

Prognostic value of obesity in patients with cancer treated with immune checkpoint inhibitors: An updated meta-analysis and systematic review

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Abstract. Accumulating interest has been surging over the past few years regarding the effects of obesity on immunotherapy. In addition to the body mass index (BMI), imaging-quantified body fat compartments have been investigated. The present study aimed to evaluate the predictive value of the BMI and computed tomography (CT)-based body fat in patients with cancer receiving immunotherapy. For this purpose, the PubMed, MEDLINE, EMBASE and Cochrane databases were searched from January 2017 to July 2022. Clinical studies evaluating the association between BMI or body fat and survival of patients with cancer treated with immune checkpoint inhibitors (ICIs) were included. In total, 15 studies reporting on the BMI were included in the meta-analysis and 16 studies evaluating body fat were included in the systematic review. According to the classification of the World Health Organization, overweight and obese patients with ICI treatment showed improved overall survival [overweight vs. normal: Hazard ratio (HR)=0.79, 95% confidence interval (CI)=0.64-0.98, P=0.03; obese vs. normal: HR=0.75, 95% CI=0.60-0.94, P=0.013] and progression-free

survival (overweight vs. normal: HR=0.82, 95% CI=0.70-0.97, P=0.02; obese vs. normal: HR=0.81, 95% CI=0.65-1.02, P=0.07). Among the articles investigating the effect of body fat composition on the efficacy of immunotherapy, a number of studies included various CT analysis techniques and cutoffs to define body fat composition. Associations of body fat with survival were contradictory in different patients with cancer treated with immunotherapy. Obesity was associated with better survival in patients with cancer treated with ICIs. Further analyses are required to demonstrate the prognostic value of body fat in patients with cancer immunotherapy.

Introduction

With the development and increased interest in cancer immunotherapy, immune checkpoint inhibitors (ICIs), including targeting programmed cell death-1 (PD-1), PD-1 ligand 1 (PD-L1) and the checkpoint T lymphocyte-associated protein 4 (CTLA-4), have emerged as a novel therapeutic strategy in certain types of cancer. However, the majority of patients showed no response to ICI therapies and numerous responders eventually developed resistance (1,2). Several biomarkers, including tumor-infiltrating lymphocytes (TILs), tumor mutational burden (TMB) and microsatellite instability (MSI), have been used to select potential responders to ICI therapy. However, these biomarkers were solely focused on tumor features and did not reflect the systemic immune status of patients (3). Therefore, exploring simpler, available patient characteristics, such as body mass index (BMI) or body composition, seems feasible to assess the association with outcomes and response to ICI therapy.

In recent years, the efficacy of ICIs in obese populations with cancer has drawn increased interest from researchers. According to statistics from the World Health Organization (WHO) for 2020, the proportion of overweight and obese individuals older than 18 years within the world population accounted for 39 and 13%, respectively (4). Epidemiological studies have established a strong association between obesity

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and multiple cancer types. Obesity was determined to be a risk factor for the incidence and progression of certain cancer types (5). While previous research has focused predominantly on the effects of obesity on altered endocrine factors, growth factors and signaling pathways, little is known about its impact on cancer immunotherapy (5). As the number of overweight and obese individuals continues to rise, the influence of obesity on cancer treatment efficacy should not be ignored.

The BMI commonly measures obesity as a marker for the nutritional state (6). Previous clinical studies have indicated that an increased BMI is associated with improved survival of patients with cancer receiving immunotherapy (7-9). For instance, obesity improved the progression-free survival (PFS) and overall survival (OS) of patients with metastatic melanoma who received targeted therapy, immunotherapy or chemotherapy (8). By contrast, another study on metastatic melanoma reported no association between obesity and outcome (10). Whether obesity is a predictive factor regarding survival of patients receiving immunotherapy needs to be further studied. Previous meta-analyses have explored the impact of the BMI on the outcomes of ICI treatment for patients with cancer, but the date of their literature search included only studies published up to 2021 (11-14). Thus, based on the latest literature, the present study aimed to evaluate the predictive value of the BMI in patients with cancer receiving immunotherapy.

As the BMI is calculated from the whole-body weight, it is not the most suitable measure for evaluating obesity (6). Recently, imaging-measured adipose distribution has been investigated to estimate the influence of obesity on the efficacy of ICI therapy. It was reported that a higher fat distribution is associated with improved survival of patients with cancer rather than the BMI (15-17). However, the results appeared to be inconsistent due to the different methods used to evaluate the body's composition. Thus, the potential association between adipose distribution and clinical outcomes in patients with cancer treated with immunotherapy remains controversial. Therefore, another objective of the present study was to explore the association between survival and different types of fat in patients treated with immunotherapy.

Materials and methods

Search strategy. A systematic literature search was conducted using the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), MEDLINE (<https://www.medline.eu/>), EMBASE (<https://www.embase.com/>) and Cochrane Library (<https://www.cochranelibrary.com/>) databases for entries of studies published between January 2017 and July 2022, with no language restrictions. The main keywords for the literature search included 'cancer', 'tumor', 'oncology', 'neoplasm', 'body mass index', 'BMI', 'obesity', 'overweight', 'weight', 'mass', 'body composition', 'body fat distribution', 'adiposity', 'fat', 'PD-1', 'PD-L1', 'CTLA-4', 'nivolumab', 'pembrolizumab', 'atezolizumab', 'avelumab', 'durvalumab', 'ipilimumab', 'tremelimumab' and 'immune checkpoint inhibitor'. Any studies missed by the electronic search were manually searched from references of included studies and relevant systematic reviews. The protocol of the current meta-analysis was registered in the International Prospective Register of Systematic Reviews

database (<https://www.crd.york.ac.uk/PROSPERO/>; accession no. CRD42022344713).

Selection criteria. Two investigators, LXY and WC, independently searched and selected articles for eligibility. If there were any disagreements, all authors jointly re-evaluated these studies. Full-text articles of clinical studies were screened. The inclusion criteria for the meta-analysis were as follows: i) Patients had been diagnosed with cancer and treated with ICIs; ii) based on the BMI, patients were categorized into normal (BMI, 18.5-24.9 kg/m²), overweight (BMI, 25.0-29.9 kg/m²) and obese (BMI, ≥30 kg/m²) or into two groups (BMI <25 kg/m² and BMI ≥25 kg/m²); iii) the survival outcomes included PFS and OS; and iv) associations between the BMI and OS or PFS were analyzed using Cox proportional hazards regression models and were reported as hazard ratio (HR) and 95% confidence interval (CI). The inclusion criteria for systematic reviews were as follows: i) Studies focused on adipose tissue distribution; ii) body fat was measured by computed tomography (CT); and iii) associations between adiposity and patient survival with cancer immunotherapy were evaluated.

Data extraction. Two authors (GH and FS) independently reviewed and extracted data from the included studies. Any discrepancy was resolved through discussion with all authors. The following data were extracted from each of the included studies in the meta-analysis: i) Name of first author, year of publication, country, sample size, percentage of male patients and study type; ii) cancer type and ICI drugs; iii) BMI cut-off value; and iv) OS and PFS.

Article quality evaluation. The quality of the included studies on the BMI was evaluated using the Newcastle-Ottawa scale (18). Quality was assessed according to the following inclusion criteria: i) representativeness of the exposed; ii) selection of the non-exposed; iii) ascertainment of exposure; iv) demonstration that outcome of interest was not present at the start; v) study controls for age and sex; vi) study controls for any additional factors (chemoradiotherapy, curative resection and drug resistance); vii) assessment of outcome; viii) follow-up time of >36 months; and ix) adequacy of follow-up of cohorts.

Sensitivity and publication bias. Contour-enhanced meta-analysis funnel plots were used to distinguish publication bias from other asymmetry causes. Publication bias was assessed using Begg's and Egger's tests. Sensitivity analysis was conducted by excluding one study at a time.

Statistical analysis. OS and PFS were used to evaluate the clinical outcomes of ICI treatment. The association between BMI and ICI efficacy in patients with cancer was measured by the hazard ratio (HR) with 95% CI. Statistical heterogeneity among the included studies was evaluated using the I² statistic. I² values of <40, 40-60, 60-75 and >75% were considered to indicate low, moderate, substantial and considerable heterogeneity, respectively. I²>40% or P<0.1 was considered to indicate statistical heterogeneity. A random-effects model was applied to calculate the summary HR and 95% CI. All analyses were performed with the meta package of R 4.0.5-win software

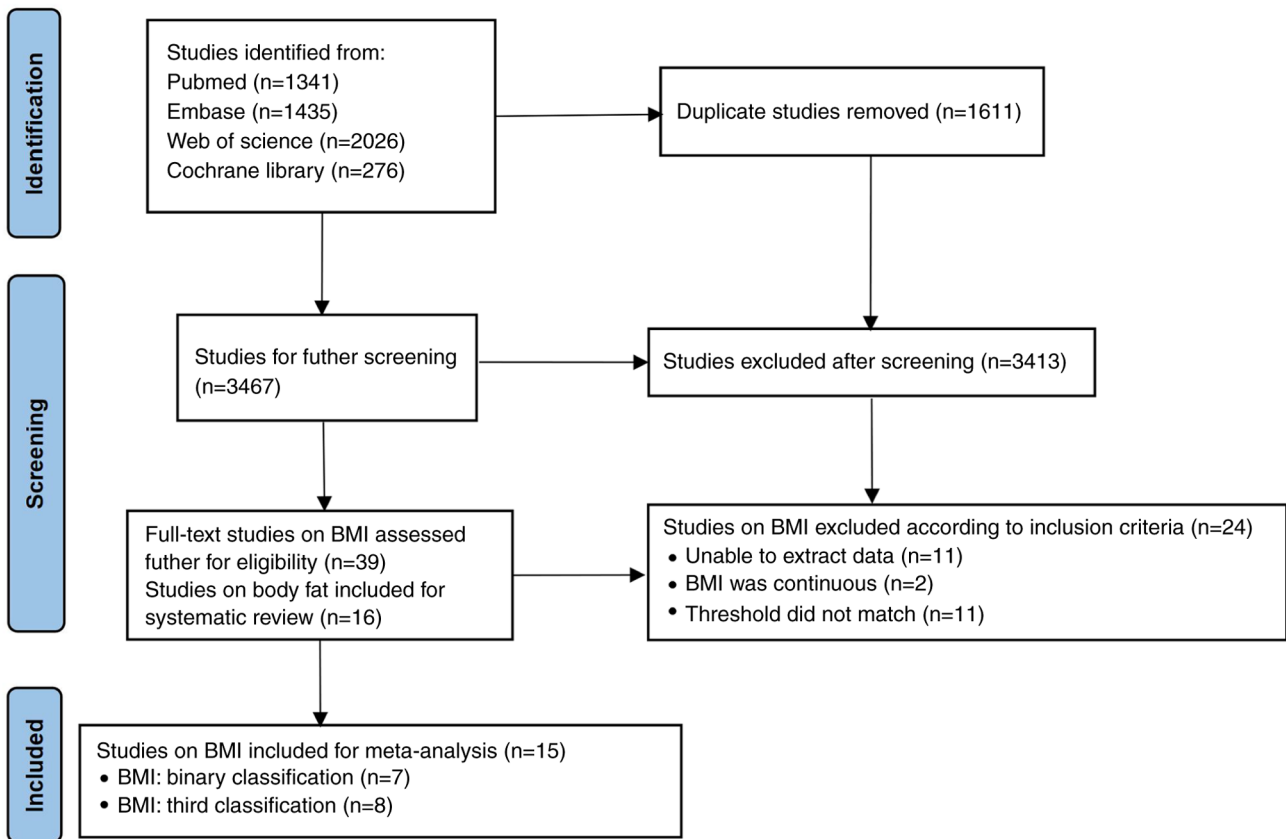


Figure 1. Flow diagram of literature search and study selection. BMI, body mass index.

(<https://rstudio.com/products/rstudio/>). A two-sided $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Study selection. A total of 5,078 studies were retrieved through the initial literature search, with 3,467 studies remaining after removing duplicates. Next, 3,413 articles were excluded through reviewing titles and abstracts. The remaining 54 studies were reviewed and screened according to the present inclusion and exclusion criteria. Finally, 15 studies reporting on the BMI (7-10,15,16,19-27) were included in the current meta-analysis (Fig. 1). The association between body fat and survival was not suitable for meta-analysis. Therefore, 16 studies reporting on body fat (15-17,24,27-38) were included in the systematic review and descriptively summarized in one table.

Characteristics of studies included in the meta-analysis. General information on the included studies reporting on the BMI is presented in Table I. All analyses were published between 2017 and 2022, of which 12 studies were retrospective and 3 studies were prospective. A total of 5,205 male and 3,105 female patients were included in the meta-analysis. The patients in the meta-analysis were from the USA, Canada, Italy, France, Israel, Spain, Australia and Japan. Melanoma was the most commonly reported cancer type. All enrolled patients were at an advanced or metastatic stage. Since the cut-off values for the BMI in the selected studies were not

consistent, 8 studies that stratified the patients based on the BMI value into normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²) and obese (≥ 30 kg/m²) groups were included, as well as 7 studies that divided the patients by their BMI value into BMI <25 kg/m² and BMI ≥ 25 kg/m² groups. With regard to the types of ICIs used, 6 studies used anti-PD-1/PD-L1 monotherapy, 1 study utilized anti-CTLA-4 monotherapy and 8 studies used anti-PD-1/PD-L1 monotherapy or anti-CTLA-4 monotherapy or their combination. The quality of the included studies was assessed with the Newcastle-Ottawa scale, which revealed high or moderate quality of evidence in the included studies (Fig. S1).

Association between BMI and OS in patients with cancer receiving immunotherapy. To evaluate the association between BMI and survival, the HR for OS in 7 studies was first analyzed, stratifying the BMI value into <25 and ≥ 25 kg/m² groups. As shown in Fig. 2, patients with a BMI ≥ 25 kg/m² exhibited increased OS compared with the BMI <25 kg/m² group (HR=0.62, 95% CI=0.47-0.83, $P=0.001$, $I^2=85\%$). Next, the OS of overweight and obese patients was compared with that of the normal group. The results of the pooled analysis showed that improved OS was observed in the overweight (HR=0.79, 95% CI=0.64-0.98, $P=0.030$, $I^2=84\%$) and obese (HR=0.75, 95% CI=0.60-0.94, $P=0.014$, $I^2=76\%$) groups compared with the normal group (Fig. 3). The heterogeneity test indicated that there was heterogeneity among the studies in terms of OS. Thus, a sensitivity analysis was performed to assess the impact of a single study on the

Table I. Baseline characteristics of included studies including the BMI.

Author, year	Sample size	Country	Study design	Males, n (%)	Cancer type	Treatment	BMI cut-off value	Outcomes	(Refs.)
Yoo, 2022	1,840	USA	Prospective cohort	1,059 (57)	Pancancer	Anti-PD-1/PD-L1, anti-CTLA4 Anti-CTLA4+anti-PD-1/PD-L1	18.5-24.9; 25-29.9; ≥ 30	PFS; OS	(9)
Tateishi, 2021	324	Japan	Retrospective cohort	235 (72)	NSCLC	Anti-PD-1/PD-L1	≥ 25 ; < 25	PFS	(26)
Espósito, 2021	153	Italy	Retrospective cohort	62 (40)	Multiple	Anti-PD-1/PD-L1	≥ 25 ; < 25	PFS; OS	(25)
Collet, 2021	272	France	Retrospective cohort	174 (63)	Multiple	Anti-PD-1/PD-L1, anti-CTLA4, anti-CTLA4+anti-PD-1/PD-L1	≥ 25 ; < 25	OS	(21)
Martini i), 2021	70	USA	Retrospective cohort	49 (70)	UC	Anti-PD-1/PD-L1	≥ 25 ; < 25	PFS; OS	(16)
Martini ii), 2021	79	USA	Retrospective cohort	58 (73)	RCC	Anti-PD-1/PD-L1	≥ 25 ; < 25	PFS; OS	(15)
Ahmed, 2021	297	USA	Prospective cohort	177 (59)	Multiple	Anti-PD-1/PD-L1, anti-CTLA4, anti-CTLA4+anti-PD-1/PD-L1	≥ 25 ; < 25	PFS; OS	(20)
Young, 2020	287	USA	Retrospective cohort	184 (64)	Melanoma	Anti-PD-1/PD-L1, anti-CTLA4, anti-CTLA4+anti-PD-1/PD-L1	18.5-24.9; 25-29.9; ≥ 30	PFS; OS	(27)
Di Filippo, 2020	1,214	French	Retrospective cohort	738 (61)	Melanoma	Anti-PD-1, anti-CTLA4	18.5-24.9; 25-29.9; ≥ 30	PFS; OS	(10)
Labadie, 2019	90	USA, Canada, Spain	Retrospective cohort	65 (72)	RCC	Anti-PD-1+anti-CTLA-4 Anti-PD-1/PD-L1	18.5-24.9; 25-29.9; ≥ 30	OS	(7)
Kichenadasse, 2019	1,434	USA, Australia	Retrospective cohort	890 (62)	NSCLC	Anti-PD-1/PD-L1	18.5-24.9; 25-29.9; ≥ 30	PFS; OS	(19)
Donnelly, 2019	423	USA	Retrospective cohort	267 (63)	Melanoma	Anti-PD-1, anti-CTLA-4 Anti-PD-1+anti-CTLA-4	18.5-24.9; 25-29.9; ≥ 30	PFS; OS	(24)
De Giorgi, 2019	313	Italy	Prospective cohort	235 (75)	RCC	Anti-PD-1/PD-L1	≥ 25 ; < 25	OS	(23)
Cortellini, 2019	976	Italy	Retrospective cohort	663 (67)	Multiple	Anti-PD-1/PD-L1	18.5-24.9; 25-29.9; ≥ 30	PFS; OS	(22)
McQuade, 2018	538	USA, Australia	Retrospective cohort	349 (64)	Melanoma	Anti-PD-1/PD-L1 Anti-CTLA-4	18.5-24.9; 25-29.9; ≥ 30	PFS; OS	(8)

BMI, body mass index; NSCLC, non-small cell lung cancer; UC, urothelial carcinoma; RCC, renal cell carcinoma; PD-1, programmed cell death protein-1; PD-L1, PD-1 ligand 1; OS, overall survival; PFS, progression-free survival; CTLA4, checkpoint T lymphocyte-associated protein 4.

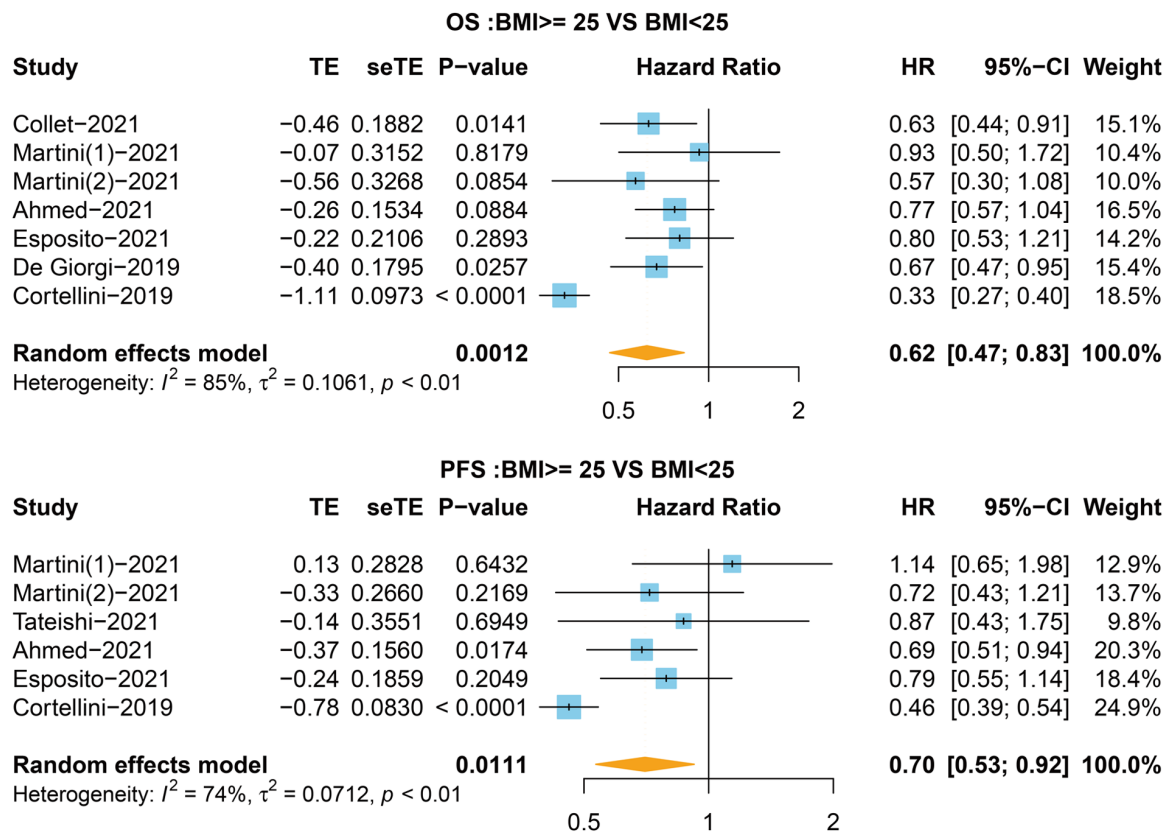


Figure 2. Association between BMI (<25 and ≥ 25 kg/m² groups) and survival in patients with cancer receiving immunotherapy. BMI, body mass index; IV, inverse variance; TE, logarithm of the effect value; se, standard error; df, degrees of freedom; PFS, progression-free survival; OS, overall survival.

overall outcomes, which revealed that the results were stable (Figs. S2 and S3).

Association between BMI and PFS in patients with cancer receiving immunotherapy. In total, 6 of the 9 studies that stratified the BMI value into <25 and ≥ 25 kg/m² groups reported the HR for PFS. As shown in Fig. 2, the BMI ≥ 25 kg/m² group was associated with improved PFS (HR=0.70, 95% CI=0.53-0.92, P=0.011) with a high level of heterogeneity ($I^2=74%$). In the third classification, compared with the normal group, the pooled HR for PFS was 0.82 (95% CI=0.70-0.97, P=0.021, $I^2=78%$) for the overweight group and 0.81 (95% CI: 0.65-1.02, P=0.070, $I^2=80%$) for the obese group (Fig. 4). The sensitivity analysis showed that no single study significantly changed the pooled results (Figs. S2 and S4). As presented in Fig. 5, funnel plots showed no significant publication bias in the present meta-analysis.

Characteristics of studies involving body fat and immunotherapy. A total of 16 studies that were published from 2019 to 2022 involving 1,888 patients focused on body fat analysis and were included in the present study. Among them, males accounted for 61.5% of patients. These studies were performed in Asia, North America and Europe. In total, 5 studies were conducted on patients with non-small cell lung cancer (NSCLC) (29-31,34,35); 3 on patients with melanoma (27,33,37); 3 on patients with multiple cancer types (25,28,32); 2 on patients with renal cancer (15,38); 1 on patients with breast cancer (36); 1 on patients with liver cancer (17); and 1 on

patients with urothelial cancer (16). The average patient age and immunotherapy drugs were similar in all the studies. Most studies adopted baseline abdominal CT images in the middle of the third lumbar vertebra (mid-L3). Subcutaneous, intermuscular, intramuscular and visceral fat were measured using different segmentation methods. The majority of studies used the Hounsfield unit (HU) value to quantify adipose tissue (-29 to +150 HU for skeletal muscle; -190 to -30 HU for subcutaneous and intermuscular fat; and -150 to -50 HU for visceral fat). Further details are presented in Table II.

Association between body fat and outcomes in patients with cancer receiving immunotherapy. Due to the different parameters and statistical methods, the findings were not consistent. As presented in Table II, in NSCLC, 2 studies showed that subcutaneous adipose tissue (SAT) was associated with prognosis. Popinat *et al* (29) reported that low subcutaneous fat mass was significantly associated with poor survival (HR=0.75, P=0.006). Degens *et al* (35) showed that loss of SAT at week 6 of treatment with nivolumab was a significant poor prognostic factor for survival. A total of 4 studies assessed the association between visceral adipose tissue (VAT) and survival (29,31,34,35), but only one of them reported that VAT loss at week 6 of treatment with nivolumab was associated with poor OS (35). Out of 3 studies, 1 study indicated that low body adipose mass was significantly associated with poor survival (HR=0.80, P=0.004) (29). Only 1 study explored the correlation between intramuscular fat and prognosis in NSCLC (31). In addition, 3 studies reported no association between skeletal

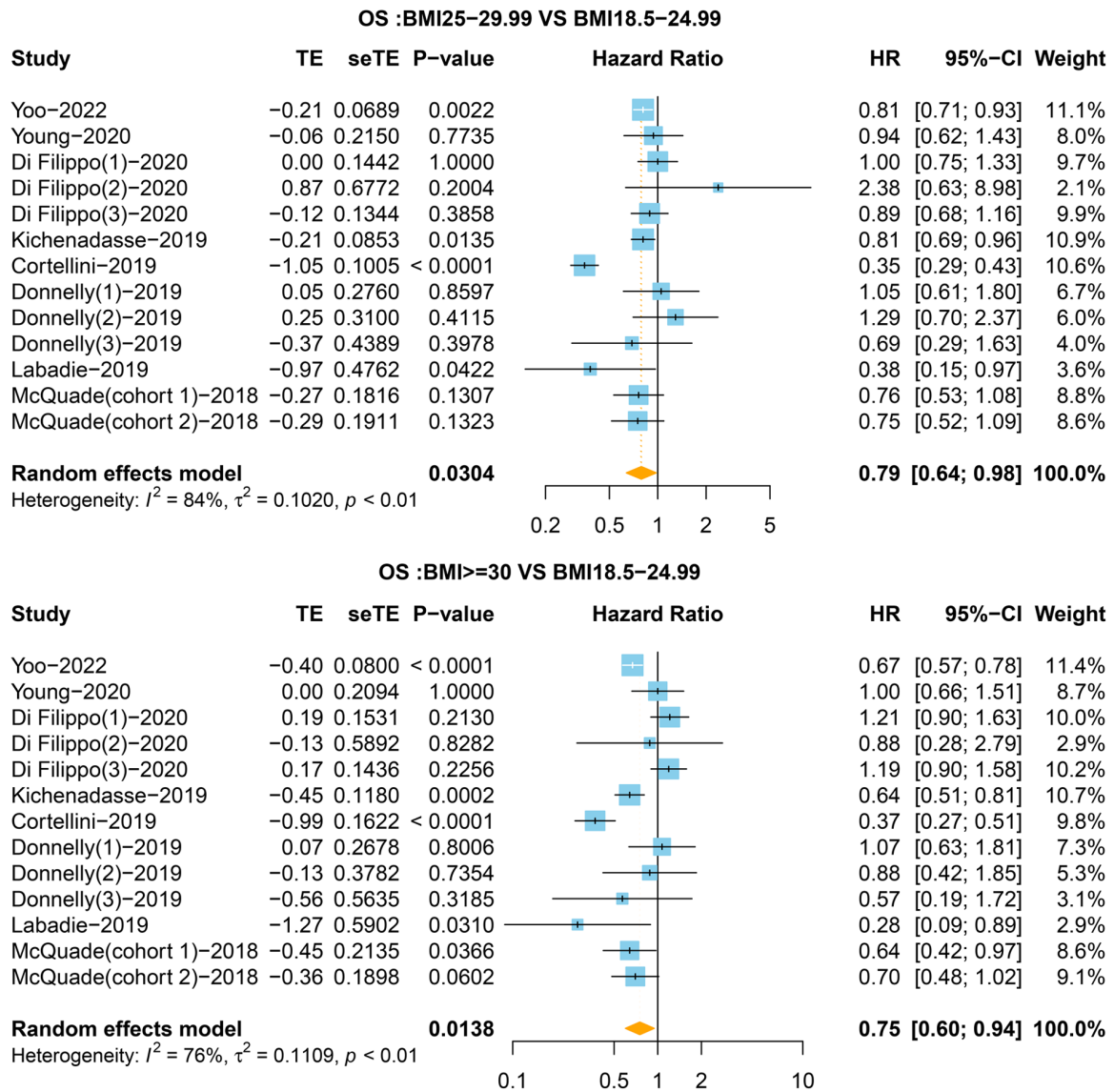


Figure 3. Association between BMI (overweight, obese and normal groups) and OS in patients with cancer receiving immunotherapy. OS, overall survival; BMI, body mass index; IV, inverse variance; TE, logarithm of the effect value; se, standard error; df, degrees of freedom.

muscle and survival (30,34,35). These studies indicated that increased body fat, rather than skeletal muscle was associated with improved survival in patients with NSCLC receiving ICI therapy.

In melanoma, SAT was not associated with survival (33). However, increased VAT or total adipose tissue (TAT) predicted favorable survival in patients treated with ICIs (27,37). In renal cell carcinoma (RCC), 1 article showed that low subcutaneous fat index (SFI), low visceral fat index (VFI) or low total fat index (TFI) were associated with significantly inferior survival in metastatic RCC (15). Of note, another article reported no association between body fat and survival in metastatic clear cell RCC (38).

In breast cancer, only 1 study found that a high quantity of subcutaneous or total abdominal fat tissue was a poor prognostic factor in patients receiving trastuzumab/pertuzumab-based first-line treatment for human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (36). Of note, visceral fat was not associated with outcome.

In urothelial carcinoma, only 1 article reported that increased SFI and VFI, and decreased intermuscular fat index (IFI) were associated with improved outcomes in patients treated with immunotherapy (16). In liver cancer, increased VAT and TAT were associated with improved survival rates in patients treated with ICIs (17).

Regarding multiple cancer types, 3 studies presented different results. Esposito *et al* (25) showed that neither subcutaneous fat area (SFA), visceral fat area (VFA) or total fat area influenced patient survival. However, a higher VFA/SFA ratio led to increased OS in patients treated with ICIs. Martini *et al* (28) reported that increased SFI and decreased IFI were associated with prolonged survival in patients with cancer treated with immunotherapy. Crombé *et al* (32) determined that changes in the subcutaneous adipose tissue index from the first day of patients' treatment to 2 months later was associated with survival, while none of the baseline fat parameters were associated with PFS in metastatic cancer patients treated with ICIs.

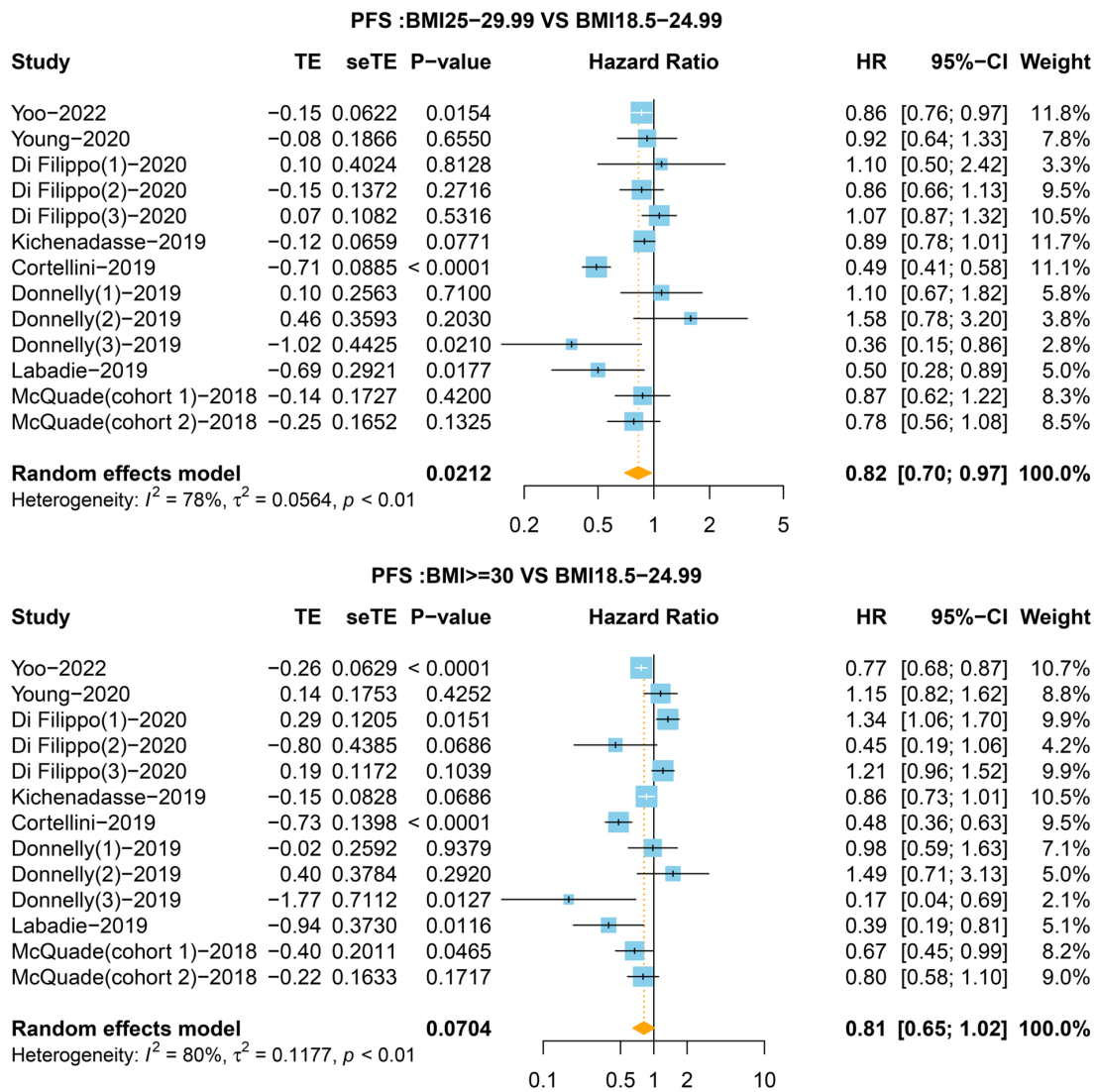


Figure 4. Association between BMI (overweight, obese and normal groups) and PFS in patients with cancer receiving immunotherapy. PFS, progression-free survival; BMI, body mass index; IV, inverse variance; TE, logarithm of the effect value; se, standard error; df, degrees of freedom.

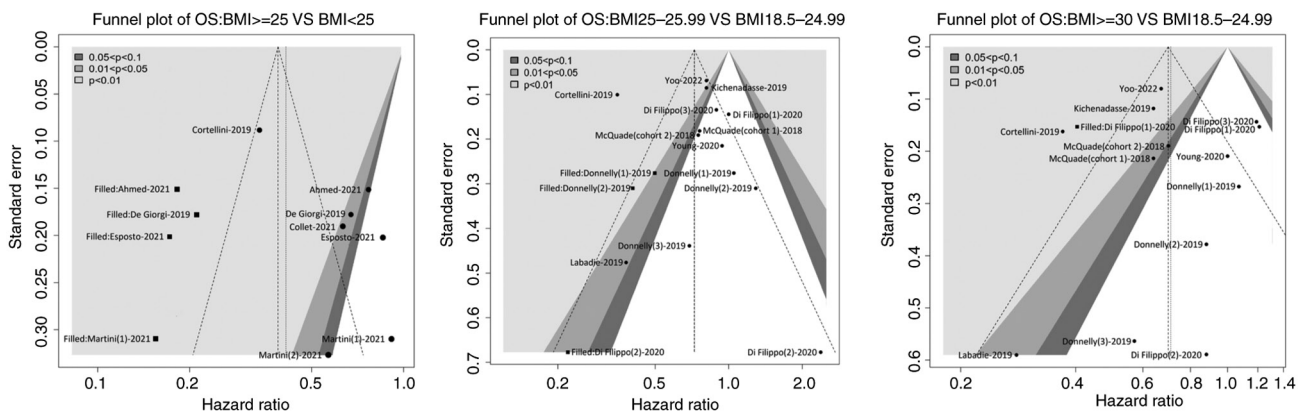


Figure 5. Funnel plot for the adjusted meta-analysis. OS, overall survival; BMI, body mass index.

Discussion

Although obesity has been considered a significant risk factor for developing several types of cancer, it appears to have a

contradictory protective effect in patients with cancer treated with targeted therapy, chemotherapy and ICIs (8,39). Thus, this ‘obesity paradox’ has propelled a reconsideration of whether defining obesity by the BMI is correct. It is widely known that

Table II. Baseline characteristics of studies involving body fat and immunotherapy.

Author, year	Country	Sample size	Cancer type	ICIs treatment	Body composition analysis method	Adipose parameters and cut-offs	Outcomes	(Refs.)
Martini, 2019	USA	90	Multiple	Anti-PD-1/ PD-L1	CT at L3; -190 to -30 HU for subcutaneous and intramuscular fat and -150 to -50 HU for visceral fat	SFI, IFI and VFI Identify the cut-off values for SFI and IFI by a recursive partitioning and regression trees method and set 3-level risk stratification (low, intermediate and high risk)	Low-risk group (SFI ≥ 73) had a significantly longer OS (HR=0.20; 95% CI: 0.09-0.46) and PFS (HR=0.38; 95% CI: 0.20-0.72) compared with patients at intermediate risk (SFI<73 and IFI<3.4) and poor risk (SFI<73 and IFI ≥ 3.4)	(28)
Popinat, 2019	France	55	NSCLC	Nivolumab	PET-CT at L3; measured by 3D automatic software	FBM, VFM and SCFM SCFM (kg/m ²): 5.0; VFM (kg/m ²): 1.38; FBM (kg/m ²): 5.7	In univariate analysis using continuous values, SCFM (HR=0.75, P=0.003) and FBM (HR=0.80, P=0.004) were significant prognostic factors	(29)
Magri, 2019	Israel	46	NSCLC	Nivolumab	CT at L3; -190 to -30 HU for subcutaneous and intramuscular adipose tissue and -150 to -50 HU for visceral adipose tissue	FFMI and FMI continuous variable	In univariate analysis, only PS, albumin and weight change were found to be statistically significantly correlated with OS	(30)
Minami, 2019	Japan	74	NSCLC	Anti-PD-1/ PD-L1	CT at L3; the skeletal muscle and adipose tissue areas were investigated by SYNAPSE VIN CENT software	IMAC, VSR and VFA IMAC (cm ² /m ²): 6.36 (men), 3.92 (women) VSR: 1.33 (men), 0.93 (women) VFA (cm ²): 100	According to multivariate analyses, IMAC was a significant prognostic factor for OS (HR=0.43, P=0.0496), but not for PFS	(31)
Young, 2020	USA	287	Melanoma	Ipilimumab+ nivolumab Pembrolizumab Nivolumab Atezolizumab	CT at L3; -150 to -50 HU for visceral fat	TATI Use tertiles	In the univariate analyses, there were no statistically significant associations between TATI (assessed by tertiles) and PFS or OS	(27)
Cromb�, 2020	France	117	Multiple	Anti-PD-1/ PD-L1 Anti-PD-L1+ anti-CTLA4	CT at L3; -190 to -30 HU for fat	SATI, VATI and TATI Use absolute change in SATI, VATI or TATI from 1st day of ICI treatment to CT1. Tertiles assessed	Δ I-SATI was correlated with PFS (HR=2.82, P=0.0004)	(32)

Table II. Continued.

Author, year	Country	Sample size	Cancer type	ICIs treatment	Body composition analysis method	Adipose parameters and cut-offs	Outcomes	(Refs.)
Martini, 2021	USA	70	Urothelial carcinoma	Pembrolizumab Atezolizumab	CT at L3; -190 to -30 HU for subcutaneous and intermuscular fat, -150 to -50 HU for visceral fat	on whole population were used for dichotomization SFI, VFI and IFI The optimal cutoff point was identified that maximizes the separation between the two groups (high vs. low) via a bias-adjusted log-rank test	High VFI was significantly associated with improved PFS (HR=1.76; P=0.040) and showed a trend toward longer OS (HR=1.82; P=0.055). High SFI was significantly associated with prolonged OS (HR=1.99; P=0.043) but had no significant association with PFS (P=0.477)	(16)
Esposito, 2021	Italy	153	Multiple	Anti-PD-1/ PD-L1	CT at L2-L3; SAT and VAT were measured by applying predefined image display settings (window width: -195 to -45 HU; center: -120 HU)	SFA, VFA and TFA Use tertiles	Univariate analysis did not show differences in OS according to VFA (1st versus 2nd tertile: HR=1.09, 95% CI 0.70 - 1.69, P=0.70; 1st vs. 3rd tertile: HR=0.78, 95% CI 0.49-1.24, P=0.29), SFA (1st vs. 2nd tertile: HR=1.00, 95% CI 0.64-1.57, P=0.99; 1st vs. 3rd tertile: HR=0.82, 95% CI 0.52-1.29, P=0.39), TFA (1st vs. 2nd tertile: HR=0.70, 95% CI 0.44-1.10, P=0.12; 1st vs. 3rd tertile: HR=0.75, 95% CI 0.48-1.18, P=0.21). However, a higher VFA/SFA ratio (1st and 2nd tertile vs. 3rd tertile) had increased OS (HR=0.88, 95% CI 0.78-1.00, P=0.047)	(25)
Faron, 2021	Germany	107	Melanoma	Anti-PD-1 Anti-PD-1+ anti-CTLA4	CT at L3/4; a deep learning model for automated body composition analysis was used for tissue segmentation	VAI and SAI The cohort was binarized according to median SMI, VAI and SAI based on gender-specific cutoffs	No significant differences in 3-year mortality regarding adipose tissue compartments were observed (low vs. high VAI, 26 vs. 30%, P=0.48; low vs. high SAI, 26 vs. 30%, P=0.731)	(33)

Table II. Continued.

Author, year	Country	Sample size	Cancer type	ICIs treatment	Body composition analysis method	Adipose parameters and cut-offs	Outcomes	(Refs.)
Baldessari, 2021	Italy	44	NSCLC	Pembrolizumab	CT at L3; -180 to -30 HU for visceral fat	SFI and VFR continuous variable	In univariate analysis, SFI and VFR were not correlated with survival	(34)
Degens, 2021	Netherlands	80	NSCLC	Nivolumab	CT at L1; -190 to -30 HU for subcutaneous and intermuscular fat, -150 to -50 HU for visceral fat	VAT and SAT The loss of VAT and SAT from baseline to week 6	Loss of body weight of >2% at week 6 was an independent predictor for poor OS (HR=2.39, 95% CI: 1.51-3.79, P<0.001). In patients with >2% body weight loss between baseline and week 6, a significant loss of VAT (P=0.047) and SAT (P=0.042) was observed, compared with patients with weight maintenance	(35)
Martini, 2021	USA	79	mRCC	Anti-PD-1	CT at L3; -190 to -30 HU for subcutaneous and intermuscular fat, -150 to -50 HU for visceral fat	SFI, IFI, VFI and TFI Each fat index was characterized as high vs. low for each variable at gender-specific optimal cuts using OS as the primary outcome through a bias-adjusted log-rank test searching algorithm	Low TFI had significantly shorter OS (HR=2.72, CI: 1.43-5.17, P=0.002), PFS (HR=1.91, CI: 1.09-3.35, P=0.025). Low SFI also had significantly shorter OS (HR=2.06, CI: 1.10-3.85, P=0.024), PFS (HR=2.02, CI: 1.21-3.37, P=0.007). Low VFR was significantly associated with shorter PFS (HR=1.94; CI: 1.18-3.21, P=0.01) but had no significant association with OS (P=0.199)	(15)
Xiao, 2022	China	172	Primary liver cancer	Anti-PD-1/ PD-L1	CT at L3; -190 to -30 HU for subcutaneous and inter-muscular fat, -150 to -50 HU for visceral fat	VATI, SATI, TATI and VSR The Youden Index was used to identify the optimal cut-off values	OS of patients with a high VATI was better (HR=0.30; 95% CI: 0.15-0.59; P=0.001) than that of patients with a low VATI; however, no difference was noted in PFS. The OS of patients with a high SATI and of those with a high TATI was better than that of patients with a low SATI (HR=0.31; 95% CI: 0.17-0.58; P<0.001) and a low TATI	(17)

Table II. Continued.

Author, year	Country	Sample size	Cancer type	ICIs treatment	Body composition analysis method	Adipose parameters and cut-offs	Outcomes	(Refs.)
Palleschi, 2022	Italy	43	HER2 positive metastatic breast cancer	Pertuzumab Trastuzumab	CT at L3; -190 to -30 HU for subcutaneous and inter-muscular fat, -150 to -50 HU for visceral fat	SFI, VFI and TAFTI SFI (cm ² /m ²): 82.97; VFI (cm ² /m ²): 37.1; TAFTI (cm ² /m ²): 118.82	(HR=0.31; 95% CI: 0.17-0.57; P<0.001); however, no difference was observed in PFS. There were no statistically significant associations between VSR and OS or PFS	(36)
Lee, 2022	Korea	266	Melanoma	Pembrolizumab Nivolumab	CT at L3; image segmentation was completed by using a commercially available deep learning-based software	SFI and VFI SFI (cm ² /m ²): 46; VFI (cm ² /m ²): 25	OS was significantly longer in patients with high VFI (mean OS, 49.1 months; 95%CI: 44.4-53.8 months), compared with patients with low VFI (mean OS, 38.0 months; 95% CI: 31.1-44.8 months) (log-rank P<0.001). SFI was not associated with OS. PFS was not significantly different between the subgroups stratified by SFI or VFI	(37)
Ged, 2022	USA	205	Metastatic clear cell renal carcinoma	Anti-PD-1/ PD-L1 Anti-PD-1+ Anti-CTLA4 Anti-PD-1+ Anti-PD-L1	CT at L3; -150 to -50 HU for visceral fat	VATI and SATI Low VATI: Males, <55 cm ² /m ² ; females, <33 cm ² /m ² ; low SATI: Males, <57 cm ² /m ² ; females, <88 cm ² /m ²	VATI and SATI were not associated with survival	(38)

NSCLC, non-small cell lung cancer; mRCC, metastatic renal cell carcinoma; BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index; SFI, subcutaneous fat index; IFI, intermuscular fat index; VFI, visceral fat index; LBM, lean body mass; MBM, muscle body mass; VFM, visceral fat mass; SCFM, sub-cutaneous fat mass; PS, performance status; IMAC, intramuscular adipose tissue content; VSR, visceral-to-subcutaneous ratio; VFA, visceral fat area; TATI, total adipose tissue index; SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VAI, visceral adipose tissue index; SAI, subcutaneous adipose tissue index; SFA, subcutaneous fat area; VFA, visceral fat area; TFA, total fat area; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAFTI, total cross-sectional area of fat tissues; HR, hazard ratio; HU, Hounsfield units; Δ , early change within the first 2 months.

obesity is characterized by large fat accumulation. Due to the method of BMI calculation, it cannot correctly distinguish different types of fat (visceral, subcutaneous, intermuscular or intramuscular). Therefore, the present study investigated the association between adiposity and clinical outcomes using the BMI and fat indices in patients with cancer subjected to ICI treatments.

The association between different BMI groups and the OS or PFS of patients with cancer treated with ICIs was first investigated. Through systematic literature screening, the current meta-analysis included 15 eligible studies containing 8,310 patients aimed to assess the impact of the BMI on the efficacy of ICIs. The results revealed that overweight and obese patients with cancer treated with ICIs exhibited improved OS and PFS. According to the weight characteristics of each population, the association between different comparative models of BMI categories and survival was examined in different countries. For instance, several Japanese studies set the cutoff values for the BMI as 18.5 or 20 kg/m², and it was found that a low BMI was a negative predictive factor in patients with NSCLC or melanoma (40,41). In a Chinese study, the cutoff value for the BMI was 24.0 kg/m². This study showed that a high BMI was associated with improved OS and PFS in patients treated with PD-1 inhibitors (42). Furthermore, Wang *et al* (43) observed a marked improvement in the clinical outcomes of obese (BMI ≥ 30 kg/m²) vs. nonobese (BMI < 30 kg/m²) patients in a cohort of 250 US patients treated with PD-L1 inhibitors for a variety of cancer types. All of these studies concluded that the BMI could be a predictive factor of immunotherapy outcomes.

Besides the BMI classification, subgroup analyses based on sex, cancer type, study region and type of ICI have also assessed the efficacy of immunotherapy. Meta-analyses showed that a high BMI was associated with a lower risk of mortality after ICI treatment in multiple cancer types, including NSCLC and melanoma (11,12). By contrast, no consistent results were obtained from these meta-analyses regarding RCC (11-14). When stratifying by sex, the results of the analysis conducted by Xu *et al* (12) suggested that male and female patients with a high BMI (≥ 25 kg/m²) who were treated with ICIs exhibited similar survival. However, according to the findings of Chen *et al* (11), an improvement in OS was observed in male patients with a higher BMI. In addition, the study revealed an association between the survival of patients and treatment with anti-PD1/PD-L1 but not with anti-CTLA-4 therapy. No association was observed between BMI and the survival of American patients (11). The difference in results may be attributed to the absence of a homogeneous cutoff value for the BMI. Therefore, a more standard cutoff value definition was required to stratify by the BMI and reduce heterogeneity between studies. Subgroup analyses based on sex, cancer type, study region and type of ICI should also be conducted to evaluate the influence of the BMI on patient survival after immunotherapy. If all the raw data from the included studies could be obtained, it may be possible to set the optimal cutoff for the BMI using statistical analysis, such as receiver operating characteristic curve analysis.

Tumor heterogeneity has been recognized to be associated with clinical outcomes for ICIs, such PD-L1 protein expression, TILs, TMB and MSI (3). The difference may affect the

influence of the BMI on the prognosis of patients with cancer treated with ICIs. In addition, different treatment procedures and regimens for various cancer types may be another factor affecting the relationship between the BMI and cancer survival. Future additional studies are needed to explore the effect of the BMI on the outcomes of different therapy methods for patients with cancer.

The complex body composition cannot be accurately reflected by the BMI alone. It has been reported that a subset of obese patients (BMI ≥ 30 kg/m²) with a healthy distribution of fat mass and normal inflammatory profile displayed a decreased risk for diseases related to obesity, such as cancer and cardiovascular diseases (44). Another study showed no influence of the BMI on the outcomes of ICI treatment in patients with RCC, while a high body fat mass was a favorable factor for immunotherapy (15). Thus, the prognostic implication of the bodily composition may be more important than that of the BMI in obese patients with cancer treated with ICIs.

Fat composition measurement is mainly based on the calculation of visceral and subcutaneous adipose tissues. Body fat is typically measured via the visceral/subcutaneous adipose area (cm²), area divided by height squared (cm²/m²) or other methods. TAT is generally considered the sum of subcutaneous and visceral adipose tissues. The adipose area can be measured by surface area (cm²) at the third lumbar landmark using a single cross-sectional CT image (45). In the present study, it was observed that the association of imaging-measured visceral, subcutaneous and total adiposity with survival was not consistent in patients with cancer receiving immunotherapy. For patients with NSCLC, RCC and urothelial cancer, increased subcutaneous adiposity was reported to be associated with improved survival (15,16,29,35). Similarly, high visceral adiposity was also associated with an increased survival rate in patients with NSCLC, melanoma, RCC, liver cancer and urothelial cancer (15-17,35,37). In addition, total adiposity was also a favorable factor in patients with NSCLC, melanoma, RCC, breast cancer and liver cancer (15,17,27,29,36). These studies suggested that a high fat distribution may be a good predictor of immunotherapy survival outcome. However, a meta-analysis of the aforementioned studies was not performed due to the inconsistent cutoff values in adipose metrics and the small number of studies on certain cancer types.

The current study confirmed an association between improved survival and high BMI or increased subcutaneous/visceral/total adiposity in patients with cancer receiving immunotherapy. A retrospective study on RCC found that patients with a higher SFI, VFI or TFI showed improved survival, while no influence of the BMI on survival outcomes of immunotherapy was observed (15). Another study on patients with HER2-positive metastatic breast cancer reported no association between BMI and cancer patient survival, but found an association between low SFI or TAFI and better outcomes (36). Based on the currently available data, it may be speculated that the body fat distribution may be strongly associated with the survival of patients with cancer subjected to immunotherapy.

Recently, the underlying mechanisms behind the positive association between obesity and immunotherapy have been explored. Adipose tissue, as an endocrine organ, influ-

ences the homeostasis of the immune system by releasing pro-inflammatory hormones such as leptin, tumor necrosis factor (TNF)- α and interleukin (IL)-6 (46). A high level of leptin in obese patients may result in increased expression of PD-1 and dysfunction of CD8⁺ T cells, which leads to a more pronounced response to immunotherapy (43). In addition, it was previously found that increased leptin secreted from adipose tissues may cause upregulation of PD-1 receptors on T cells through signal transduction and activator of transcription 3 (47). Elevated PD-1 expression is associated with increased T-cell exhaustion, which may explain why targeted PD-1 therapy may improve survival outcomes in obese populations (48). Obesity induces chronic low-grade inflammation, which is accompanied by innate and adaptive immune suppression and immune aging acceleration (49). For instance, obesity-associated hyperinsulinemia reduced T regulatory cells, thus inhibiting IL-10 and TNF- α production via the AKT/mTOR signaling pathway (50). Natural killer cells, which are responsible for innate immunity and anticancer functions, have been shown to be impaired in obese patients (51). Furthermore, obesity may lead to an imbalance in the ratio of M1/M2 macrophages, thus resulting in an upregulation of M1 'pro-inflammatory' macrophages and a downregulation of M2 'anti-inflammatory' macrophages (52). The above factors caused exacerbation of the chronic inflammatory state. This evidence suggests that alterations of the anti-tumor immune function in obese patients may explain the favorable outcomes of cancer immunotherapy.

Different adipose tissues have various regulatory roles in the body's immune microenvironment and metabolism, which may impact cancer survival. In the present study, one of the articles included reported that increased VAT, but not SAT, predicted favorable survival in patients with liver cancer treated with ICIs (17). A possible explanation for this is that visceral fat may increase a range of inhibitory immune checkpoints on the surface of T cells, including T-cell immunoglobulin and ITIM domain, adenosine A2a receptor, PD-L2 and CD160, which may be beneficial for ICIs to control anticancer immunity (53). A total of 2 studies reviewed in the present study showed that subcutaneous fat was significantly associated with survival, while there was no association between visceral fat and survival (34,38). A potential explanation is that high subcutaneous fat indicates a better nutritional status and it resists the energy consumption caused by tumors. Another reason may be that subcutaneous fat may induce the expression of PD-1 on T cells by secreting leptin, thereby improving the response to immunotherapy (43,54). Further studies are needed to explore the mechanisms of different types of body fat affecting the survival outcomes of immunotherapy.

Several limitations in the current meta-analysis need to be considered. First, certain confounding risk factors across studies, such as age, sex, cancer type and immunotherapy regimen may have increased the heterogeneity among studies. Furthermore, the HR provided in certain studies was not available; thus, these studies were excluded to improve the accuracy of the results. In addition, since certain studies did not stratify the BMI cutoff value according to the WHO, only studies categorizing patients based on the BMI into three groups (normal, overweight and obese) or into two groups (BMI <25 kg/m² and BMI \geq 25 kg/m²) were included, which

may have resulted in certain selection bias. Finally, due to the different parameters and statistical methods, the association between body fat and survival was not quantitatively determined by any meta-analysis.

In conclusion, the study of body fat composition as a predictive marker in cancer immunotherapy is an area of compelling interest. Clinical CT scans may provide precise estimates of adipose tissue beyond the BMI for predicting the effectiveness of immunotherapy. Identifying the accurate quantification ability and cutoff values of different indicators of adipose tissue is a challenging endeavor, but it is likely to improve the current understanding of the effects of obesity on cancer patient survival. Body composition evaluation is an effective method for predicting the efficacy of cancer immunotherapy. Defining the biological mechanisms linking obesity and efficacy of immunotherapy will provide guidance for obese patients receiving cancer immunotherapy.

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Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Authors' contributions

XYL, SF and CW performed data collection and meta-analysis. HG and LQY completed the systematic review. XGS and DPL contributed to the conception and design of the study. HG and DPL checked and confirmed the authenticity of the raw data. All authors revised the manuscript and read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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