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ORIGINAL ARTICLE

The predictive value of body mass index on prognosis and adverse events of cancers treated with immunotherapy: a systematic review and meta-analysis

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Abstract

Objective High body mass index (BMI) greater than 25 kg/m^2 has a complex relationship with cancers. The aim of this systematic review and meta-analysis is to explore controversy over whether BMI is correlated with outcomes including survival and immunotherapy-related adverse events (irAEs) in cancer patients treated with immunotherapy.

Methods We searched PubMed, Embase, Web of Science, and The Cochrane Library for relevant studies published up to June 2020. Title/abstract screening, full-text review, data extraction, and quality assessment were performed independently. Subgroup analysis was based on sex, treatment lines, the status of programmed death-ligand 1 (PD-L1), and tumor types. Sensitivity analysis was performed by synthesizing studies that adjusted for certain covariates or studies with good quality. Statistical heterogeneity was evaluated by the I^2 value. Meta-analysis was performed with hazard ratio (HR) / odds ratio (OR) and 95% confidence intervals (CIs) as the effect measures.

Results Twenty studies were included for survival and irAEs analyses. Patients with high BMI who underwent immunotherapy had longer overall survival (OS) (pooled hazard ratio, pHR = 0.71 [95% CI: 0.59–0.85]) and progression-free survival (PFS) (pHR = 0.76 [95% CI: 0.65–0.88]) than those with low BMI; at the same time, high-BMI patients had increased irAEs (OR = 2.54 [95% CI: 1.12–5.79]).

Conclusion In general, high BMI was correlated with improved OS and PFS in patients treated with immunotherapy along with a high risk of irAEs. However, discrepant findings from subgroup analyses urgently call for further analysis.

Keywords BMI · Immunotherapy · Cancers · Meta-analysis · Adverse effects

Introduction

Numerous population-based studies have demonstrated that occurrence and progression of tumors are related to BMI, especially in breast cancer and colorectal cancer [1–3]. The correlation of BMI and clinical outcomes in advanced cancer patients has been investigated as well, however, without conclusive results [4–6]. Recent clinical studies have demonstrated that high BMI is associated with improved response and survival in cancer patients treated with targeted therapy and immunotherapy, but not with chemotherapy [4, 7]. Though immune checkpoint inhibitors (ICIs) such as anti-programmed death-1 (PD-1) and PD-L1 antibodies have dramatically improved survival in various cancers [8, 9], how to identify the small proportion of patients who will benefit from immunotherapy is the key challenge because many attempts have failed. Several multicenter studies have reported that patients with high BMI benefit more from ICIs

Yafei You and Chang Jiang contributed equally to this work.

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treatment in solid malignant tumors, including non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC) [10, 11]. Conversely, a retrospective multicohort analysis has reported that BMI is not associated with improved OS and PFS in immunotherapy in metastatic melanoma [12]. Moreover, a pooled analysis of 16 articles including 4090 cancer patients has shown that BMI ≥ 30 is associated with better outcomes in cancer patients treated with ICIs [13]. Since immunotherapy was first introduced, only two individual pooled analyses and a meta-analysis have focused on BMI. Based on the limited data available so far, it appears that the correlation between BMI and immunotherapeutic benefit may differ by tumor types. Besides the benefit, the correlation of BMI and irAEs has been reported in few studies recently, however, with different conclusion. The proliferation of immunotherapeutic studies involving more cancer patients and a wider spectrum of cancers provides an opportunity to confirm the correlation of BMI with survival benefits and irAEs in general and also possibly to investigate the precise relationship in subgroups of patients.

In this systematic review and meta-analysis, we explore the prognostic value of BMI in cancers treated with immunotherapy grouped by sex, treatment lines, the status of PD-L1, tumor types. Similarly, we examine the association between BMI and irAEs.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to report our meta-analysis[14].

Literature search

We systematically conducted an independent review of the PubMed, Embase, Web of Science, and The Cochrane Library databases on clinical trials in English. The search strategy is outlined in Supplemental Table 1. A supplementary search of the Web of Science, Embase, and The Cochrane Library databases was also performed to ensure that no additional studies were overlooked.

Eligibility criteria

The inclusion criteria were: (1) BMI and immunotherapy data; (2) study outcomes were OS, PFS, and irAEs; (3) clinical trials; (4) the effect estimates and corresponding 95% confidence intervals (CIs) were reported directly or could be calculated indirectly from published data. The references of relevant reports were also reviewed manually. If more than one publication was found for the same trial, the most recent, complete, and updated version was included in the final analysis. Subgroup analyses for survival were conducted according to tumor types, sex, treatment lines, and the status of PD-L1. The principal exclusion criteria were overlapping publications, lack of relevant outcome data; similarly, preliminary data not yet reported were not included. The flow diagram of eligible studies is shown in Fig. 1.

Data extraction and quality assessment

Data were extracted from the eligible studies included according to the PRISMA statement: (1) study characteristics (first author, year of publication, total sample), BMI cutoff value, OS, PFS and irAEs, HRs for PFS, OS and OR for irAEs with the relative 95% CI; (2) tumor types, sex, treatment lines, and the status of PD-L1. The quality of the included studies was assessed according to Newcastle–Ottawa Scale criteria [15].

Statistical analysis

Statistical analyses were carried out using the statistical package STATA (v.14.0). We used HRs to summarize the association between BMI and immunotherapy benefit, simultaneously, OR was applied to summarize the association between BMI and irAEs. If a study did not report the HR and its 95% CI directly, they were calculated from the available data. Statistical heterogeneity in the results between studies included in the meta-analysis was examined using Cochrane's Q statistic, and inconsistency was quantified with the I^2 statistic [$100\% \times (Q - df)/Q$], which estimates the percentage of total variation across studies due to heterogeneity rather than chance. $P < 0.10$ for the Q statistic and/or $I^2 > 50\%$ were considered to show statistically significant heterogeneity. Summary HRs were calculated using random-effects (RE) or fixed-effects (FE) models depending on the heterogeneity of the included studies (RE model when $I^2 > 50\%$ and FE model when $I^2 \leq 50\%$). An overall analysis was conducted by evaluating all relevant studies. Simultaneously, funnel plots were constructed to highlight outlying studies and to examine publication bias. Forest plots were used to summarize and visualize the HR or OR with 95% CIs for each study and for the aggregated estimates from the RE or FE models.

Results

Search results and patient characteristics

There were 771 potentially relevant publications identified in this study. In the end, twenty studies were included for survival [7, 10–12, 16–29] and irAEs [7, 10, 12, 19, 30, 31] analysis. Descriptive characteristics were shown in Table 1.

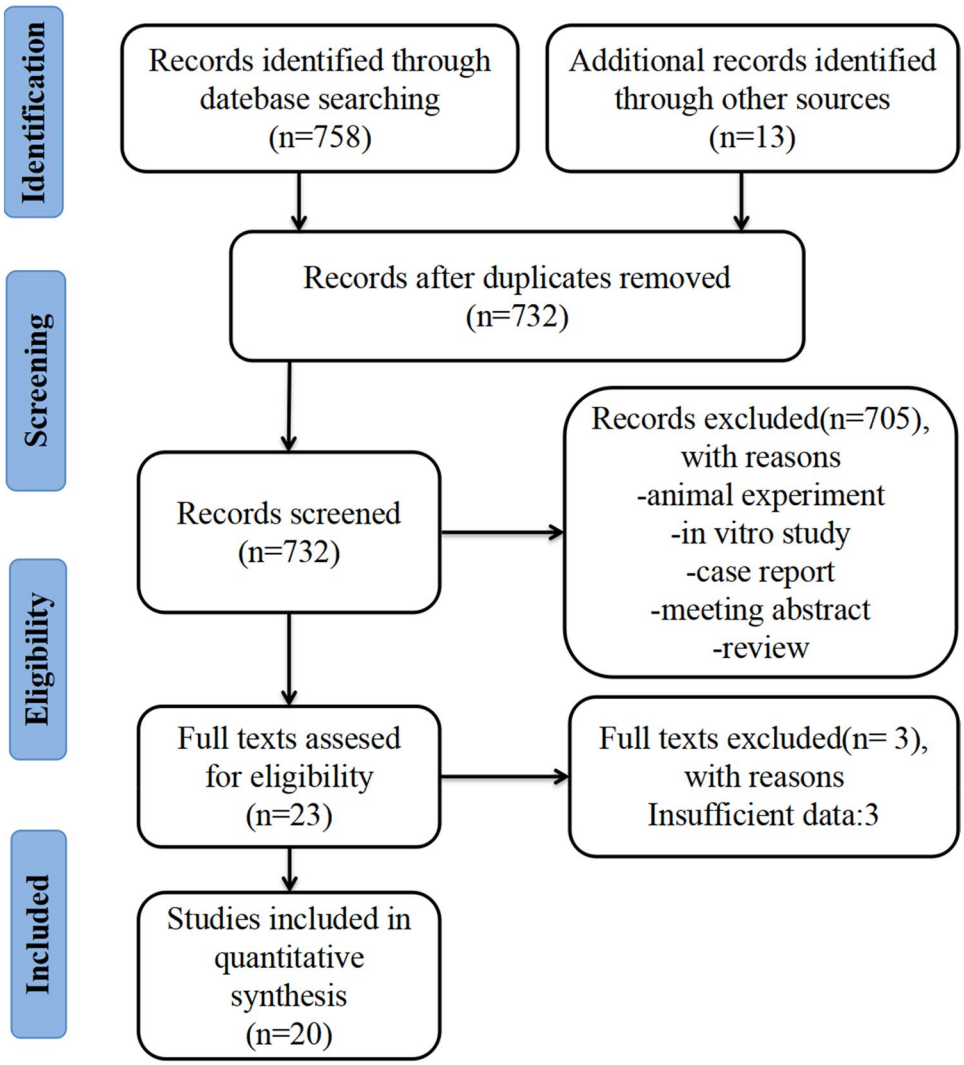


Fig. 1 Flow diagram of identifying eligible studies

The primary cancers were melanoma, lung cancer, and renal cell carcinoma. Most of the patients were from the USA. The common ICIs were nivolumab, pembrolizumab, and atezolizumab. BMI cutoff value of most articles was 25 kg/m^2.

Primary outcome

When these outcomes were analyzed according to BMI (the high or low BMI cutoff value was referenced to the article showed in Table 1), patients with high BMI who underwent immunotherapy had longer OS (pHR = 0.71 [95% CI: 0.59–0.85]) and longer PFS (pHR = 0.76 [95% CI: 0.65–0.88]) than those with low BMI (Fig. 2a, b). The χ^2 test for study heterogeneity was significant ($P < 0.001$), suggesting that the reported results of the individual trials differ substantially. When we divided the population in the high BMI group into BMI ≥ 25 and BMI ≥ 30, respectively, we found the pHRs were 0.64 (95% CI: 0.48–0.86, $P = 0.003$) for OS and 0.73 (95% CI: 0.58–0.92, $P = 0.007$) for PFS in BMI ≥ 30 group. The pHRs were 0.72 (95% CI: 0.50–1.03, $P = 0.069$) for OS and 0.75 (95% CI: 0.53–1.06, $P = 0.101$) for PFS in BMI ≥ 25 group (Fig. 3a, b). Thus, its apparent BMI ≥ 30 benefited more from ICIs.

At the same time, as shown in Fig. 4a, the patients with BMI ≥ 25 experienced a higher risk of any grade of irAEs compared to those with BMI < 25 (OR = 2.54 [95% CI: 1.12–5.79], $I^2 = 91.1\%$, $P = 0.026$). The comparable results were seen in G3/G4 irAEs (OR = 1.95 [95% CI: 1.46–2.62], $I^2 = 29.2\%$, $P < 0.001$) (Fig. 4b). Of note, cancer patients with high BMI were inclined to have better OS and PFS from immunotherapy, while simultaneously exhibiting a higher risk of adverse events.

Subgroup analysis

Sex, treatment lines, the status of PD-L1, and tumor types were chosen for subgroup analysis with the aim of finding who could obtain a survival benefit in the high BMI

Table 1 Baseline characteristics of included retrospective studies

Author	Year	Total sample	Male %	Median age	Cancer types	Treatment	Region	BMI cutoff value	Primary outcomes
Cortellini [10]	2019	976	663(67.93)	68	Multiple cancers	Pembrolizumab, nivolumab, or atezolizumab	Europe	25	OS, PFS, irAEs
Gomes [16]	2017	187	108(57.75)	58	Metastatic melanoma	Ipilimumab	South America	25	PFS
Kichenadasse [11]	2019	1434	890(62.06)	64	Advanced NSCLC	Atezolizumab	Multiple region	25,30	OS, PFS
Zhi [17]	2018	703	NA	NA	Advanced NSCLC	Nivolumab or pembrolizumab	North America	25,30	OS
McQuade 1 [7]	2018	207	138(66.67)	NA	Metastatic melanoma	Ipilimumab plus dacarbazine	North America	25,30	OS, PFS, irAEs
McQuade 2 [7]	2018	329	213(64.74)	NA	Metastatic melanoma	Pembrolizumab, nivolumab or atezolizumab	North America	25,30	OS, PFS, irAEs
Richtig [12]	2018	76	46(60.53)	NA	Metastatic melanoma	Ipilimumab	Australia	25	OS, PFS, irAEs
Labomascus [18]	2018	162	65(40.12)	68	Advanced NSCLC	Nivolumab or pembrolizumab	North America	24.69	OS
Dumenil [19]	2018	67	46(68.66)	68.5	Advanced NSCLC	Nivolumab	Europe	18.5	OS, PFS, irAEs
Dizman [20]	2018	235	172(73.19)	65	Advanced RCC	Immunotherapy	North America	25	OS
Ibrahimi [21]	2018	198	NA	62	Multiple cancers	Immunotherapy	North America	30	OS, PFS
Lalani [22]	2019	147	104(70.75)	NA	Advanced RCC	Immunotherapy	North America	25	OS
Wang [23]	2019	250	114(45.60)	61.7	Multiple cancers	Immunotherapy	North America	30	OS, PFS
Kondo [24]	2018	39	24(61.54)	65	Metastatic melanoma	Nivolumab	Asia	20	PFS
Taniguchi [25]	2017	201	135(67.16)	68	Advanced NSCLC	Nivolumab	Asia	20	PFS
Shiroyama [26]	2018	201	135(67.16)	68	Advanced NSCLC	Nivolumab	Asia	18.5	PFS
Bergerot [27]	2019	42	28(66.67)	NA	Advanced RCC	Nivolumab, atezolizumab, or avelumab	North America	25	OS
Ichihara 1 [28]	2020	84	68(80.95)	71	Advanced NSCLC	pembrolizumab	Asia	22	OS, PFS
Ichihara 2 [28]	2020	429	338(78.79)	69	Advanced NSCLC	Pembrolizumab, nivolumab or atezolizumab	Asia	22	OS, PFS
Sanchez [29]	2019	203	151 (74.38)	62	Advanced RCC	Immunotherapy	North America	30	OS
Cortellini [30]	2020	1070	724(67.66)	68	Multiple cancers	Immunotherapy	Europe	25	irAEs
Valentine [31]	2017	32	NA	NA	Metastatic melanoma	Pembrolizumab or nivolumab	Europe	25	irAEs

Multiple cancers refer to NSCLC, melanoma, RCC, and others. The included articles of McQuade and Ichihara contain two cohorts, which labeled Author 1 and Author 2 in different rows of Table. *NSCLC* non-small cell lung cancer, *RCC* renal cell carcinoma, *irAEs* immunotherapy-related adverse events, *NA* not applicable

group and analyzing the source of heterogeneity. As shown in this study, men with high BMI were more likely to get an OS benefit from immunotherapy (pHR = 0.60 [95% CI: 0.45–0.81], $p = 0.001$) than were women (pHR = 0.69 [95% CI: 0.46–1.06], $p = 0.09$), as well as for PFS (pHR = 0.62 [95% CI: 0.49–0.78, $p < 0.001$] vs pHR = 0.86 [95% CI: 0.51–1.44], $p = 0.566$, respectively), as shown in Fig. 5a and b. The overall compared result was $p < 0.001$ for OS and $p = 0.004$ for PFS. ICIs in second or subsequent line could produce longer OS (pHR = 0.71 [95% CI: 0.62–0.82], $p < 0.001$) than first or second line (pHR = 0.68 [95% CI: 0.46–1.00], $p = 0.05$ for OS), as shown in Fig. 5c. In terms of PFS, both of ≥ 2nd (pHR = 0.79 [95% CI: 0.70–0.89], $p < 0.001$) and first or second (pHR = 0.65 [95% CI:

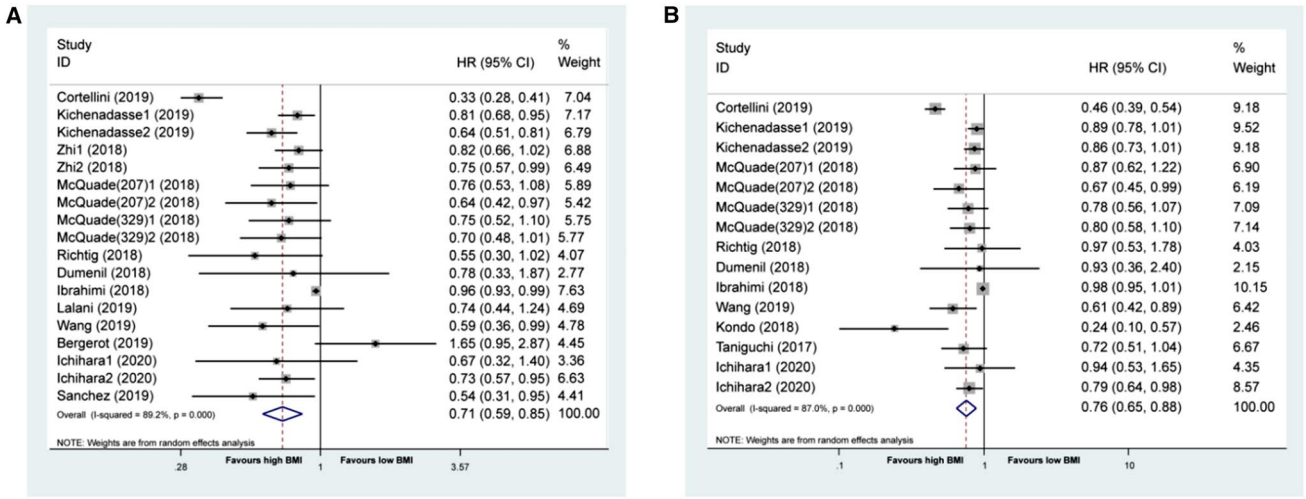


Fig. 2 Association between BMI and prognosis in cancer patients treated with ICIs. **a.** Forest plot for association between BMI and OS in cancer patients treated with ICIs. **b.** Forest plot for association between BMI and PFS in cancer patients treated with ICIs. *BMI* body mass index, *OS* overall survival, *PFS* progression free survival, *ICIs* immune checkpoint inhibitors. The included articles of Kichenadasse, Zhi, McQuade, and Ichihara contain different cohorts and/or different BMI cutoff value, which labeled Author 1, Author 2 and even Author(sample) 1, Author(sample) 2. Below is the same as above

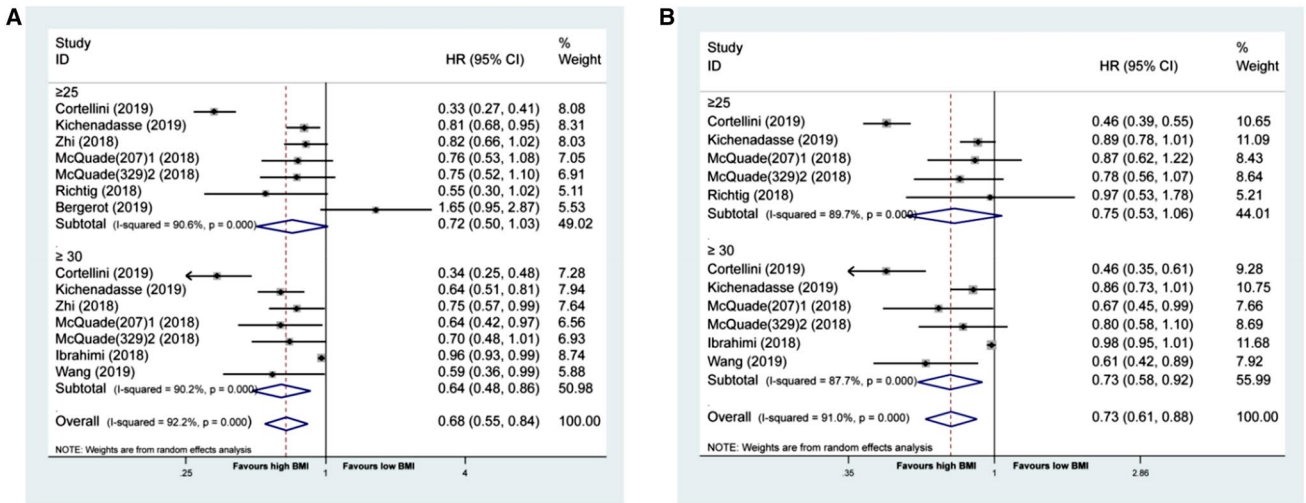


Fig. 3 Association between BMI and prognosis in high BMI cancer patients treated with ICIs. **a.** Forest plot for association between BMI and OS in cancer patients treated with ICIs, stratified by BMI ≥ 25 and BMI ≥ 30. **b.** Forest plot for association between BMI and PFS in cancer patients treated with ICIs, stratified by BMI ≥ 25 and BMI ≥ 30

0.48–0.90], $p = 0.008$) could benefit from immunotherapy regardless of BMI, as shown in Fig. 5d. We found an improvement in survival of patients with high BMI in advanced NSCLC (OS: pHR = 0.76 [95% CI: 0.69–0.83], PFS: pHR = 0.85 [95% CI: 0.78–0.93]) and metastatic melanoma (OS: pHR = 0.70 [95% CI: 0.58–0.84], PFS: pHR = 0.75 [95% CI: 0.60–0.93]), but not RCC (OS: pHR = 0.87 [95% CI: 0.46–1.46]), as shown in Fig. 5e, f. When we examined BMI and PD-L1 status together, we found that patients with both high BMI and positive PD-L1 had longer OS (pHR = 0.62 [95% CI: 0.45–0.84]) and longer PFS (pHR = 0.83 [95% CI: 0.73–0.95]), as shown in Fig. 5g, h.

Because few studies reported data relevant to the relationship between BMI and irAEs, only treatment lines and tumor types were chosen for subgroup analysis. In general, the incidence of any grade of irAEs was independent of BMI for subgroups defined by the first or second treatment line (OR = 2.42 [95% CI: 0.88–6.68]) and by ≥ 2nd line (OR = 1.50 [95% CI: 0.68–3.30]). However, first or second

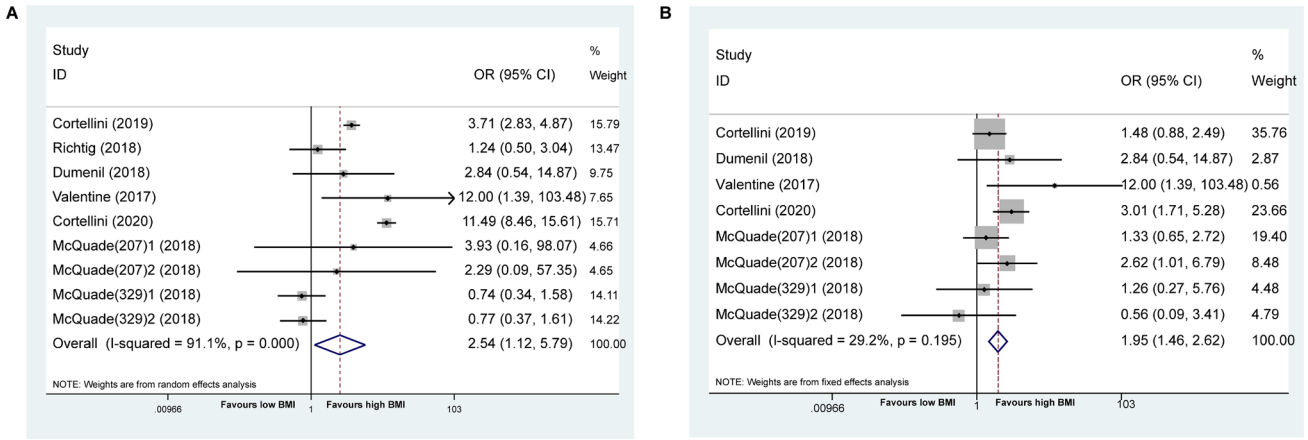


Fig. 4 Association between BMI and irAEs in cancer patients treated with ICIs. **a.** Forest plot for association between BMI and any grade of irAEs treated with ICIs. **b.** Forest plot for association between BMI and G3/G4 irAEs treated with ICIs. *irAEs* immunotherapy-related adverse events

line immunotherapy had a high risk of G3/G4 irAEs in the high BMI group (OR = 1.87 [95% CI: 1.38–2.52]) but not for ≥ 2nd line (OR = 2.84 [95% CI:0.0.54–14.87]), as shown in Fig. 6a, b. For the tumor types, there was no difference in metastatic melanoma for any grade of irAEs (OR = 1.14 [95% CI: 0.62–2.09]) and for G3/G4 irAEs (OR = 1.74 [95% CI: 0.88–3.44]), as shown in Fig. 6c, d.

Heterogeneity analysis, publication bias, and sensitivity analysis

As shown in Fig. 2, there was great heterogeneity of this meta-analysis. According to subgroup analysis and Galbraith plot, the dominating sources of heterogeneity were from the studies of Cortellini [10], Bergerot [27], Kondo [24], and Ibrahim [21] (Fig. 7a, b). Indiscriminate tumor types might be the reason, which brought in considerable confounders. What's more, Kondo and Bergerot's studies contained a very small sample size. The funnel plots, assessment of publication bias, are shown in Fig. 7c and d. Meanwhile, the Egger's regression test had significant publication biases for OS ($p = 0.015$) and PFS ($p = 0.018$). At last, filled funnel plot of OS ($p < 0.001$) and PFS ($p = 0.001$) reflected the same results (Fig. 7e and f), which indicated the result of the publication bias was robust. The sensitivity analysis for OS and PFS was performed to test the reliability of this finding. As shown in Fig. 7g and h, the result attested all the studies was located within the confidential interval and the study of Cortellini mainly resulted in the heterogeneity.

Discussion

By pooling the individual studies, we found a significant association between high BMI and improved clinical outcomes in cancer patients receiving ICIs relative to outcomes in patients with low BMI. Moreover, we confirmed that overweight/obese patients were related to a greater incidence of irAEs (irAEs of any grade or G3/G4 irAEs). All in all, there might be an epiphenomenon: the better the outcomes among patients with higher BMI, the higher the incidence of irAEs within the same BMI categories.

BMI could potentially be used as a proxy for poor performance status (PS) in real-world data studies; for example, higher BMI is associated with better PS [17]. Some retrospective studies have also shown that PS status is closely related to the efficacy of immunotherapy [32, 33]. Both BMI and PS are partly associated with obesity; the clinical characteristics of obesity may provide some explanations of why high BMI is correlated with good outcomes and irAEs of ICIs treatments. In fact, obesity has a highly complicated association with cancers. Although obesity increases the occurrence of certain types of cancers, such as breast cancers and colorectal cancer, obesity protects against worse outcomes in patients with advanced cancers, such as lung cancers that are associated with wasting [34]. Moreover, previous studies have suggested that high BMI is associated with better outcomes from surgery, radiotherapy, and some types of chemotherapy [35–37] in patients with lung cancer [35, 36]. The biological basis of the association between obesity and the immune system is just beginning to be understood. It is possible that obesity may induce a low-grade systemic meta-inflammation and impaired immune response. Most individuals who are obese harbor inflamed adipose tissue, which resembles chronically injured tissue, with immune

cell infiltration and remodeling, which have been found to possibly promote breast and other cancers [38]. Elevated plasma levels of inflammatory markers are correlated with the degree of obesity [39]. Obesity might induce macrophage activation via toll-like receptor 4 (TLR4), thereby stimulating NF-κB signaling. This, in turn, activates transcription of proinflammatory genes including COX-2, IL-6, IL-1β, and TNFα [40]. Moreover, obesity induces T-cell dysfunction and increases the exhausted PD-1–positive T-cell phenotype in fat and tumor microenvironment through leptin production, which may be the link between obesity and immune response [23, 41]. Leptin is characteristically present at high levels in obesity and can affect T-cell function [42, 43]. The increased PD-1 expression correlates with upregulation of phospho-STAT3, a major downstream mediator of leptin signaling, which is also known to induce PD-1 expression on T cells through distal regulatory elements that interact with the PD-1 gene promoter. The identified association between high BMI and OS with atezolizumab appears to be particularly strong in the PD-L1–positive population, lending further support to the presence of a T-cell dysfunction state in patients with obesity. Atezolizumab, through its mechanism of action of PD-1/PD-L1 axis inhibition on T cells, might induce a favorable response in patients with obesity with an established T-cell exhausted state. A novel idea explains that overweight/obese patients might have a different composition of gut microbiota, which would cause the different benefit from immunotherapy [44–46].

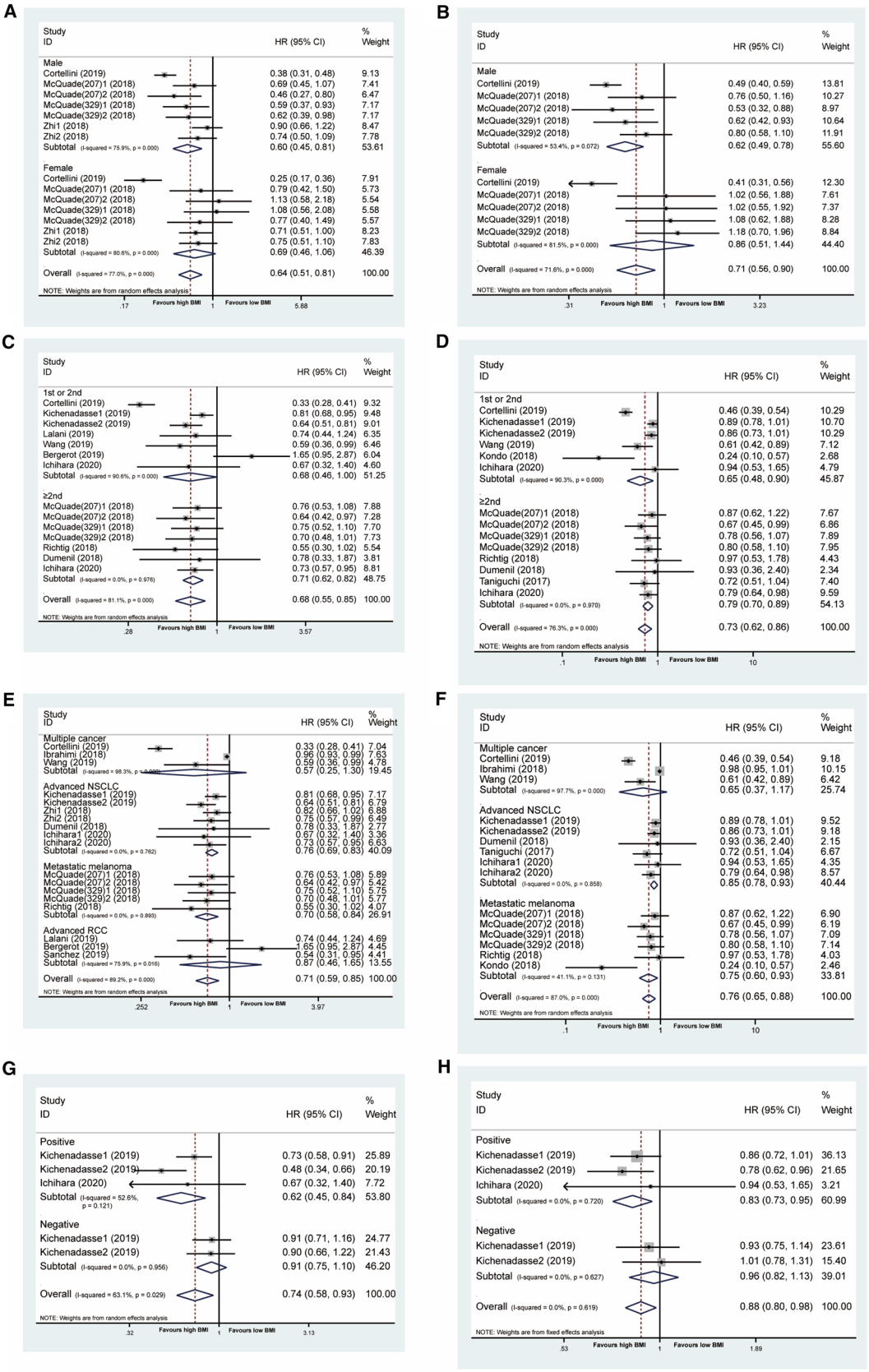
As for irAEs, the predictor is not established either. Mirsoian et al. have already revealed that obesity might play a critical role in the induction of immunotherapy toxicities [47], also confirmed in our study. Obesity is hallmarked by a self-sustaining inflammatory response termed "meta-inflammation" [48]. A recent study has attested that immunotherapy that is effective against tumors in young, lean mice can cause lethal inflammation in obese mice. Another reason might be that ICI dosages are based on weight, so we could speculate that overweight/obese patients inevitably have been exposed to higher risks of developing irAEs because of having received higher doses. However, the mechanisms by which BMI affects irAEs remain unknown.

The positive correlation of higher BMI with better survival and severe irAEs did not exist in all patient groups as found in our study. In fact, male patients reportedly tend to have better survival from ICI treatment compared to females [49]. This capacity of tumors in women to evade immune surveillance could make advanced tumors in women less immunogenic and enriched with stronger mechanisms of immune escape than similar tumors in men, and thus, they might become more resistant to immunotherapies [50]. More importantly, the increased susceptibility of women to autoimmune disorders could also make them more likely to develop immune checkpoint inhibitor-related adverse events, potentially leading to a higher rate of treatment discontinuation [51]. With regard to BMI, the correlation was only seen in male patients as well. A potential hormonal mediator of the BMI effects is related to the difference between the sexes [52]; however, the real reasons have not been clarified. Early ICI studies mainly focused on melanoma and NSCLC apparently because of their distinctive immunological characteristics, but now increasing tumor types have been found in which ICI yields an advantage, for example urothelial cancer (UC) and RCC. However, the correlation of BMI and survival has not been seen in RCC, and the different correlation may be due to small patient numbers in RCC studies or higher immunity of melanoma and NSCLC. Meanwhile, based on 204 existing meta-analyses and system reviews, Kyrgiou et al. eventually verified that the risk of eleven types of cancer (containing RCC) was strongly associated with obesity, while the association between other types of cancer (containing NSCLC and melanoma) and obesity was uncertain [53]. The same result came from the International Agency for Research on Cancer (IARC) working group [54]. Nonetheless, what surprised us was that the relationship of higher BMI and severe irAEs was not confirmed in melanoma, for which this analysis included relatively large numbers of patients and studies. The absence of correlation may be due to an included study that assessed adverse events as not more frequent in patients with normal BMI than in patients who were overweight and obese. It indicates that the correlation of BMI and irAEs needs further investigation. It is easy to understand the combination of high BMI with positive PD-L1 to find patients with better OS and PFS, since obesity induces T-cell dysfunction and increases the exhausted PD-1 positive T-cell phenotype [41]. With regard to treatment lines, our results indicated ≥ 2nd line immunotherapy with high BMI tended to have larger survival benefit than first or second line with high BMI. However, first or second line immunotherapy had a high risk of G3/G4 irAEs in high BMI group but not for ≥ 2nd line. This discrepancy may be caused by having more data available now for the second line and above.

Limitations

There are several limitations in our study: 1. Our study has the risk of publication bias. One of the bias and cause of heterogeneity is the analysis of "multiple cancers" and that the main conclusions could be clearly drawn only for melanoma and NSCLC.

Another heterogeneity roots in the disunity of the treatment regimen and sample population. 2. The cutoff value for BMI differs in the included studies. 3. Our study just evaluates the baseline BMI but not the longitudinal BMI, which is underpowered to explain the dynamic effect of BMI on immunotherapy efficacy. 4. BMI may be not a good indicator


A
Study ID
HR (95% CI)
% Weight
Male
Cortellini (2019) 0.38 (0.31, 0.48) 9.13
McQuade(207)1 (2018) 0.69 (0.45, 1.07) 7.41
McQuade(207)2 (2018) 0.46 (0.27, 0.80) 6.47
McQuade(329)1 (2018) 0.59 (0.37, 0.93) 7.17
McQuade(329)2 (2018) 0.62 (0.39, 0.98) 7.17
Zhi1 (2018) 0.90 (0.66, 1.22) 8.47
Zhi2 (2018) 0.74 (0.50, 1.09) 7.78
Subtotal (I-squared = 75.9%, p = 0.000) 0.60 (0.45, 0.81) 53.61
Female
Cortellini (2019) 0.25 (0.17, 0.36) 7.91
McQuade(207)1 (2018) 0.79 (0.42, 1.50) 5.73
McQuade(207)2 (2018) 1.13 (0.58, 2.18) 5.54
McQuade(329)1 (2018) 1.08 (0.56, 2.08) 5.58
McQuade(329)2 (2018) 0.77 (0.40, 1.49) 5.57
Zhi1 (2018) 0.71 (0.51, 1.00) 8.23
Zhi2 (2018) 0.75 (0.51, 1.10) 7.83
Subtotal (I-squared = 80.6%, p = 0.000) 0.69 (0.46, 1.06) 46.39
Overall (I-squared = 77.0%, p = 0.000) 0.64 (0.51, 0.81) 100.00
NOTE: Weights are from random effects analysis
.17 Favours high BMI 1 Favours low BMI 5.88
B
Study ID
HR (95% CI)
% Weight
Male
Cortellini (2019) 0.49 (0.40, 0.59) 13.81
McQuade(207)1 (2018) 0.76 (0.50, 1.16) 10.27
McQuade(207)2 (2018) 0.53 (0.32, 0.88) 8.97
McQuade(329)1 (2018) 0.62 (0.42, 0.93) 10.64
McQuade(329)2 (2018) 0.80 (0.58, 1.10) 11.91
Subtotal (I-squared = 53.4%, p = 0.072) 0.62 (0.49, 0.78) 55.60
Female
Cortellini (2019) 0.41 (0.31, 0.56) 12.30
McQuade(207)1 (2018) 1.02 (0.56, 1.88) 7.61
McQuade(207)2 (2018) 1.02 (0.55, 1.92) 7.37
McQuade(329)1 (2018) 1.08 (0.62, 1.88) 8.28
McQuade(329)2 (2018) 1.18 (0.70, 1.96) 8.84
Subtotal (I-squared = 81.5%, p = 0.000) 0.86 (0.51, 1.44) 44.40
Overall (I-squared = 71.6%, p = 0.000) 0.71 (0.56, 0.90) 100.00
NOTE: Weights are from random effects analysis
.31 Favours high BMI 1 Favours low BMI 3.23
C
Study ID
HR (95% CI)
% Weight
1st or 2nd
Cortellini (2019) 0.33 (0.28, 0.41) 9.32
Kichenadasse1 (2019) 0.81 (0.68, 0.95) 9.48
Kichenadasse2 (2019) 0.64 (0.51, 0.81) 9.01
Lalani (2019) 0.74 (0.44, 1.24) 6.35
Wang (2019) 0.59 (0.36, 0.99) 6.46
Bergerot (2019) 1.65 (0.95, 2.87) 6.04
Ichihara (2020) 0.67 (0.32, 1.40) 4.60
Subtotal (I-squared = 90.6%, p = 0.000) 0.68 (0.46, 1.00) 51.25
≥2nd
McQuade(207)1 (2018) 0.76 (0.53, 1.08) 7.88
McQuade(207)2 (2018) 0.64 (0.42, 0.97) 7.28
McQuade(329)1 (2018) 0.75 (0.52, 1.10) 7.70
McQuade(329)2 (2018) 0.70 (0.48, 1.01) 7.73
Richtig (2018) 0.55 (0.30, 1.02) 5.54
Dumenil (2018) 0.78 (0.33, 1.87) 3.81
Ichihara (2020) 0.73 (0.57, 0.95) 8.81
Subtotal (I-squared = 0.0%, p = 0.976) 0.71 (0.62, 0.82) 48.75
Overall (I-squared = 81.1%, p = 0.000) 0.68 (0.55, 0.85) 100.00
NOTE: Weights are from random effects analysis
.28 Favours high BMI 1 Favours low BMI 3.57
D
Study ID
HR (95% CI)
% Weight
1st or 2nd
Cortellini (2019) 0.46 (0.39, 0.54) 10.29
Kichenadasse1 (2019) 0.89 (0.78, 1.01) 10.70
Kichenadasse2 (2019) 0.86 (0.73, 1.01) 10.29
Wang (2019) 0.61 (0.42, 0.89) 7.12
Kondo (2018) 0.24 (0.10, 0.57) 2.68
Ichihara (2020) 0.94 (0.53, 1.65) 4.79
Subtotal (I-squared = 90.3%, p = 0.000) 0.65 (0.48, 0.90) 45.87
≥2nd
McQuade(207)1 (2018) 0.87 (0.62, 1.22) 7.67
McQuade(207)2 (2018) 0.67 (0.45, 0.99) 6.86
McQuade(329)1 (2018) 0.78 (0.56, 1.07) 7.89
McQuade(329)2 (2018) 0.80 (0.58, 1.10) 7.95
Richtig (2018) 0.97 (0.53, 1.78) 4.43
Dumenil (2018) 0.93 (0.36, 2.40) 2.34
Taniguchi (2017) 0.72 (0.51, 1.04) 7.40
Ichihara (2020) 0.79 (0.64, 0.98) 9.59
Subtotal (I-squared = 0.0%, p = 0.970) 0.79 (0.70, 0.89) 54.13
Overall (I-squared = 76.3%, p = 0.000) 0.73 (0.62, 0.86) 100.00
NOTE: Weights are from random effects analysis
.1 Favours high BMI 1 Favours low BMI 10
E
Study ID
HR (95% CI)
% Weight
Multiple cancer
Cortellini (2019) 0.33 (0.28, 0.41) 7.04
Ibrahimi (2018) 0.96 (0.93, 0.99) 7.63
Wang (2019) 0.59 (0.36, 0.99) 4.78
Subtotal (I-squared = 98.3%, p = 0.000) 0.57 (0.25, 1.30) 19.45
Advanced NSCLC
Kichenadasse1 (2019) 0.81 (0.68, 0.95) 7.17
Kichenadasse2 (2019) 0.64 (0.51, 0.81) 6.79
Zhi1 (2018) 0.82 (0.66, 1.02) 6.88
Zhi2 (2018) 0.75 (0.57, 0.99) 6.49
Dumenil (2018) 0.78 (0.33, 1.87) 2.77
Ichihara1 (2020) 0.67 (0.32, 1.40) 3.36
Ichihara2 (2020) 0.73 (0.57, 0.95) 8.63
Subtotal (I-squared = 0.0%, p = 0.762) 0.76 (0.69, 0.83) 40.09
Metastatic melanoma
McQuade(207)1 (2018) 0.76 (0.53, 1.08) 5.89
McQuade(207)2 (2018) 0.64 (0.42, 0.97) 5.42
McQuade(329)1 (2018) 0.75 (0.52, 1.10) 5.75
McQuade(329)2 (2018) 0.70 (0.48, 1.01) 5.77
Richtig (2018) 0.55 (0.30, 1.02) 4.07
Subtotal (I-squared = 0.0%, p = 0.893) 0.70 (0.58, 0.84) 26.91
Advanced RCC
Lalani (2019) 0.74 (0.44, 1.24) 4.69
Bergerot (2019) 1.65 (0.95, 2.87) 4.45
Sanchez (2019) 0.54 (0.31, 0.95) 4.41
Subtotal (I-squared = 75.9%, p = 0.016) 0.87 (0.46, 1.65) 13.55
Overall (I-squared = 89.2%, p = 0.000) 0.71 (0.59, 0.85) 100.00
NOTE: Weights are from random effects analysis
.252 Favours high BMI 1 Favours low BMI 3.97
F
Study ID
HR (95% CI)
% Weight
Multiple cancer
Cortellini (2019) 0.46 (0.39, 0.54) 9.18
Ibrahimi (2018) 0.98 (0.95, 1.01) 10.15
Wang (2019) 0.61 (0.42, 0.89) 6.42
Subtotal (I-squared = 97.7%, p = 0.000) 0.65 (0.37, 1.17) 25.74
Advanced NSCLC
Kichenadasse1 (2019) 0.89 (0.78, 1.01) 9.52
Kichenadasse2 (2019) 0.86 (0.73, 1.01) 9.18
Dumenil (2018) 0.93 (0.36, 2.40) 2.15
Taniguchi (2017) 0.72 (0.51, 1.04) 6.67
Ichihara1 (2020) 0.94 (0.53, 1.65) 4.35
Ichihara2 (2020) 0.79 (0.64, 0.98) 8.57
Subtotal (I-squared = 0.0%, p = 0.858) 0.85 (0.78, 0.93) 40.44
Metastatic melanoma
McQuade(207)1 (2018) 0.87 (0.62, 1.22) 6.90
McQuade(207)2 (2018) 0.67 (0.45, 0.99) 6.19
McQuade(329)1 (2018) 0.78 (0.56, 1.07) 7.09
McQuade(329)2 (2018) 0.80 (0.58, 1.10) 7.14
Richtig (2018) 0.97 (0.53, 1.78) 4.03
Kondo (2018) 0.24 (0.10, 0.57) 2.46
Subtotal (I-squared = 41.1%, p = 0.131) 0.75 (0.60, 0.93) 33.81
Overall (I-squared = 87.0%, p = 0.000) 0.76 (0.65, 0.88) 100.00
NOTE: Weights are from random effects analysis
.1 Favours high BMI 1 Favours low BMI 10
G
Study ID
HR (95% CI)
% Weight
Positive
Kichenadasse1 (2019) 0.73 (0.58, 0.91) 25.89
Kichenadasse2 (2019) 0.48 (0.34, 0.66) 20.19
Ichihara (2020) 0.67 (0.32, 1.40) 7.72
Subtotal (I-squared = 52.6%, p = 0.121) 0.62 (0.45, 0.84) 53.80
Negative
Kichenadasse1 (2019) 0.91 (0.71, 1.16) 24.77
Kichenadasse2 (2019) 0.90 (0.66, 1.22) 21.43
Subtotal (I-squared = 0.0%, p = 0.956) 0.91 (0.75, 1.10) 46.20
Overall (I-squared = 63.1%, p = 0.029) 0.74 (0.58, 0.93) 100.00
NOTE: Weights are from random effects analysis
.32 Favours high BMI 1 Favours low BMI 3.13
H
Study ID
HR (95% CI)
% Weight
Positive
Kichenadasse1 (2019) 0.86 (0.72, 1.01) 36.13
Kichenadasse2 (2019) 0.78 (0.62, 0.96) 21.65
Ichihara (2020) 0.94 (0.53, 1.65) 3.21
Subtotal (I-squared = 0.0%, p = 0.720) 0.83 (0.73, 0.95) 60.99
Negative
Kichenadasse1 (2019) 0.93 (0.75, 1.14) 23.61
Kichenadasse2 (2019) 1.01 (0.78, 1.31) 15.40
Subtotal (I-squared = 0.0%, p = 0.627) 0.96 (0.82, 1.13) 39.01
Overall (I-squared = 0.0%, p = 0.619) 0.88 (0.80, 0.98) 100.00
NOTE: Weights are from fixed effects analysis
.53 Favours high BMI 1 Favours low BMI 1.89

◂**Fig. 5** Subgroup analyses of the relationship between BMI and prognosis in ICIs treated cancer patients. **a.** Forest plot for association between BMI and OS in cancer patients treated with ICIs, stratified by sex. **b.** Forest plot for association between BMI and PFS in cancer patients treated with ICIs, stratified by sex. **c.** Forest plot for association between BMI and OS in cancer patients treated with ICIs, stratified by treatment lines. **d.** Forest plot for association between BMI and PFS in cancer patients treated with ICIs, stratified by treatment lines. **e.** Forest plot for association between BMI and OS in cancer patients treated with ICIs stratified by tumor types. **f.** Forest plot for association between BMI and PFS in cancer patients treated with ICIs stratified by tumor types. **g.** Forest plot for association between BMI and OS in cancer patients treated with ICIs stratified by PD-L1 status. **h.** Forest plot for association between BMI and PFS in cancer patients treated with ICIs stratified by PD-L1 status

of fat accumulation. visceral fat, subcutaneous fat, and muscular tissue will be alternative.

Conclusion

Our meta-analysis provides strong evidence that cancer patients with high BMI are more likely to benefit from immunotherapy than those with normal BMI; the association is especially strong for patients who are male or PD-L1 positive or receiving second line or above treatment. BMI might be an effective prognostic marker for immunotherapy.

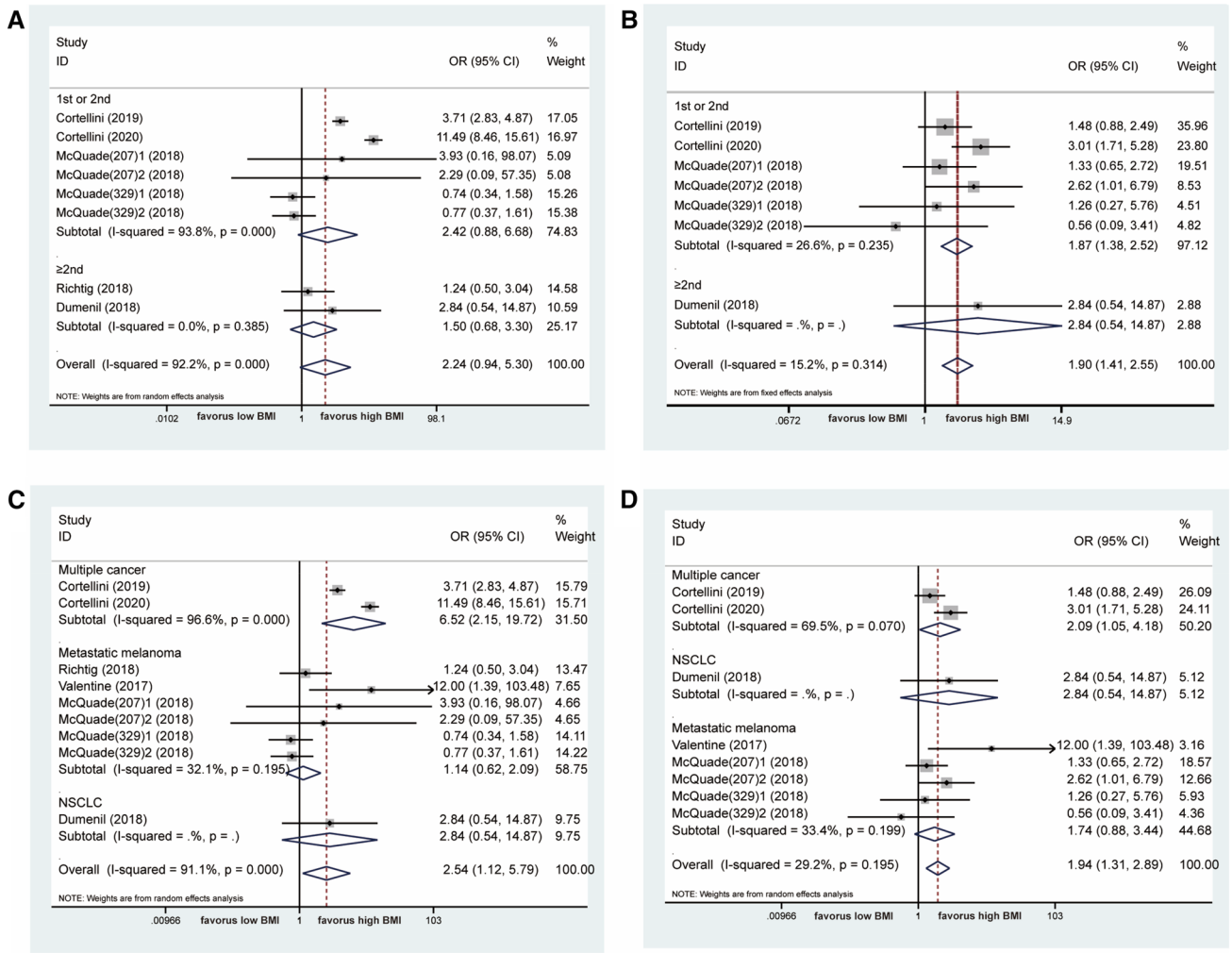


Fig. 6 Subgroup analyses of the relationship between BMI and irAEs in ICIs treated cancer patients. **a.** Forest plot for association between BMI and any grade of irAEs treated with ICIs stratified by treatment lines. **b.** Forest plot for association between BMI and G3/G4 irAEs treated with ICIs stratified by treatment lines. **c.** Forest plot for association between BMI and any grade of irAEs treated with ICIs stratified by tumor types. **d.** Forest plot for association between BMI and G3/G4 irAEs treated with ICIs stratified by tumor types

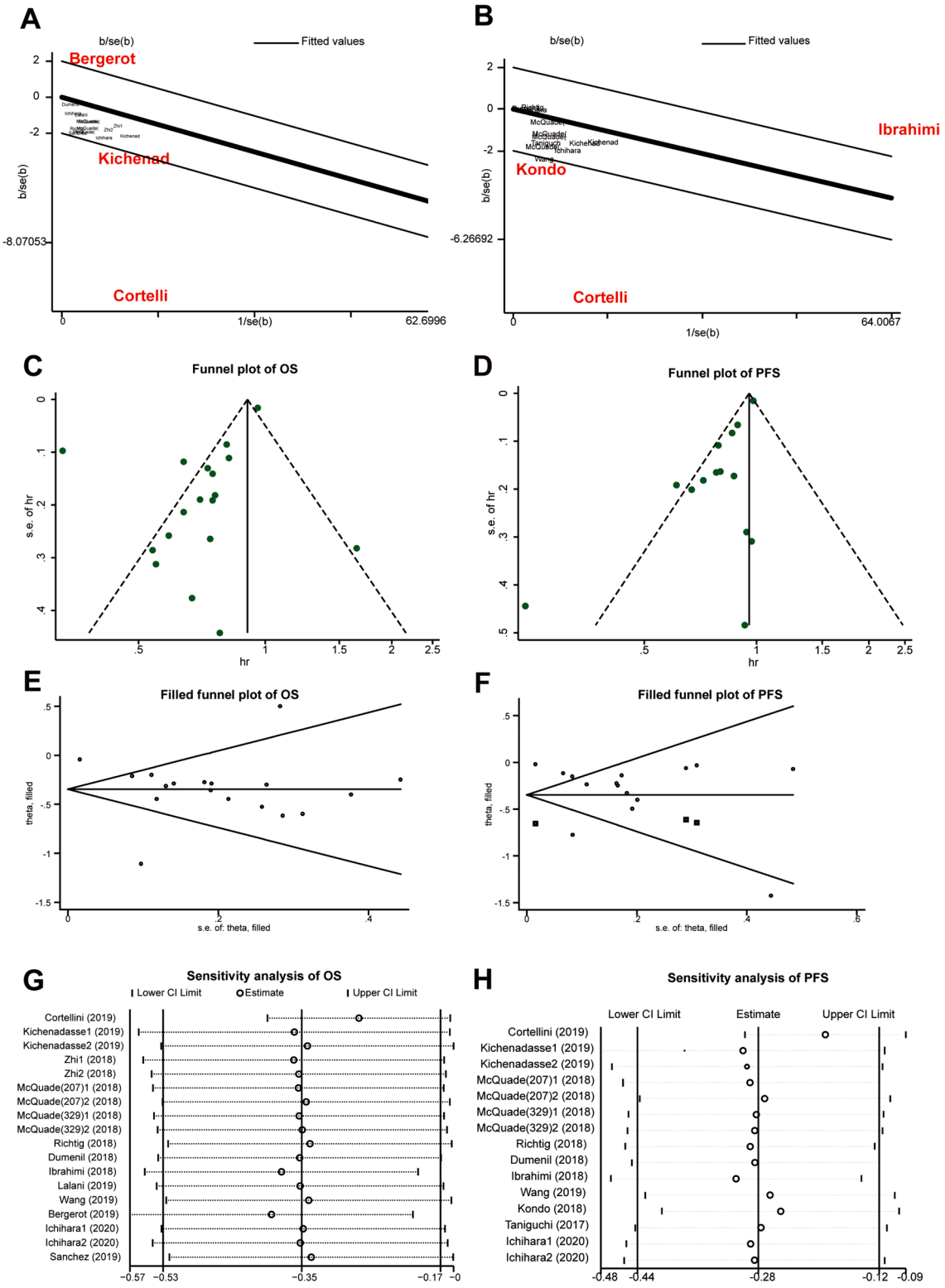


Fig. 7 Heterogeneity analysis, publication bias, and sensitivity analysis. **a.** heterogeneity analysis of OS by Galbraith plot, **b.** heterogeneity analysis of PFS by Galbraith plot, **c.** funnel plot of OS, **d.** funnel plot of PFS, **e.** filled funnel plot of OS, **f.** filled funnel plot of PFS, **g.** sensitivity analysis of OS, and **h.** sensitivity analysis of PFS

However, high BMI is also related to higher incident of irAEs. Baseline BMI should therefore be considered as a stratification factor in future immune checkpoint inhibitor therapy trials.

Authors Contribution X.L.P and Y.Y.F designed the study. Y.Y.F, J.C, and P.K.W designed the statistical plan. Y.Y.F performed the key analyses. Y.Y.F, J.C, and P.K.W generated and collected the data. H.W.Z, W.L, and J.Y.N assisted in data interpretation. Y.Y.F wrote the manuscript. X.L.P revised the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval As this study was based on published data, no ethics approval was sought for the study.

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