57)	0.437	1.12 (0.82 to 1.53)	0.468
BMI								
Underweight (<18.5 kg/m^2)	1.16 (0.42 to 3.22)	0.780	1.04 (0.37 to 2.92)	0.938	1.11 (0.40 to 3.09)	0.845	1.27 (0.45 to 3.53)	0.653
Normal (18.5–22.9 kg/m^2)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Overweight (23.0–24.9 kg/m^2)	1.11 (0.76 to 1.62)	0.581	1.22 (0.83 to 1.80)	0.317	1.27 (0.82 to 1.95)	0.280	1.38 (0.93 to 2.05)	0.107
Obese (≥25 kg/m^2)	0.82 (0.58 to 1.15)	0.250	1.01 (0.67 to 1.52)	0.975	1.01 (0.62 to 1.63)	0.973	0.99 (0.69 to 1.42)	0.955
Continuous, per 3 kg/m^2	0.88 (0.77 to 0.99)	0.040	0.93 (0.78 to 1.10)	0.404	0.89 (0.74 to 1.07)	0.199	0.93 (0.82 to 1.05)	0.226
Obesity								
Non-obese (BMI <25 kg/m^2)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Obese (BMI ≥25 kg/m^2)	0.78 (0.58 to 1.05)	0.104	0.90 (0.63 to 1.29)	0.573	0.86 (0.59 to 1.24)	0.416	0.85 (0.63 to 1.16)	0.312
SFI§	0.97 (0.91 to 1.03)	0.347	–	–	–	–	–	–
VFI§	0.95 (0.89 to 1.01)	0.104	0.98 (0.91 to 1.05)	0.556	–	–	0.97 (0.91 to 1.03)	0.359
SII¶	1.06 (1.03 to 1.08)	<0.001	1.05 (1.03 to 1.08)	<0.001	1.05 (1.03 to 1.08)	<0.001	–	–

All models were adjusted for the following covariates: age (>65 years/≤65 years), sex (male/female), treatment agent (pembrolizumab/nivolumab), stage (III/IV), line of treatment (first line/non-first line), and *BRAF* mutational status (mutated/wild-type).
*Model II$_{Muscle}$ was adjusted for covariates plus SMI in cm^2/m^2 (continuous).
†Model II$_{Fat}$ was adjusted for covariates plus VFI in cm^2/m^2 (continuous).
‡Model II$_{SII}$ was adjusted for covariates plus SII in 10^9/L (continuous).
§Continuous, per 10 cm^2/m^2.
¶Continuous, per 100×10^9/L.
BMI, body mass index; SFI, subcutaneous fat index; SII, systemic immune-inflammation index; SMI, skeletal muscle index; TFI, total fat index; VFI, visceral fat index.

Table 4 Interaction of obesity, adiposity, and SII with stage and sex for overall survival and progression-free survival

Characteristic	Stage* III (n=97) HR (95% CI)	Stage* IV (n=169) HR (95% CI)	P for interaction	Sex† Male HR (95% CI)	Sex† Female HR (95% CI)	P for interaction
Overall survival						
Obesity‡	0.76 (0.21 to 2.73)	0.60 (0.35 to 1.05)	0.446	0.55 (0.29 to 1.06)	0.72 (0.33 to 1.55)	0.772
SFI§	0.75 (0.51 to 1.11)	0.93 (0.82 to 1.05)	0.141	0.84 (0.68 to 1.05)	0.94 (0.82 to 1.08)	0.710
VFI§	0.95 (0.74 to 1.23)	0.85 (0.75 to 0.97)	0.058	0.92 (0.78 to 1.09)	0.84 (0.71 to 0.99)	0.232
SII¶	1.03 (0.85 to 1.25)	1.08 (1.05 to 1.11)	0.341	1.09 (1.04 to 1.14)	1.08 (1.03 to 1.12)	0.535
Progression-free survival						
Obesity‡	0.78 (0.45 to 1.34)	0.78 (0.54 to 1.12)	0.962	0.68 (0.45 to 1.02)	0.83 (0.53 to 1.30)	0.613
SFI§	1.02 (0.93 to 1.12)	0.94 (0.87 to 1.02)	0.400	0.93 (0.82 to 1.05)	0.98 (0.91 to 1.05)	0.506
VFI§	1.03 (0.93 to 1.15)	0.91 (0.84 to 0.99)	0.140	0.92 (0.83 to 1.01)	0.96 (0.88 to 1.04)	0.767
SII¶	1.04 (0.97 to 1.11)	1.05 (1.03 to 1.08)	0.503	1.06 (1.03 to 1.10)	1.05 (1.02 to 1.08)	0.596

*Adjusted for the age (>65 years/≤65 years), sex (male/female), treatment agent (pembrolizumab/nivolumab), line of treatment (first line/non-first line), and *BRAF* mutational status (mutated/wild-type).
†Adjusted for the age (>65 years/≤65 years), treatment agent (pembrolizumab/nivolumab), stage (III/IV), line of treatment (first line/non-first line), and *BRAF* mutational status (mutated/wild-type).
‡Defined as BMI ≥25 kg/m^2. Patients with a BMI <25 kg/m^2 were used as reference.
§Continuous, per 10 cm^2/m^2.
¶Continuous, per 100×10^9/L.
BMI, body mass index; SFI, subcutaneous fat index; SII, systemic immune-inflammation index; SMI, skeletal muscle index; VFI, visceral fat index.

of skeletal muscle mass.[24 25] A previous study reporting an association between low leptin plasma levels and shorter OS[26] could also be in line with our study results, given that leptin is released from adipose tissue and is likely elevated in patients with obesity.

Obesity is associated with an increased risk of melanoma among males,[27] thicker tumor at presentation,[28] and worse postoperative survival.[29] However, McQuade *et al*[7] reported that this association seems to be reversed when systemic therapy is administered, resulting in improved OS in patients with obesity. Notably, this association was mainly observed in patients receiving ICI therapy rather than in those receiving chemotherapy. Likewise, Naik *et al*[30] and Donnelly *et al*[31] reported that overweight or obese patients treated with ICI for melanoma had a lower risk of mortality, which is also comparable to our study results. However, our findings contradict the previous report by Naik *et al*[30] that found that skeletal muscle mass status could be the underlying mechanism of the obesity paradox. Whereas serum creatinine level they adopted as a surrogate for skeletal muscle mass status could be influenced by renal function or meat intake, we measured the cross-sectional area of skeletal muscle at the level of the third lumbar vertebrae, which correlates directly and significantly with whole-body muscle mass.[32]

Meanwhile, some studies have reported contradictory findings. Rutkowski *et al*[33] analyzed patients who received ICI or mitogen-activated pathway kinase inhibitors for

Table 5 Efficacy outcomes stratified by VFI and SII

Variables	Low VFI (<25 cm^2/m^2) (n=108)	High VFI (≥25 cm^2/m^2) (n=158)	P value	Low SII* (<850×10^9/L) (n=202)	High SII* (≥850×10^9/L) (n=61)	P value	Total (n=266)
ORR, % (95% CI)	38.0 (28.8 to 47.8)	41.8 (34.0 to 49.9)	0.535	45.5 (38.5 to 52.7)	23.0 (13.2 to 35.5)	0.002	40.2 (34.3 to 46.4)
DCR, % (95% CI)	56.5 (46.6 to 66.0)	69.6 (61.8 to 76.7)	0.028	72.8 (66.1 to 78.8)	37.7 (25.6 to 51.0)	<0.001	64.3 (58.2 to 70.0)
Best overall response							
CR, n (%)	23 (21.3)	29 (18.4)	–	45 (22.3)	7 (11.5)	–	52 (19.5)
PR, n (%)	18 (16.7)	37 (23.4)	–	47 (23.3)	7 (11.5)	–	55 (20.7)
SD, n (%)	20 (18.5)	44 (27.8)	–	55 (27.2)	9 (14.8)	–	64 (24.1)
PD, n (%)	37 (34.3)	40 (25.3)	–	45 (22.3)	30 (49.2)	–	77 (28.9)
Not assessed, n (%)	10 (9.3)	8 (5.1)	–	10 (5.0)	8 (13.1)	–	18 (6.8)

*SII was missing in three patients.
CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SII, systemic immune-inflammation index; VFI, visceral fat index.

metastatic melanoma and found no impact of BMI on OS, PFS, and DCR in the ICI cohort. Another study by Young *et al*[34] investigated the effect of body composition along with BMI on the prognosis of patients with metastatic melanoma. They found no significant relationship between BMI and clinical outcomes, whereas they concluded that the association between body composition and improved clinical outcomes was modest, based on a tendency toward worse outcomes in patients with higher adiposity and lower muscle quantity and quality. While our study analyzed the body composition characteristics of subcutaneous fat and visceral fat as continuous variables, their study used tertiles to categorize total fat. In addition to these methodological differences, the fact that our study population differ from the previous studies seems to be the most crucial difference between our study and the previous studies.[7 30 31 33 34] Most importantly, our study population consisted of Asians, unlike the previous studies that were conducted in the Western countries. We used the Asia-Pacific classification[16] as the BMI criteria for obesity, and the proportion of patients with a BMI ≥25 kg/m^2 was 38.7%, lower than that of those previous studies. Notably, small sample size of patients with morbid obesity may have influenced our findings, given that the mortality curve for BMI is U-shaped with increased mortality at both ends.[35] In this context, the question remains whether the prognostic value of obesity, visceral adiposity, and SII persists even in non-Asians or patients with higher BMI, including morbid obesity. In addition to this issue, further studies are also required to explore whether sex-specific association, not observed in our study in contrast to previous studies by Naik *et al*[30] and Young *et al*[34] exists or not. Furthermore, the distinctly high prevalence of acral and mucosal subtypes, which are predominant melanoma subtypes in Asians as opposed to Caucasians,[36 37] may also be one of the other possible explanations for our results.

Accumulating evidence suggests a contradictory role of obesity and/or adipose tissue and their derived adipokines as potential mediators in cancer-related processes with both tumor-promoting and tumor-suppressive effects. Obesity increases PD-1 expression,[8] releases more PD-1 protein from T cells,[38] and secretes more adiponectin and leptin from adipose tissue.[39 40] These lead to increased T cell exhaustion and dysfunction, promoting tumor growth and progression.[8] Conversely, the link between obesity and ICI therapy becomes more clear at this point, since these agents remove inhibitory signals of T cell activation and mount an effective antitumor response.[41] In line with this, obesity is associated with heightened efficacy of ICI therapy, explaining the survival benefit of obesity in previous studies.[7 30 31] Our results showing the prognostic value of visceral adiposity seem to further support the theory that leptin serves as a link between obesity and improved clinical outcomes.[8] However, the question arises as to why patients with obesity and/or visceral adiposity in our study had no significant PFS benefit despite OS gain and tendency of a positive association between VFI and DCR. Future studies are warranted to determine whether adipokines could explain the survival benefit in patients with melanoma with more visceral fat and to determine if factors other than tumor response, such as improved energy or nutritional reserves, lead to longer OS.

As a recently introduced serum inflammatory biomarker, SII is believed to serve as a useful prognostic indicator in patients with cancer with a high prognostic value,[42] presumably because of its ability to reflect the balance between pro-tumor and anti-tumor immune status and responses to systemic inflammation.[10 43] Interestingly, we observed a significant inverse correlation between VFI and SII, in addition to the fact that the prognostic impact of VFI was dependent on SII, in contrast to previous studies that described obesity to be associated with increased SII[44] and chronic inflammation.[9] Although the mechanism underlying the inverse correlation between VFI and SII remains unclear, suppressive pathways that counteract the chronic inflammatory status during obesity-associated inflammation could be a possible explanation.[8] Vankrunkelsven *et al*[45] also reported that obesity attenuates inflammation during sepsis, with a 50% decrease in plasma tumor necrosis factor-α increase in leptin-deficient and diet-induced mice with obesity compared with that in lean mice. However, the possibility of reverse causation still exists, given that our results are based on observational studies and cannot determine the true causal relationships between VFI and SII. Consequently, the question also persists whether the systemic inflammatory response leads to cancer cachexia and debilitates patient prognosis or whether reduced visceral adiposity aggravates systemic inflammation. As reverse causation is one of the most important methodological issues in the obesity paradox,[46 47] identifying their causal relationship using propensity score matching could be an interesting topic worth investigating.

Our study had some limitations. First, this retrospective study was conducted at a single tertiary center. In particular, the cut-off values for body composition features, except SMI, require further validation in a separate cohort. Second, reverse causality may exist, as previously described. Although we adjusted for clinically relevant covariates to mitigate the effect of reverse causality, this might not have been eliminated. In addition to residual confounding factors, other unmeasured covariates could also have contributed to the study results. Third, the sample size of patients with morbid obesity was small as discussed, which may require further validation in a different patient population. Fourth, treatment-related toxicities including immune-related adverse events were not evaluated. Given that obesity has been reported to be associated with higher rates of ICI-related toxicity in patients with advanced melanoma,[48] exploring this association in terms of body composition may also be an interesting topic for future research.

In conclusion, visceral adiposity and systemic inflammation drive the obesity paradox in patients with unresectable or metastatic melanoma undergoing ICI therapy.

In addition, our results imply that the protective effect of visceral adiposity could be attributed to its inverse correlation with systemic inflammation. Systemic inflammation may underlie the obesity paradox and should be considered a prognostic marker associated with, OS, PFS, and tumor response. Future studies should investigate the causal relationship between visceral adiposity and systemic inflammation to define the mechanism that links them with patient survival.

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Contributors JHL designed the study, performed the statistical analysis, and wrote the manuscript. SH performed data analyses and wrote the manuscript. JL supervised the study, provided the clinical samples, and collected the data. SC supervised the study. All authors have reviewed the manuscript. All authors approved the final version of the manuscript. JHL is responsible for the overall content as a guarantor.

Funding This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR20C0025).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This retrospective study was approved by the Institutional Review Board of Samsung Medical Center (IRB file no. 2021-06-173), and the requirement for informed consent was waived. This study was performed in accordance with the principles of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets used and/or analyzed during this study are available with the corresponding author on reasonable request.

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SUPPLEMENTAL MATERIAL

Next Gene Sequencing (NGS)

Patients were screened using next-generation sequencing (NGS) with TruSight Oncology (TSO) 500 (Illumina, San Diego, CA, USA), a panel targeting 500+ cancer genes as described previously.[1] [2] To examine *BRAF* mutation in all samples, DNA library was developed by a hybrid capture-based TSO 500 DNA/RNA NextSeq Kit, following the manufacturer's protocol. Sequence data of all samples were measured to identify clinically relevant class of genomic alterations. Annotation of filtered data acquired from the TSO 500 pipeline were done through the Ensembl Variant Effect Predictor Annotation Engine[1] with information from databases, such as gnomAD genome and exome, 1000 genomes, COSMIC, dbSNP, ClinVar, RefSeq, and Ensembl.

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