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

Ji Hyun Lee, Sujin Hyung, Jeeyun Lee, Sang-Hee Choi

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) 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 cm²/m² 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 100×10⁹/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. 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. 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.\(^1\)

Obesity is recognized as a major preventable cause of cancer mortality;\(^2\) 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 segmentation 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 ≤22.4 cm\(^2\)/m\(^2\) in men and ≤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 (≥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. B 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. 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/m²). Other variables, except for CT-determined sarcopenia and obesity, were treated continuously (per 10 cm²/m² for SMI, SFI, and VFI; per 100×10⁹/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/second-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 cm²/m²), VFI (continuous, per 10 cm²/m²), and SII (continuous, per 100×10⁹/L), respectively, to explore whether their prognostic value depended on skeletal muscle mass, visceral adiposity, and inflammatory status. Variables relevant to adjusting covariates (eg, BMI 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 χ² 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/m². 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 cm²/m², 25 cm²/m², and 850×10⁹/L, respectively. Consequently, patients were stratified into high (≥46 cm²/m², n=157, 59.0%) and low SFI (<46 cm²/m², n=109, 41.0%) groups, high (≥25 cm²/m², n=158, 59.4%) and low VFI (<25 cm²/m², n=108, 40.6%) groups, and high (≥850×10⁹/L, n=61, 22.9%) and low SII (<850×10⁹/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
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 (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/m². Likewise, patients with obesity had a 40% decreased risk of death compared with patients without obesity. An increase of 10 cm²/m² 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 IIMuscle), whereas the association observed in BMI and obesity disappeared on adjustment for VFI (table 2; model IIFat).

An increase of 100×10⁹/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 IISII).

**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 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/m²)*                | 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 (cm²/m²)*               | 47.2 (41.3–54.0) |
| CT-determined sarcopenia, n (%) | 105 (39.5%) |
| SFI (cm²/m²)*               | 51.4 (37.6–69.2) |
| VFI (cm²/m²)*               | 35.0 (17.0–52.8) |
| SII (10⁹/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.

![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.](image)
BMI increased by 3 kg/m\(^2\). However, this association demonstrating a 12% decreased risk of progression as a high BMI was associated with a favorable prognosis, associated with PFS, with an increase of 100\times10^9/L in SII adjustment for SMI, VFI, or SII. SII was independently proportional hazard regression model, with or without 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).

### Discussion
Our analyses of patients with melanoma showed that BMI was a significant prognostic marker after ICI therapy, with ORR and DCR significantly higher in patients with low BMI (37.7% vs 72.8%, p<0.001) when compared with patients with high BMI. Patients with high BMI 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 BMI. However, ORR was not significantly different between patients with low BMI and patients with high BMI (38.0% vs 41.8%, p=0.535) (table 5).

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

| Characteristic          | Model I    | P value | Model II* | P value | Model II† | P value | Model II‡ | P value |
|-------------------------|------------|---------|-----------|---------|-----------|---------|-----------|---------|
|                         | HR (95% CI)|         | HR (95% CI)|         | HR (95% CI)|         | HR (95% CI)|         |
| 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) |   -  |   -       |   -  |   -       |   -  |   -       |   -  |
| 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) |   -  |   -       |   -  |   -       |   -  |   -       |   -  |
| Obese (≥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 |   -       |   -  |   -       |   -  |
| VFI§                   | 0.88 (0.79 to 0.99) | 0.029 | 0.86 (0.76 to 0.98) | 0.025 |   -       |   -  |   -       |   -  |
| 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 (II/IV), line of treatment (first line/non-first line), and BRAF mutational status (mutated/wild-type).

*Model II* was adjusted for covariates plus SMI in cm\(^2\)/m\(^2\) (continuous).
†Model II was adjusted for covariates plus VFI in cm\(^2\)/m\(^2\) (continuous).
‡Model II 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.
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, 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, 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, presuming that the beneficial influence of adiposity is attributed to its protectiveness with respect to muscle loss. These hypotheses seem convincing since skeletal muscle mass has been widely recognized as a prognostic factor; 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

| Characteristic                        | Model I |          | Model II<sub>base</sub> |          | Model II<sub>SFI</sub> |          | Model II<sub>VFI</sub> |          | Model II<sub>SII</sub> |          |
|--------------------------------------|---------|----------|-------------------------|----------|------------------------|----------|------------------------|----------|------------------------|----------|
|                                      | HR (95% CI) | P value | 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) | –       | 1.12 (0.82 to 1.53) | 0.437    | 1.12 (0.82 to 1.53) | 0.468    |
| 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/m²)           | 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/m²)            | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| Overweight (23.0–24.9 kg/m²)        | 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/m²)                   | 0.89 (0.58 to 1.35) | 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/m²             | 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/m²)           | 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    |
| Obese (BMI ≥25 kg/m²)               |         |          |             |         |             |         |             |         |             |         |
| SFI<sub>j</sub>                     | 0.97 (0.91 to 1.03) | 0.347  | –          | –         | –          | –        | –          | –        | –          | –        |
| VFI<sub>j</sub>                     | 0.95 (0.89 to 1.01) | 0.104  | 0.98 (0.91 to 1.05) | 0.556    | –          | –        | –          | –        | –          | –        |
| SII<sub>j</sub>                     | 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<sub>base</sub> was adjusted for covariates plus SMI in cm²/m² (continuous).
Model II<sub>SFI</sub> was adjusted for covariates plus VFI in cm²/m² (continuous).
Model II<sub>VFI</sub> was adjusted for covariates plus SII in 10⁹/L (continuous).
Model II<sub>SII</sub> was adjusted for covariates plus BMI in cm²/m² (continuous).

Continous, per 10 cm²/m².
Continous, per 100×10⁹/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.
of skeletal muscle mass. A previous study reporting an association between low leptin plasma levels and shorter OS 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, thicker tumor at presentation, and worse postoperative survival. However, McQuade et al 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 and Donnelly et al 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 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.

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

| Table 4 Interaction of obesity, adiposity, and SII with stage and sex for overall survival and progression-free survival |
| Characteristic | Stage* | | | Sex† | | |
| | III (n=97) | IV (n=169) | P for interaction | Male | Female | P for interaction |
| | HR (95% CI) | HR (95% CI) | | HR (95% CI) | HR (95% CI) | |
| 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/m². Patients with a BMI <25 kg/m² were used as reference.
§Continuous, per 10 cm²/m².
¶Continuous, per 100×10⁹/L.
BMI, body mass index; SFI, subcutaneous fat index; SII, systemic immune-inflammation index; SMI, skeletal muscle index; VFI, visceral fat index.

| Table 5 Efficacy outcomes stratified by VFI and SII |
| Variables | Low VFI (<25 cm²/m²) (n=108) | High VFI (≥25 cm²/m²) (n=158) | P value | Low SII* (<850×10⁹/L) (n=202) | High SII* (≥850×10⁹/L) (n=61) | P value | Total (n=266) |
| | ORR, % (95% CI) | DCR, % (95% CI) | 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. 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 differs from the previous studies seems to be the most crucial difference between our study and the previous studies. 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 as the BMI criteria for obesity, and the proportion of patients with a BMI $\geq 25$ 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. 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. and Young et al., exists or not. Furthermore, the distinctly high prevalence of acral and mucosal subtypes, which are predominant melanoma subtypes in Asians as opposed to Caucasians, 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, releases more PD-1 protein from T cells, and secretes more adiponectin and leptin from adipose tissue. These lead to increased T cell exhaustion and dysfunction, promoting tumor growth and progression.

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. In line with this, obesity is associated with heightened efficacy of ICI therapy, explaining the survival benefit of obesity in previous studies. 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. 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, presumably because of its ability to reflect the balance between pro-tumor and anti-tumor immune status and responses to systemic inflammation. 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 and chronic inflammation. 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. Vankunkselaars et al. also reported that obesity attenuates inflammation during sepsis, with a 50% decrease in plasma tumor necrosis factor-$\alpha$ 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, 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, 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.

**Author affiliations**  
1Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, The Republic of Korea  
2Innovative Institute for Precision Medicine, Samsung Medical Center, Seoul, The Republic of Korea  
3Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, The Republic of Korea

**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: HR2000025).

**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 the study are available with the corresponding author on reasonable request.

**Supplemental material**  
This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access**  
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**  
Ji Hyun Lee http://orcid.org/0000-0002-8382-5436  
Sujin Hyung http://orcid.org/0000-0003-1192-0972  
Jeeyun Lee http://orcid.org/0000-0002-4911-6165  
Sang-Hee Choi http://orcid.org/0000-0002-4068-3016

**REFERENCES**  
1 Erdel E, Torres SM. A new understanding in the epidemiology of melanoma. Expert Rev Anticancer Ther 2010;10:1811–23.

2 Thompson JF, Scolyer RA, Kefferd RF. Cutaneous melanoma in the era of molecular profiling. Lancet 2009;374:362–5.

3 Olbyt M, Rajczykowski M, Widlak W. Biological factors behind melanoma response to immune checkpoint inhibitors. Int J Mol Sci 2020;21. doi:10.3390/ijms21114071. [Epub ahead of print: 06 Jun 2020].

4 Nie R-C, Chen G-M, Wang Y, et al. Association between body mass index and survival outcomes in patients treated with immune checkpoint inhibitors: meta-analyses of individual patient data. J Immunoother 2021;44:371–5.

5 Ligibel JA, Alfano CM, Courneya KS, et al. American Society of clinical oncology position statement on obesity and cancer. J Clin Oncol 2014;32:3568–74.

6 McAuley PA, Blair SN. Obesity paradoxes. J Sports Sci 2011;29:773–82.

7 McCauley 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;19:310–22.

8 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;25:141–51.

9 Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444:860–7.

10 Huang H, Liu Q, Zhu L, et al. Prognostic value of preoperative systemic immune-inflammation index in patients with cervical cancer. Sci Rep 2019;9:3284.

11 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1. Eur J Cancer 2009;45:228–47.

12 Shen W, Punyaniya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol 2004;97:2333–8.

13 Mourtzakis M, Prado CMM, Liefers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33:997–1006.

14 Prado CMM, Liefers 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;9:629–35.

15 Gershensonwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:472–92.

16 World Health Organization, Regional Office for the Western Pacific. The Asia-Pacific perspective: redefining obesity and its treatment. Sydney Health Communications Australia; 2000.

17 Bucdzies J, Klauschen F, Sinn BV, et al. Cutoff finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. PLoS One 2012;7:e51862.

18 Oreopoulos A, Ezelekowita JA, McAlister FA, et al. Association between direct measures of body composition and prognostic factors in chronic heart failure. Mayo Clin Proc 2010;85:609–17.

19 Gonzalez MC, Pastore CA, Orlandi SP, et al. Obesity paradox in cancer: new insights provided by body composition. Am J Clin Nutr 2014;99:999–1005.

20 Murphy RA, Reinders I, Garcia ME, et al. Adipose tissue, muscle, and function: potential mediators of associations between body weight and mortality in older adults with type 2 diabetes. Diabetes Care 2014;37:3213–9.

21 Perna S, Guido D, Grassi M, et al. Association between muscle mass and adipo-metabolic profile: a cross-sectional study in older subjects. Clin Interv Aging 2015;10:499–504.

22 Kim Y-Y, Lee J, Jeong WK, et al. Prognostic significance of sarcopenia in microsatellite-stable gastric cancer patients treated with programmed death-1 inhibitors. Gastric Cancer 2021;24:457–66.

23 Kim EY, Kim YS, Park I, et al. Prognostic significance of CT-Determined sarcopenia in patients with small-cell lung cancer. J Thorac Oncol 2015;10:1795–9.

24 Xu MC, Huelster HL, Hatcher JB, et al. Obesity is associated with longer survival independent of sarcopenia and Myosteatosis in metastatic and/or castrate-resistant prostate cancer. J Urol 2021;205:800–5.

25 Lee JH, Yoon YC, Kim HS, et al. Obesity is associated with improved postoperative overall survival, independent of skeletal muscle mass in lung adenocarcinoma. J Cachexia Sarcopenia Muscle 2022;13:1076–86.

26 Kerenidi T, Lada M, Tsaroucha A, et al. Clinical significance of serum adipokines levels in lung cancer. Med Oncol 2013;30:507.
27 Sergentanis TN, Antoniadis AG, Gogas HJ, et al. Obesity and risk of malignant melanoma: a meta-analysis of cohort and case-control studies. Eur J Cancer 2013;49:642–57.
28 Harrell Shreckengost CS, Tanig M, Farley CR, et al. The impact of obesity on surgically treated locoregional melanoma. Ann Surg Oncol 2021;28:6140–51.
29 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;137:1792–5.
30 Naik GS, Walkar SS, Johnson AEW, 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;7:89.
31 Donnelly D, Bajaj S, Yu J, et al. The complex relationship between body mass index and response to immune checkpoint inhibition in metastatic melanoma patients. J Immunother Cancer 2019;7:222.
32 Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95.
33 Rutkowski P, Indini A, De Luca M, et al. Body mass index (BMI) and outcome of metastatic melanoma patients receiving targeted therapy and immunotherapy: a multicenter international retrospective study. J Immunother Cancer 2020;8:e001117.
34 Young AC, Quach HT, Song H, et al. Impact of body composition on outcomes from anti-PD1 +/- anti-CTLA-4 treatment in melanoma. J Immunother Cancer 2020;8:e000821.
35 Dixon JB, Egger GJ. A narrow view of optimal weight for health generates the obesity paradox. Am J Clin Nutr 2014;99:969–70.
36 Altiere L, Wong MK, Peng DH, et al. Mucosal melanomas in the racially diverse population of California. J Am Acad Dermatol 2017;76:250–7.
37 Chang JW-C. Acral melanoma: a unique disease in Asia. JAMA Dermatol 2013;149:1272–3.
38 Finelli C. Obesity and immunotherapy: the surprisingly positive association! Immunotherapy 2020;12:541–4.
39 Zhang X, Liu Y, Shao H, et al. Obesity paradox in lung cancer prognosis: evolving biological insights and clinical implications. J Thorac Oncol 2017;12:1478–88.
40 Boura P, Loukides S, Grapsa D, et al. The diverse roles of adiponectin in non-small-cell lung cancer: current data and future perspectives. Future Oncol 2015;11:2193–203.
41 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252–64.
42 Wang Y, Li Y, Chen P, et al. Prognostic value of the pretreatment systemic immune-inflammatory index (SII) in patients with non-small cell lung cancer: a meta-analysis. Ann Transl Med 2019;7:433.
43 Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.
44 Furuncu○ğlu Y, Tulgar S, Dogan AN, et al. How obesity affects the neutrophil/lymphocyte and platelet/lymphocyte ratio, systemic immune-inflammatory index and platelet indices: a retrospective study. Eur Rev Med Pharmacol Sci 2016;20:1300–6.
45 Vankrunkelsven W, Derde S, Gunst J, et al. Obesity attenuates inflammation, protein catabolism, dyslipidaemia, and muscle weakness during sepsis, independent of leptin. J Cachexia Sarcopenia Muscle 2022;13:418–33.
46 Park Y, Peterson LL, Colditz GA. The Plausibility of obesity paradox in Cancer-Point. Cancer Res 2018;78:1898–903.
47 Lennon H, Badrick E, Serrin M, et al. Body-Mass index and metastatic melanoma outcomes. Lancet Oncol 2018;19:e225.
48 Hu JB, Ravichandran S, Rushing C, et al. Higher BMI, but not sarcopenia, is associated with Pembrolizumab-related toxicity in patients with advanced melanoma. Anticancer Res 2020;40:5245–54.