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REVIEW

Pretreatment body mass index and clinical outcomes in cancer patients following immune checkpoint inhibitors: a systematic review and meta-analysis

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Abstract

Background This systematic review and meta-analysis aimed to evaluate the association between pretreatment body mass index (BMI) and clinical outcomes in cancer patients treated with immune checkpoint inhibitors (ICIs).

Methods Systematical searches of PubMed, Embase, and the Cochrane Library databases were carried out. Studies reporting on the association between BMI and outcomes of ICIs were included. The intended outcomes included overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and immune-related adverse events (irAEs). Quantitative analyses and dose–response meta-analyses were performed under random effect models.

Results Twenty-two eligible studies involving 5686 cancer patients treated with ICIs were identified.
Compared to those with lower BMI, patients with higher BMI obtained a significant benefit on OS (HR = 0.698, 95% CI 0.614–0.794, $P < 0.001$; $I^2 = 45.9\%$) and PFS (HR = 0.760, 95% CI 0.672–0.861, $P < 0.001$; $I^2 = 37.9\%$). Most stratified analyses for OS and PFS also showed similar pooled risk estimates. For an increment of every 5 kg/m^2 in BMI, the risk for death reduced by approximately 15.6% (HR = 0.844, 95% CI 0.752–0.945, $P = 0.003$). Moreover, patients with higher BMI had a remarkably better ORR (OR = 0.468, 95% CI 0.263–0.833, $P = 0.010$; $I^2 = 73.6\%$) than that of those with lower BMI. However, no statistically significant differences were found in the incidence of any grade irAEs ($P = 0.073$) and ≥ 3 grade irAEs ($P = 0.105$) between higher and lower BMI.

Conclusion Higher BMI is significantly associated with improved outcomes in patients treated with ICIs. Further large-scale prospective research is warranted to better illuminate the association between BMI and outcomes from ICIs.

Keywords Body mass index · Immune checkpoint inhibitors · Outcome · Cancer patients · Meta-analysis

Introduction

In recent years, cancer immunotherapy based on immune checkpoint inhibitors (ICIs) has become an increasingly attractive approach for diverse malignancies [1, 2]. With the emerging clinical trials in ICIs, several monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death-1 (PD-1) or PD ligand 1 (PD-L1), which achieved encouraging anti-tumor activity, have been gradually approved for the treatment of multiple cancers. Despite the durable responses of ICIs reported in previous studies, only a limited number of patients can benefit from these agents. If not selected, the response rates seem unsatisfactory for several cancer entities, such as non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC), with a response rate lower than 20% [3, 4] and 30% [5, 6], respectively. Moreover, immune-related adverse

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events (irAEs) vary greatly across individual patients, with a small proportion of them suffering from severe irAEs, especially when combination regimens are used. Therefore, there is an urgent need to discover robust predictive biomarkers for clinical outcome and toxicities of ICIs, to identify the subgroups who can benefit from these immunotherapeutic agents.

So far, several candidate biomarkers have been recognized to be associated with clinical outcomes for ICIs, such as the expression of PD-L1 protein, tumor-infiltrating lymphocytes(TILs), tumor mutational burden(TMB) and microsatellite instability (MSI) [7]. Among them, PD-L1 expression by immunohistochemistry on tumor cells was the first biomarker associated with treatment response to PD-1 inhibitors [8]. Numerous studies have generally shown better objective response and longer overall survival of PD-L1 positive patients, compared with the PD-L1 negative subgroup [4, 9, 10]. Other trials, however, yielded contradictory results, in which some patients whose tumor was PD-L1-negative could also achieve clinical benefit with anti-PD-1/PD-L1 therapies [3, 11–14]. A meta-analysis also demonstrated that PD-L1 expression alone was not yet sufficient in selecting patients for PD-1/PD-L1 blockade therapy [15]. Based on these findings, the prognostic value of PD-L1 expression by immunohistochemistry alone for routine clinical use remains to be established.

More recently, substantial efforts are ongoing to elucidate the potential role of patient-associated factors such as age, sex, and body mass index (BMI) in the prediction of clinical outcomes from immunotherapy. Traditionally, it has been reported that high BMI is significantly associated with a higher risk of incidence and death for multiple cancers [16, 17]. However, recent clinical data demonstrate that obesity, defined by increased BMI (≥ 30 kg/m^2), is associated with improved outcomes of cancer patients treated with targeted therapy or ICIs, which may be supported by the contrasting/paradoxical impact of obesity on cancer immune responses [18–21]. Notably, higher BMI was also significantly related to a higher occurrence of irAEs [22]. Despite a growing body of evidence that indicates a favorable efficacy with ICIs in patients with higher BMI, however, contradictory findings have also been reported [23, 24]. From these studies, it can be concluded that several factors, including heterogeneity in cancer type, age, and BMI threshold, make it hard to define the predictive value of BMI for outcomes after ICIs therapy.

Although there was one pooled analysis exploring the impact of obesity on the outcomes of ICIs for cancer patients, the analysis was limited by the relatively inadequate power and the small number of primary studies included [25]. Herein, with recently accumulated evidence, we performed a more comprehensive systematic review and meta-analysis to evaluate the association between BMI and clinical outcomes in cancer patients treated with ICIs.

Methods

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [26].

Search strategy and selection criteria

We carried out the systematic review of literature by searching PubMed, Embase, and the Cochrane Library databases from the inception of each database until 18th, May 2020 with no language restrictions. The main keywords for the literature search included cancer, body mass index, overweight, obesity, PD-1, PD-L1, CTLA-4, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, and tremelimumab. The complete search strategy was available in Supplementary: Table S1. In addition, the reference lists of relevant studies were also searched with hand.

Two investigators (HZC and DQW) independently performed the search and selected articles for eligibility. If there were any disagreements, the study would be re-evaluated by a third investigator (YXT). Full-text publications of original prospective or retrospective studies were included. The main criteria for eligibility were as following:(1) the studies in which cancer patients were treated with anti-CTLA-4, anti-PD-1/PD-L1, or combination therapy; (2) the studies where the association between baseline BMI and clinical outcomes of ICIs was evaluated; (3) the studies in which any of clinical endpoints such as objective response rate(ORR), progression-free survival (PFS), overall survival (OS) or irAEs were reported; (4) the studies from which the related data could be extracted directly or calculated indirectly; (5) the studies that were written in English. Studies were excluded if they were reviews, case reports, comments, letters, editorials, animal studies or conference abstracts. Other studies were also removed if they lacked sufficient information. When the same study population appeared in multiple publications, or patient cohort was overlapping between different articles, the most updated and complete studies were included.

Data extraction and quality assessment

Two investigators (HZC and DQW) independently performed study data collection, which included: (1) characteristics of studies included (first author, publication year, area, type of studies, sample size, follow-up time); (2) characteristics of patients (age, sex, disease, study drugs, BMI categories); (3) treatment outcomes (OS, PFS, ORR, and irAEs). Hazard ratios (HRs) and their corresponding 95% confidence intervals(CIs) for PFS or OS were also extracted

from original studies. When results in both univariate and multivariate analyses were available, we preferred results in the multivariate analysis. If the information needed was not reported, or not available after contacting the authors, the study was discarded.

Since all the studies included were non-randomized observational studies, the Newcastle–Ottawa Scale(NOS) criteria were adopted to evaluate the quality of studies [27]. The total scores ranged from 0 to 9 points, with a score of lower than five indicating poor quality, five to seven indicating medium quality, and higher than seven representing high quality.

BMI definition and categories

BMI was defined as the ratio of weight in kilograms divided by squared height in meters. According to the classification of World Health Organization, four BMI categories were defined: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–25.0 kg/m^2), overweight (BMI 25–30.0 kg/m^2), and obesity (BMI ≥ 30.0 kg/m^2). Since not all the identified studies compared the differences between the four groups for outcomes and the cut-off values of BMI varied, we compared the effect of higher BMI with lower BMI on outcomes of ICIs for convenience. The higher BMI group was defined by a BMI value of ≥ cut-off in each study, otherwise it was identified as the lower BMI group. When studies reported more than two BMI categories, the results for each BMI category were collected. When performing the pooled analysis, we only included one comparison for each study, selected as the comparison between the highest with the lowest category of BMI available in the study.

Statistical analysis

The impacts of BMI on the clinical outcomes of ICIs measured in terms of OS, PFS, ORR, and irAEs for patients were analyzed. HR with 95% CI was used for the pooled analyses of OS and PFS, and odds ratio (OR) was selected as the effect size of ORR and irAEs. Categorical meta-analyses were conducted by comparing the higher BMI with a lower BMI. Besides, we also evaluated the association between different comparative models of BMI categories (overweight vs normal weight, obese vs normal weight, underweight vs normal weight, obese/overweight vs normal/underweight) and the intended outcomes (OS and PFS).

In addition, the dose–response meta-analysis was performed to assess the association of BMI with OS and PFS. The HRs of OS and PFS for every 5 kg/m^2 increment in BMI were estimated by generalized least-squares for trend estimation [28]. The mean or median of each BMI category per study was collected, if not available, the midpoint of the upper and lower boundaries in each BMI category was estimated. When the lowest or highest category was open-ended, the same interval as the adjacent category was used to estimated midpoints. If the lowest BMI category was not considered as the reference group in studies, the method of Hamling et al. was chosen to transform the data [29].

Statistical heterogeneity among studies was evaluated using Cochran's Q test and the inconsistency index(I^2). Heterogeneity was regarded as low ($I^2 < 25\%$), moderate ($25\% \le I^2 < 50\%$), and high ($I^2 > 50\%$) [30]. Considering the inherent clinical heterogeneity between studies included in this analysis, we selected a random effect model according to the method of DerSimonian and Laird [31]. Sensitivity analyses and subgroup analyses were carried out to explore the potential sources of heterogeneity. These subgroups involved sex of patients (male vs. female), type of cancer (melanoma vs. NSCLC vs RCC vs multiple cancers), type of ICIs (anti-PD-1/PD-L1 vs. anti-CTLA4) and study regions (Europe vs. America vs Asia vs others). Funnel plots, Egger's tests, and Begg's tests were used to examine publication bias [32, 33]. All the statistical analyses were conducted on Stata version 15.0. Two-sided $P < 0.05$ was considered statistically significant.

Results

Systematic search and study characteristics

In total, 613 publications were identified through the initial literature search, and 459 were retained after 154 duplicated records were removed. After screening for titles and abstracts, 406 studies were excluded because of irrelevant topics, conference abstracts, reviews, letters, case reports or insufficient information. After reviewing the remaining 57 articles via the full-text view, 35 were further removed, due to data duplication, conference abstracts or unavailable data. Ultimately, 22 studies published between 2017 and 2020 were included in the final meta-analysis [18–21, 23, 24, 34–49]. The flow chart of the literature selection was illustrated in Supplementary Fig 1.

All eligible studies were retrospective studies of cohorts or clinical trials. Overall, there were 5686 patients with cancer included in our analysis, with a sample size ranging from 35 to 1434 per study. The median age ranged from 61.7 to 70 years (13 studies provided the data), with a slight majority of patients (65.3%) being male. Seven studies were conducted in Europe, six were conducted in Asia, five were from the USA, one and three were from Australia and multiple areas, respectively. Among these studies, six studies included patients with melanoma, eight with NSCLC, three with RCC, and the remaining five studies with other types or multiple cancers. All patients enrolled were at advanced or metastatic settings. With regards to the types of ICIs used,

17 studies focused on anti-PD-1/PD-L1 monotherapy, only one on anti-CTLA-4 monotherapy, and four studies reported anti-PD-1/PD-L1 monotherapy or in combination with anti-CTLA-4 therapy. The cut-off values of BMI varied among various studies, ranging from 18.5 to 35 kg/ m^2, and the most common cut-off value was 25 kg/m^2 or 30 kg/m^2. The major characteristics of all included studies were summarized in Table 1.

The results of Newcastle–Ottawa Scale for quality assessment were shown in Table 1. Sixteen studies were considered as having a high quality, with a score of eight points. Six studies had medium quality, with a score of ranging from 6 to 7 points.

Association between BMI and overall survival

19 out of all included studies, covering 5447 patients, evaluated the impact of BMI on OS. As shown in Fig. 1a, patients in higher BMI groups obtained a significant benefit on OS compared with those in lower BMI group (HR = 0.698, 95% CI 0.614–0.794, $P < 0.001$), with a moderate level of heterogeneity ($I^2 = 45.9\%$, $P = 0.012$) between the studies. The sensitivity analysis, which was carried out by removing one study at each time, showed that the pooled results were not significantly changed by any single study (Supplementary: Figure S1).

Subgroup analyses for OS were further carried out. When stratifying by cancer type, significantly positive impact of higher BMI on OS was observed in patients with melanoma (HR = 0.700, 95% CI 0.506–0.968, $P = 0.031$; $I^2 = 40.6\%$, $P = 0.011$), NSCLC (HR = 0.803, 95% CI 0.736–0.877, $P < 0.001$; $I^2 = 0\%$, $P = 0.817$) and multiple malignancies (HR = 0.491, 95% CI 0.397–0.607, $P < 0.001$; $I^2 = 0\%$, $P = 0.649$). However, no such impact was found in patients with RCC ($P = 0.377$), probably due to the limited number of studies pooled ($n = 3$). When stratifying by sex, significantly better OS was achieved in the higher BMI group compared to the lower BMI group for the subgroups of male patients ($P < 0.001$), but not in females ($P = 0.211$). In addition, subgroup analyses by types of ICIs and study regions revealed that no significant association between BMI and OS was observed in patients treated with anti-CTLA-4 therapy ($P = 0.238$), or patients from America ($P = 0.289$). Detailed results of subgroup analyses for OS were summarized in Table 2.

Association between BMI and progression-free survival

PFS data was available in 17 studies involving 5162 patients. According to a random-effect model on the basis of the heterogeneity test ($I^2 = 37.9\%$, $P = 0.049$), higher BMI was also associated with improved PFS, with a pooled HR of 0.760 (95% CI 0.672–0.861, $P < 0.001$) (Fig. 1b). The stability of the result was assessed by sensitivity analysis, which revealed that the results were stable (Supplementary: Figure S2).

Table 2 summarized the results of subgroup analyses for PFS. Similarly, subgroup analyses did not find any evidence of a significant association between BMI and PFS in patients with melanoma ($P = 0.220$), patients treated with anti-CTLA-4 therapy ($P = 0.252$), or patients from America ($P = 0.390$). When stratifying by sex, higher BMI was significantly associated with better PFS in males (HR = 0.627, 95% CI 0.454–0.867 $P = 0.005$; $I^2 = 44.8\%$, $P = 0.142$), whereas no significant association was found in females ($P = 0.698$).

Association between different BMI categories and OS or PFS

The association between different comparative models of BMI categories and the intended outcomes (OS and PFS) was further examined. As shown in Fig. 2, compared with normal weight patients, the pooled HRs for OS were 0.652 (95% CI 0.496–0.859, $P = 0.002$; $I^2 = 70.9\%$, $P = 0.002$) for overweight patients, 0.617 (95% CI 0.477–0.797, $P < 0.001$; $I^2 = 48.4\%$, $P = 0.060$) for obese patients, and 2.087(95% CI 1.113–3.913, $P = 0.022$; $I^2 = 77.0\%$, $P = 0.013$) for underweight patients. Significantly better OS was also found in obese/underweight patients compared with normal/underweight patients (HR = 0.638, 95% CI 0.515–0.790, $P < 0.001$), with a moderate level of heterogeneity ($I^2 = 33.0\%$, $P = 0.165$).

In terms of PFS, when compared with normal weight patients, patients who were overweight (HR = 0.796, 95% CI 0.668–0.947, $P = 0.010$; $I^2 = 47.8\%$, $P = 0.074$) or obese (HR = 0.788, 95% CI 0.644–0.963, $P = 0.020$; $I^2 = 46.1\%$, $P = 0.072$) achieved significantly longer PFS. Nevertheless, being underweight was significantly associated with increased risk for disease progression, compared to being normal weight (HR = 1.834, 95% CI 1.208–2.782, $P = 0.004$; $I^2 = 32.7\%$, $P = 0.226$). In addition, compared with those were normal/underweight, obese/underweight patients showed a 25% lower risk for disease progression (HR = 0.755, 95% CI 0.662–0.862, $P < 0.001$), without any heterogeneity ($I^2 = 0\%$, $P = 0.634$) (Supplementary Fig. 2).

Dose–response meta-analysis

Five and four studies for OS and PFS, respectively, were included in dose–response analyses. A positive association between BMI increase and OS was observed. For an increment of every 5 kg/m^2 in BMI, the risk for death reduced by approximately 15.6% (HR = 0.844, 95% CI 0.752–0.945, $P = 0.003$). However, the pooled results showed there was no

Table 1 The baseline characteristics of included studies

Author	Year	Country	Study design	Malignancy	Treatment	Sample	Male (%)	Median age (range)	BMI categories (kg/m^2)	Outcomes	Median follow-up (months)	NOS score
Bergerot	2019	USA	Retrospective	RCC	Nivo, Atezo, Ipi + Nivo	42	28 (66.67)	49–84	< 25, ≥ 25	OS	NR	6
Cortellini	2019	Italy	Retrospective	Multiple	Pembro, Nivo, Atezo	976	663 (67.9)	68(24–92)	< 25, ≥ 25, < 18.5, 18.5–25, 25–29.9, ≥ 30	ORR, TTF, PFS, OS, irAEs	17.2	8
De Giorgi	2019	Italy	Retrospective	RCC	Nivo	313	235 (75.1)	65 (40–84)	< 25, ≥ 30	ORR, DCR, OS	NR	8
Donnelly	2019	USA	Retrospective	Melanoma	Anti-CTLA-4, anti-PD-1, Combination	423	267 (63.1)	NR	< 25, 25–29.9, ≥ 25	PFS, OS	1.4–173.3	8
Dumenil	2018	France	Retrospective	NSCLC	Nivo	67	46 (69.0)	68.5 (60–77)	< 18.5, ≥ 18.5	DCR, PFS, OS, irAEs	NR	8
Heidelberger	2017	France	Retrospective	Melanoma	Nivo, Pebro	68	36 (53.0)	65 (22–91)	< 18.5, 18.5–25, 25–30, ≥ 30	irAEs, ORR	6 (0.5–18)	6
Ichihara	2020	Japan	Retrospective	NSCLC	Nivo, Pembro, Atezo	513	406 (79.1)	28–93	< 22, ≥ 22, < 18.5, 18.5–24.9,24.9–30, ≥ 30	PFS, OS	NR	7
Katayama	2020	Japan	Retrospective	NSCLC	Nivo, Pembro, Atezo	35	24 (68.6)	70 (48–83)	< 20, ≥ 20	PFS, OS	NR	8
Kichenadasse	2019	Australia	Retrospective	NSCLC	Atezo	1434	890 (62.0)	64 (57–70)	18.5–24.9,25–29.9, ≥ 30	PFS, OS, irAEs	NR	8
Kondo	2018	Japan	Retrospective	Melanoma	Nivo	39	24 (61.5)	65 (28–84)	< 20, ≥ 20	PFS, OS	11.9 (5.0–36.1)	8
Labadie	2019	Multicenter	Retrospective	RCC	Pembro, Nivo, Atezo	90	65 (72.2)	66 (17–92)	< 18.5, 18.5–25, 25–30, ≥ 30	PFS, OS	NR	8
Magri	2019	Italy	Retrospective	NSCLC	Nivo	46	28 (60.87)	65 (39–85)	Continuous	OS	22	8
Martini	2019	USA	Retrospective	Multiple	Immunotherapy	90	53 (59.0)	NR	< 25, ≥ 25	PFS, OS	NR	8
McQuade	2018	Multicenter	Retrospective	Melanoma	Anti-PD-1/PD-L1	538	349 (64.87)	23–88	18.5–24.9, 25–29.9, ≥ 30	PFS, OS, ORR, irAEs	38.4 (35.6–40.4)	8
Minami	2020	Japan	Retrospective	NSCLC	anti-PD-1/PD-L1	74	48 (64.9)	61.3–75	< 18.5, ≥ 18.5	PFS, OS	NR	8
Naik	2019	USA	Retrospective	Melanoma	Pembro, Nivo, Nivo + Ipi	139	79 (56.8)	NR	< 25, 25–35, ≥ 35	PFS, OS	25.3	8
Popinat	2019	France	Retrospective	NSCLC	Nivo	55	41 (75.0)	63.5 (37.8–82.4)	< 25.1, ≥ 25.1	OS	NR	6
Qi	2019	China	Retrospective	Multiple	Anti-PD-1	85	42 (49.4)	NR	< 24, ≥ 24	PFS, OS, DCR	11.0 (1.5–28.8)	8
Richtig	2018	Multicenter	Retrospective	Melanoma	Ipi	76	46 (60.5)	NR	< 25, ≥ 25	ORR, PFS, OS	NR	6
Shiroyama	2018	Japan	Retrospective	NSCLC	Nivo	201	135 (67.2)	68 (27–87)	< 18.5, ≥ 18.5	PFS, OS	12.4	8
Wang	2019	USA	Retrospective	Multiple	Anti-PD-1/PD-L1	250	114 (45.6)	61.7 (23–91)	< 30, ≥ 30	PFS, OS	NR	8
Rogado	2020	Spain	Retrospective	Multiple	Anti-PD-1	132	95 (71.9)	69 (32–86)	< 25, ≥ 25	ORR, PFS, irAEs	6 (0.5–32)	7

BMI body mass index, *RCC* renal cell carcinoma, *NSCLC* non-small cell lung cancer, *Atezo* atezolizumab, *Nivo* nivolumab, *Pembro* pembrolizuma, *Ipi* Ipilimumab, *CTLA-4* cytotoxic T lymphocyte associate protein-4, *PD-1* programmed cell death protein-1, *PD-L1* programmed cell death-ligand 1, *OS* overall survival, *PFS* progression-free survival, *ORR* objective response rate, ir*AEs* immune-related adverse events, *TTF* time to treatment failure, *DCR* disease control rate, *NR* not reported

linear association between BMI increase(5 kg/m^2) and PFS (HR = 0.956, 95% CI 0.873–1.046, $P = 0.325$). The results of the dose–response analyses were presented in Supplementary Fig. 3a, b.

Association between BMI and objective response rate or adverse events

Only three of the 22 studies including 1306 patients provided ORR data. The pooled OR for ORR was 0.468 (95% CI 0.263–0.833, $P = 0.010$) based on a random effect model, which indicated patients with higher BMI had a significantly better ORR than that of those with lower BMI (Supplementary Fig. 4). There was evidence of high heterogeneity ($I^2 = 73.6\%$, $P = 0.023$).

Furthermore, the association between BMI and the incidence rates of irAEs was evaluated in six studies involving 2713 patients. As shown in Supplementary Fig. 2, compared with patients in lower BMI group, patients in higher BMI group tended to experience a higher frequency of any grade irAEs, although the result was not statistically significant (OR = 2.025, 95% CI 0.937–4.374, $P = 0.073$). However, the potential sources of heterogeneity should be taken into account according to the I^2 statistic and Cochran's Q test ($I^2 = 91.9\%$, $P < 0.001$). Similarly, the pooled risk estimates of three studies showed that BMI was not significantly associated with the incidence of ≥ 3 grade irAEs (OR = 1.243, 95% CI 0.955–1.617, $P = 0.105$), with no heterogeneity ($I^2 = 0.0\%$, $P = 0.416$) (Supplementary Fig. 4).

Publication bias

The funnel plot indicated no publication bias in all the pooled analyses (Supplementary: Figure S3). Besides, the Begg's and Egger's test also revealed no evidence of substantial publication bias for OS (Begg's test: $P = 0.450$, Egger's test: $P = 0.112$) and PFS (Begg's test: $P = 0.263$, Egger's test: $P = 0.219$). Similarly, no significant publication bias was found in other meta-analyses.

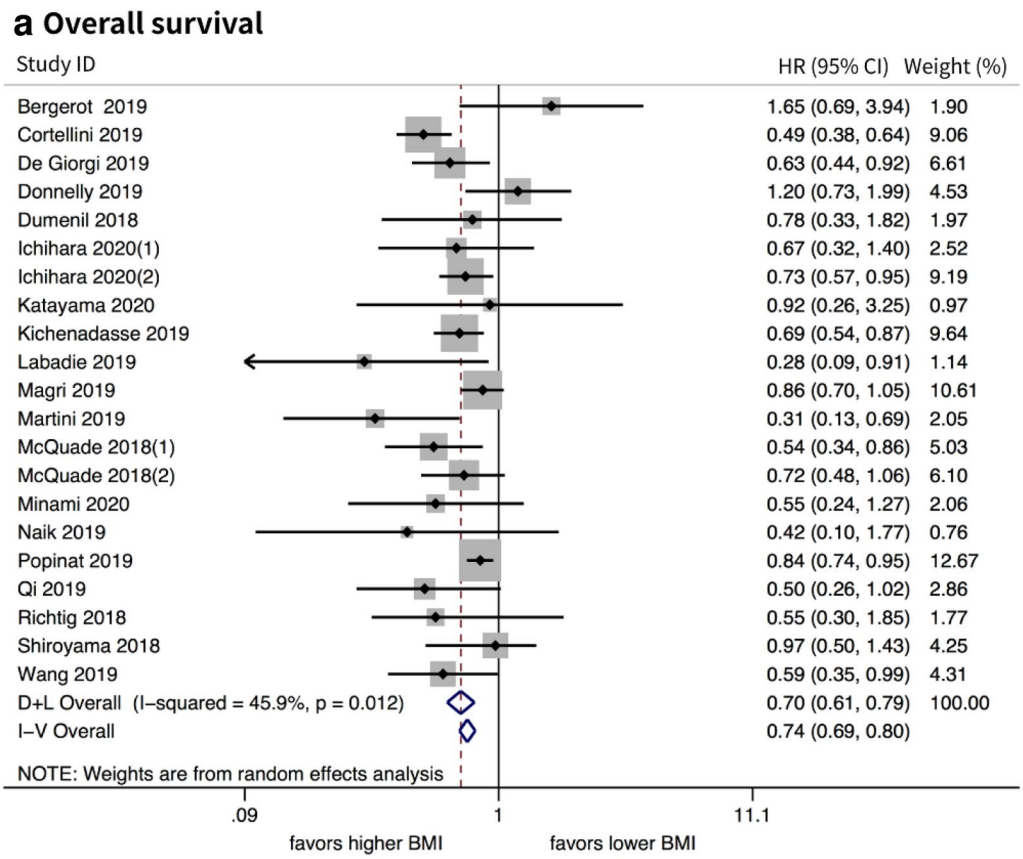
Discussion

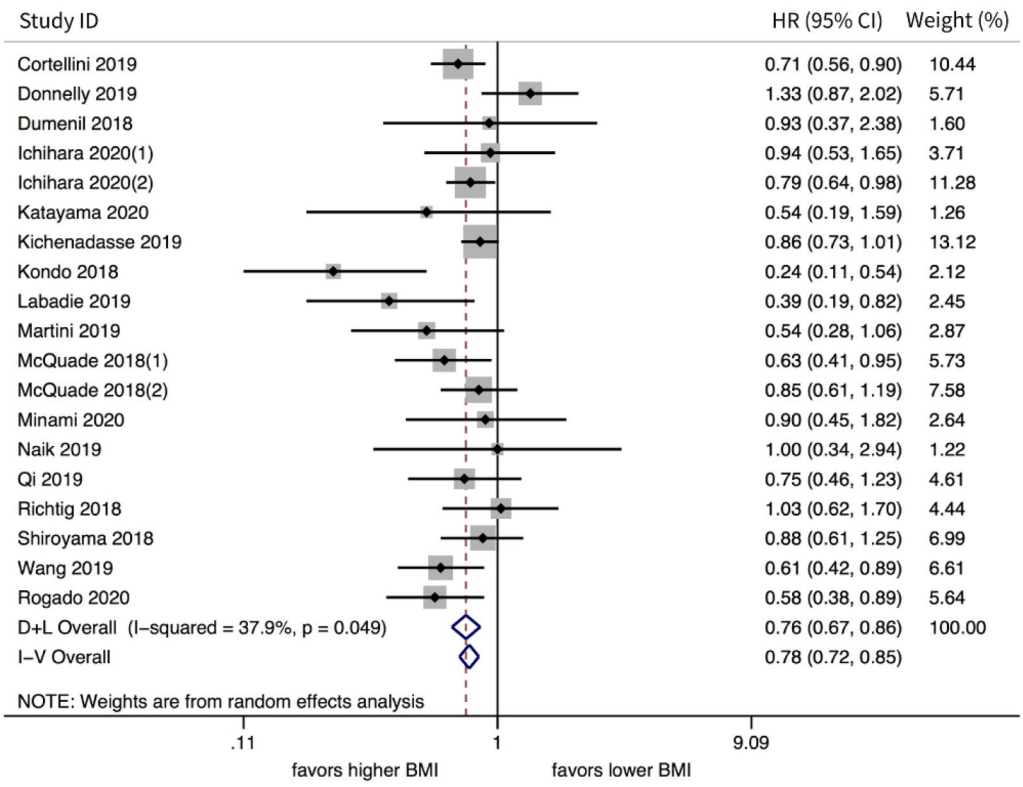
This meta-analysis focuses on the effect of pretreatment BMI on clinical outcomes of cancer patients treated with ICIs. The results of our categorical meta-analysis revealed that compared to those with lower BMI, patients with higher BMI showed markedly improved OS and PFS, with 30% and 24% lower risk for mortality and disease progression, respectively. The pooled results for most subgroup analyses, which involved sex of patients, type of cancer, type of ICIs, and study regions, were not observably influenced. The limited number of studies on ORR also suggested the existence of a positive association. Our findings suggest that BMI may be a promising predictive biomarker for outcomes in cancer patients following ICIs.

Fig. 1 Meta-analysis of the association between body mass index (BMI) and overall survival and progression-free survival (higher BMI group vs. lower BMI group). **a** overall survival; **b** progression-free survival ▶

The association between different comparative models of BMI categories and the intended outcomes was also examined in the current study. Compared with those who were normal-weight, both overweight and obese patients showed a statistically significant OS benefit, with 35% and 38% lower risk for mortality, respectively. Regarding PFS, being overweight or obese was associated with a lower risk for disease progression, compared to being normal weight. In addition, we also evaluated the contribution of underweight to survival. With normal weight as a reference category, both significantly inferior OS and PFS were found in underweight patients, though only three studies were pooled. Since BMI categories varied greatly across the included studies, the relationship between BMI and survival was further examined using the dose–response meta-analysis, indicating that an increment of each 5 kg/m^2 in BMI corresponded to a 15.6% lower risk of mortality. Considering the findings above and the lack of publication bias, we confirmed that higher BMI was associated with better OS and PFS for patients with cancer who received ICIs treatment.

Previously, BMI has already been proved to be a potential indicator for improved survival in patients with NSCLC or RCC following targeted therapy, chemotherapy or surgery [50–52]. In consistent with these findings, subsequent evidence indicates that high BMI is associated with superior survival outcomes in cancer patients following ICIs [18–20]. It appears that the association between BMI and outcomes in cancer patients is complicated. The survival advantage from high BMI, which can be conferred within other treatment interventions, may be not specific to ICIs. Whether the presence of "obesity paradox", wherein obesity is related to increased risk of cancers but shows a survival benefit, is influenced by different treatment strategies remains unclear. The biological mechanisms behind the positive association between BMI and ICIs are also not well understood. It is possible that patients with higher BMI may have better nutritional status, thus potentially increasing immune response [53]. In addition, preclinical data indicated that obesity could lead to T cell aging, tumor progression, a higher level of PD-1 expression, and an exhausted T-cell dysfunction, which was partly due to leptin production. However, the PD-1-mediated T cell dysfunction and increased PD1 expression made tumors more sensitive to checkpoint blockade, allowing survival benefit for patients treated with anti-PD1 therapy in the setting of obesity [21]. It is still unclear whether


a Overall survival
Study ID
HR (95% CI) Weight (%)
Bergerot 2019 1.65 (0.69, 3.94) 1.90
Cortellini 2019 0.49 (0.38, 0.64) 9.06
De Giorgi 2019 0.63 (0.44, 0.92) 6.61
Donnelly 2019 1.20 (0.73, 1.99) 4.53
Dumenil 2018 0.78 (0.33, 1.82) 1.97
Ichihara 2020(1) 0.67 (0.32, 1.40) 2.52
Ichihara 2020(2) 0.73 (0.57, 0.95) 9.19
Katayama 2020 0.92 (0.26, 3.25) 0.97
Kichenadasse 2019 0.69 (0.54, 0.87) 9.64
Labadie 2019 0.28 (0.09, 0.91) 1.14
Magri 2019 0.86 (0.70, 1.05) 10.61
Martini 2019 0.31 (0.13, 0.69) 2.05
McQuade 2018(1) 0.54 (0.34, 0.86) 5.03
McQuade 2018(2) 0.72 (0.48, 1.06) 6.10
Minami 2020 0.55 (0.24, 1.27) 2.06
Naik 2019 0.42 (0.10, 1.77) 0.76
Popinat 2019 0.84 (0.74, 0.95) 12.67
Qi 2019 0.50 (0.26, 1.02) 2.86
Richtig 2018 0.55 (0.30, 1.85) 1.77
Shiroyama 2018 0.97 (0.50, 1.43) 4.25
Wang 2019 0.59 (0.35, 0.99) 4.31
D+L Overall (I–squared = 45.9%, p = 0.012) 0.70 (0.61, 0.79) 100.00
I–V Overall 0.74 (0.69, 0.80)
NOTE: Weights are from random effects analysis
.09
1
11.1
favors higher BMI
favors lower BMI


b Progression-free survival
Study ID
HR (95% CI) Weight (%)
Cortellini 2019 0.71 (0.56, 0.90) 10.44
Donnelly 2019 1.33 (0.87, 2.02) 5.71
Dumenil 2018 0.93 (0.37, 2.38) 1.60
Ichihara 2020(1) 0.94 (0.53, 1.65) 3.71
Ichihara 2020(2) 0.79 (0.64, 0.98) 11.28
Katayama 2020 0.54 (0.19, 1.59) 1.26
Kichenadasse 2019 0.86 (0.73, 1.01) 13.12
Kondo 2018 0.24 (0.11, 0.54) 2.12
Labadie 2019 0.39 (0.19, 0.82) 2.45
Martini 2019 0.54 (0.28, 1.06) 2.87
McQuade 2018(1) 0.63 (0.41, 0.95) 5.73
McQuade 2018(2) 0.85 (0.61, 1.19) 7.58
Minami 2020 0.90 (0.45, 1.82) 2.64
Naik 2019 1.00 (0.34, 2.94) 1.22
Qi 2019 0.75 (0.46, 1.23) 4.61
Richtig 2018 1.03 (0.62, 1.70) 4.44
Shiroyama 2018 0.88 (0.61, 1.25) 6.99
Wang 2019 0.61 (0.42, 0.89) 6.61
Rogado 2020 0.58 (0.38, 0.89) 5.64
D+L Overall (I–squared = 37.9%, p = 0.049) 0.76 (0.67, 0.86) 100.00
I–V Overall 0.78 (0.72, 0.85)
NOTE: Weights are from random effects analysis
.11
1
9.09
favors higher BMI
favors lower BMI

other non-immune factors contribute to the effect of obesity on checkpoint inhibition. Taken together, the biological basis of the relationships between BMI and ICIs outcomes remains unclear, hence further investigations are needed to elucidate these mechanisms. In addition, BMI should be considered as a stratification factor in a prospective randomized study with non-ICI control arm, to better define its role in checkpoint inhibitors therapy.

Interestingly, significant sex-associated differences in the influence of BMI on outcomes in the context of immunotherapy, have been previously described. It appeared that the significantly positive impact of high BMI on outcomes was observed across males, but not among females [20, 44]. However, inconsistent results have also been reported [18]. A recent pooled analysis conducted by Xu et al. confirmed the significant association between obesity and improved survival in cancer patients following ICIs, irrespective of sex [25]. Indeed, the relationship between sex, BMI, and immunotherapy is complex, and the underlying mechanisms of sex-related differences remain ambiguous. Gender-based differences in hormones, body mass composition or muscle mass may contribute to different BMI effects [54, 55].

Table 2 Subgroup analyses of the associations between BMI and outcomes

	Subgroup	Number of studies	Pooled results		Heterogeneity test		Publication Bias test	
			HR (95 CI%)	*P*	I^2	*P*	*P* (Begg's)	*P* (Egger's)
Overall survival	All studies	19	0.698 (0.614–0.794)	< 0.001	45.9	0.012	0.450	0.112
	Cancer type							
	MM	4	0.700 (0.506–0.968)	0.031	40.6	0.011	1	0.642
	NSCLC	8	0.803 (0.736–0.877)	< 0.001	0	0.817	0.602	0.377
	RCC	3	0.698 (0.315–1.548)	0.377	68.8	0.041	1	0.955
	Multiple/other	4	0.491 (0.397–0.607)	< 0.001	0	0.649	0.734	0.655
	Sex							
	Male	3	0.450 (0.291–0.695)	< 0.001	56.7	0.074	0.089	0.062
	Female	3	0.630 (0.305–1.300)	0.211	76.2	0.060	0.734	0.960
	ICIs used							
	Anti-PD1/PD-L1	15	0.706 (0.626–0.797)	< 0.001	36.8	0.070	0.620	0.134
	Anti-CTLA-4	3	0.719 (0.417–1.242)	0.238	70.0	0.036	1	0.866
	Study region							
	Europe	5	0.709 (0.561–0.894)	0.004	74.5	0.003	0.462	0.416
	America	5	0.731 (0.410–1.304)	0.289	67.2	0.016	0.806	0.641
	Asia	5	0.724 (0.592–0.884)	0.002	0	0.705	1	0.717
	Others	4	0.650 (0.543–0.779)	< 0.001	0	0.513	0.086	0.095
Progression-free survival	All studies	17	0.760 (0.672–0.861)	< 0.001	37.9	0.049	0.263	0.219
	Cancer type							
	MM	5	0.786 (0.536–1.154)	0.220	69.9	0.005	1	0.505
	NSCLC	6	0.841 (0.750–0.944)	0.003	0	0.828	0.368	0.900
	Multiple/other	5	0.662 (0.561–0.780)	< 0.001	0	0.968	0.462	0.285
	Sex							
	Male	3	0.627 (0.454–0.867)	0.005	44.8	0.142	0.089	0.020
	Female	3	0.911 (0.568–1.461)	0.698	54.1	0.088	1	0.653
	ICIs used							
	Anti-PD1/PD-L1	14	0.762 (0.663–0.875)	< 0.001	42.3	0.043	0.533	0.501
	Anti-CTLA-4	3	0.828 (0.599–1.144)	0.252	24.6	0.266	1	0.270
	Study region							
	Europe	3	0.687 (0.561–0.841)	< 0.001	0	0.58	1	0.898
	America	4	0.807 (0.496–1.315)	0.390	67.0	0.028	0.734	0.986
	Asia	6	0.746 (0.587–0.948)	0.017	39.6	0.127	0.230	0.338
	Others	4	0.787 (0.638–0.971)	0.026	39.8	0.156	0.221	0.313

BMI body mass index, *MM* melanoma, *NSCLC* non-small cell lung cancer, *RCC* renal cell carcinoma, *CTLA-4* cytotoxic T lymphocyte associate protein-4, *PD-1* programmed cell death protein-1, *PD-L1* programmed cell death-ligand 1, *HR* hazard ratio

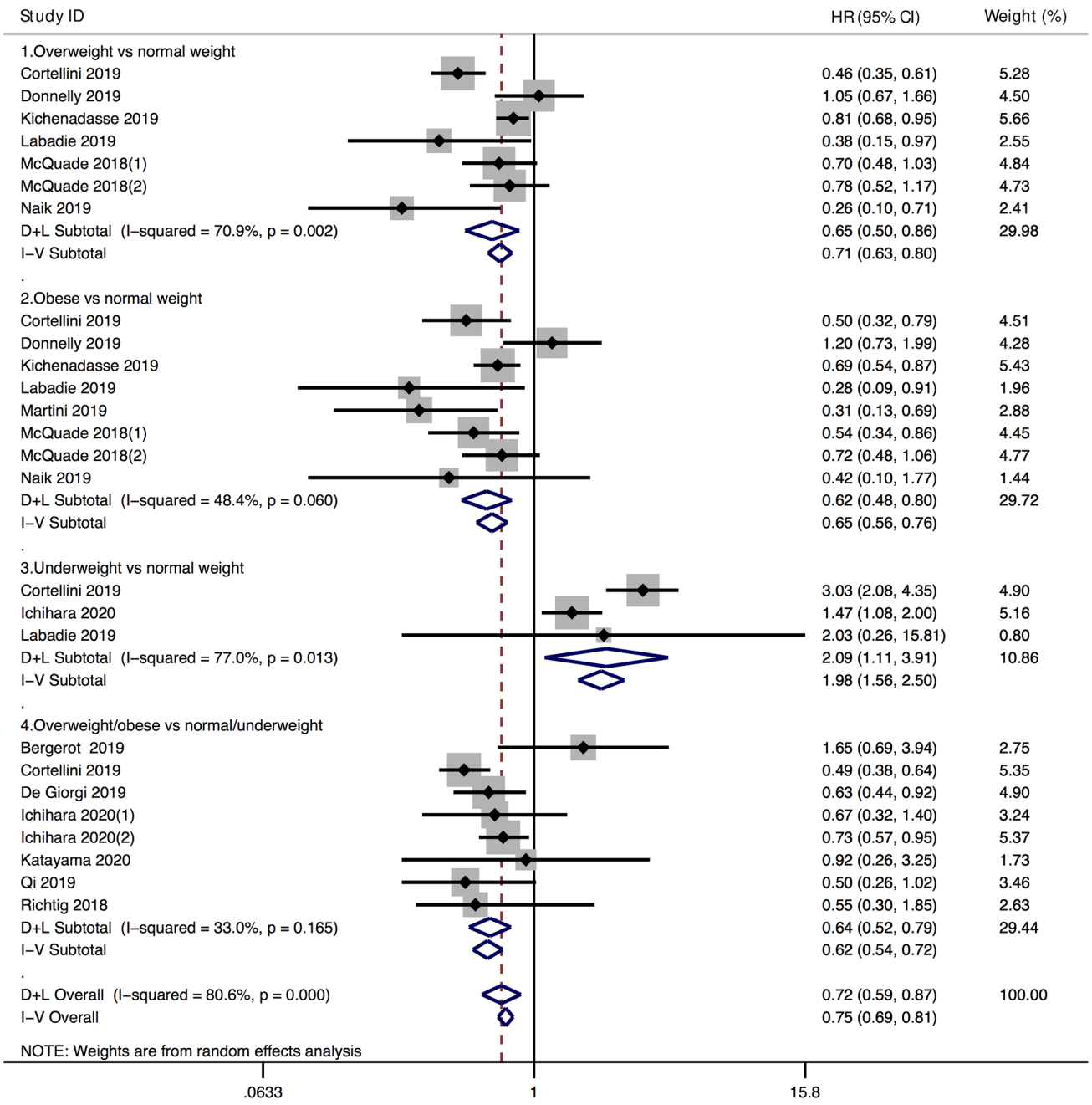


Fig. 2 Meta-analysis of the association between different comparative models of body mass index (BMI) categories and overall survival

Contrary to the previous pooled analysis [25], stratified analyses in our study demonstrated that the association between BMI and outcomes varied by sex, in which higher BMI was associated with OS and PFS benefit in male patients rather than females. These conflicting results may be explained by the different studies included between these two analyses. The small sample included, with only three studies available in both analyses, may be another reason contributing to the inconsistent results. In consideration of the inadequate statistical power, more robust evidence that focuses on the association between BMI and response to immunotherapy in the context of sex is required.

Notably, despite the limited sample size, our study observed that patients with higher BMI had a significantly higher ORR, implying the positive impact of overweightedness or obesity on the efficacy of ICIs. On the other hand,

we also found that patients in higher BMI group tended to have a higher risk of any grade irAEs ($P = 0.073$). However, with the considerably obvious heterogeneity among different studies observed, caution must be applied. Furthermore, no significant differences were found in the frequency of ≥ 3 grade irAEs between higher BMI and lower BMI group. To some extent, these findings were not in line with the previous pooled analysis conducted by Xu et al. in which overweight or obesity patients developed a significantly higher incidence of adverse events [25]. Compared with their study, we updated the search and included two recent studies [19, 48], which may be the underlying reason for the discrepancy. Given these non-duplicate results, further investigations with larger samples are warranted to evaluate the association between BMI and ORR or the incidence of irAEs.

Finally, several important limitations in the present study need to be considered. The major limitation lies in the fact that all included studies were retrospective in nature, leading to some inevitable sources of bias. Another limitation is that some confounding risk factors across studies, such as age, sex, treatment, cancer type, BMI cutoff value, etc., might influence the association between BMI and ICIs. Nonetheless, to minimize these impacts, HRs obtained from multivariate analyses were favored in our study, and stratified analyses by several important factors were performed. Moreover, the sample sizes were relatively small in several meta-analyses, which limited the power of our analysis. For instance, only three and six studies with ORR and irAEs data available, respectively, were included in the analyses. We were unable to conduct subgroup analyses for ORR because of the insufficient sample size, thus failing to explore the potential sources of heterogeneity. Similar concerns also existed in the dose–response analyses and in several subgroup analyses. Therefore, these results must be interpreted with caution, and further research is required to provide more definitive evidence.

Conclusion

In conclusion, the results of this systematic review and meta-analysis supported that higher BMI prior to the treatment of ICIs was significantly associated with improved OS and PFS in cancer patients receiving ICIs, regardless of the different comparative models of BMI categories. Most stratified analyses also showed similar pooled risk estimates. In addition, the limited number of studies on ORR also suggested the existence of a positive association. Regarding adverse events, no statistically significant differences were found in the incidence of any grade and ≥ 3 grade irAEs between higher and lower BMI. Further large-scale prospective research is warranted to better illuminate the association between BMI and outcomes from ICIs. Besides, considerably more work regarding the biological mechanisms underlying these associations will be worthwhile.

Author contributions YKS, HZC, and DQW designed the study. HZC and DQW performed the systematic search. HZC, DQW, QFZ, YXT, and YZ selected eligible articles and conducted the quality assessment. HZC and DQW analyzed, interpreted the data, and drafted the manuscript. YKS revised the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability All data and material analyzed during this study are included in this article.

Compliance with ethical standards

Conflict of interest All the authors declare no conflicts of interest.

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