Effect of body mass index on the efficacy of immune checkpoint inhibitors in patients with advanced cancer: Is the obesity paradox real?

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Abstract

**Background:** Recent studies have shown that an increased body mass index (BMI) is associated with an improved response to immune checkpoint inhibitors (ICIs). We evaluated the association between BMI and response to the ICIs in solid tumors.

**Methods:** We retrospectively analyzed patients with advanced cancer treated with ICIs at one academic center between 2014-2022. We calculated the BMI based on the weight of the patients when they started ICI treatment and divided the patients into two groups: underweight/normal weight (BMI < 25) and overweight/obese (BMI \( \geq \) 25) and compared the treatment responses between these two groups. After excluding underweight patients, we also compared the progression-free survival (PFS) and overall survival (OS) of normal-weight, overweight, and obese patients.

**Results:** Overall, 130 patients were evaluated. The median age was 61, and 83.8% were male. 53 (40.7) patients had BMI <25 and 77 (59.3) patients had a BMI \( \geq \) 25. In underweight/normal patients, median PFS was 7.7 months (95% CI: 4.9–10.4) vs 8.7 months (95% CI: 2.6–14.9) in overweight/obese patients (HR 1.03, 95% CI: 0.69–1.53, \( p = 0.865 \)). In underweight/normal patients, the median OS was 22.1 months (95% CI: 11.1-33.1) compared to 21.3 months (95% CI: 13.8–28.8) in overweight/obese patients (HR 1.02, 95% CI: 0.67–1.57, \( p = 0.898 \)). The objective response rate (ORR) was 39.6% in underweight/normal patients and 40.3% in overweight/obese patients (\( p = 0.942 \)). After excluding underweight patients, there were also no significant differences in PFS (\( p = 0.962 \)), OS (\( p = 0.609 \)), and ORR (\( p = 0.815 \)) between patients of normal weight, overweight, and obesity.

**Conclusion:** In patients with advanced cancer treated with ICIs, there is no impact of BMI on PFS, OS, or ORR. Prospective studies are required to evaluate the prognostic impact of dynamic changes of BMI on the response to ICIs.

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of a significant number of cancer patients. Antibodies that target programmed cell death 1 (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) have been approved for the majority of solid malignancies (1–6). Although durable responses were obtained, ICIs only benefit a small number of patients. The most well-established predictive markers to date are PD-L1 expression, microsatellite instability, and tumor mutational burden (7). Moreover, while some predictive factors have been identified, it is evident that additional predictive factors are required to precisely identify which patients benefit from ICIs.

Numerous clinical factors have been demonstrated to correlate with the efficacy of ICIs. It has been demonstrated that the use of antibiotics in the early phases of ICIs treatment is associated with decreased response rates (8). While the presence of immune-related adverse events (irAEs) was positively correlated with the ICIs response, the use of steroids for cancer-related symptoms had a negative impact on the ICIs response (9). Recent studies have shown a correlation between body mass index (BMI) and
the efficacy of ICIs, with overweight and obese patients exhibiting improved responses (10, 11). This seems to contradict the long-standing notion that obesity increases tumor development, promotes progression, and is associated with worse outcomes (12, 13). However, the positive effect of obesity on the response to ICIs is not observed in patients treated with chemotherapy (14). In a preclinical model, this obesity paradox was found to be associated with T cell exhaustion and dysfunction caused by leptin signaling, and it has been suggested that PD-1 blockade significantly reversed this T cell exhaustion in obese mice (15). Although several studies have found positive correlations between high BMI and ICIs response, it is unclear whether a high BMI correlates with an improved outcome. For instance, in a study of 287 patients with metastatic melanoma, no association was found between BMI and overall survival (OS), or progression-free survival (PFS) (16).

Here, we conducted a retrospective study to determine if BMI had any effect on treatment responses in patients with advanced cancer who were treated with ICIs.

Materials and methods

Patients

The medical records of 130 patients with advanced cancer treated with ICIs at one academic center between 2014–2022 were reviewed. All patients received anti-PD-(L)1 monotherapy or in combination with targeted agents at a fixed dose. Only patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–1 were included. Tumor responses were assessed using the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1.

BMI was calculated using the patients' weight on the first day of ICIs treatment. BMI was calculated by dividing the patients' weight (in kilograms) by the square of their height (in meters). The BMI classification was based on the World Health Organization (WHO) classification: underweight, BMI < 18.5; normal, 18.5 ≤ BMI ≤ 24.9; overweight, 25 ≤ BMI ≤ 29.9; obesity ≥ 30. First, we compared the patients by categorizing them into underweight/normal (BMI < 25) and overweight/obese (BMI ≥ 25) categories. Then, in order to compare the treatment responses of overweight and obese patients with those of normal-weight patients, we analyzed the data excluding the underweight patients.

We evaluated whether BMI categories (underweight/normal and overweight/obese) are associated with PFS, OS, and objective response rate (ORR). In addition, we compared clinical variables such as age, gender, number of metastatic sites, tumor types, and type of therapy between the two groups. Then, we compared the PFS, OS, and ORR of the overweight and obese groups with those of patients of normal weight. We also analyzed PFS and OS separately for both males and females using the binominal cut-off (BMI < 25 and BMI ≥ 25). The study was approved by the institutional ethical review board, and the need for informed consent was waived because of the retrospective nature of this study. All patients were followed up until death or data lock on April 19, 2023.

Statistical Analysis
The characteristics of the patients were compared with the Fisher or Chi-squared test for categorical data and a t-test for continuous data. OS was defined as the time from initiation of ICI to death from any cause. PFS was defined as the time from the initiation of ICI to the progression or death from any cause. No-event patients were censored at the end of the last follow-up. The association between BMI, OS, and PFS was analyzed using Cox hazards regression models and reported as hazard ratios (HR) with 95% confidence intervals (CI). The Kaplan-Meier method was used to calculate survival curves, median PFS, and median OS. Using the Chi-squared test, ORR differences were analyzed. Statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant. The statistical analyses were conducted using SPSS version 23.

Results

130 patients with advanced cancer were evaluated. The median age was 61 (range 23–91). 21 (16.2%) patients were female, and 109 (83.8%) patients were male. 81 (62.3%) of patients were naïve and 49 (37.7%) of patients had chemotherapy before ICI. None of the patients had previously received ICIs. The cancer types were 54.6% non-small cell lung cancer (NSCLC), 16.2% renal cell carcinoma (RCC), 13.8% bladder cancer, 10.8% gastric cancer, and 4.6% colorectal cancer (CRC). 108 patients (83.1%) received a single-agent ICI as PD-1 or PD-L1 inhibitors, and 22 (16.9%) received a combination ICI with targeted therapies. All patients received PD-(L)1 blockade and targeted treatments as fixed doses. 68 (52.3%) patients had at least two or more metastatic sites (Table 1). The median weight was 73.8 kg (range 37–118), and the median BMI was 25.9 kg (range 15.8–46.4). According to WHO classification, 6 (4.6%) patients were underweight, 47 (36.2%) had normal weight, 54 (41.5%) were overweight, and 23 (17.7) were obese.

First, we compared patients based on the BMI cutoff of 25: underweight/normal versus overweight or obese. 53 (40.8%) patients had a BMI < 25, while 77 (59.2%) patients had a BMI ≥ 25. There were no significant differences between the two groups’ baseline clinicopathologic characteristics (Table 1). When we compared PFS between two groups, there were no significant differences. In underweight/normal patients, median PFS was 7.7 months (95% CI: 4.9–10.4) vs 8.7 months (95% CI: 2.6–14.9) in overweight/obese patients (HR 1.03, 95% CI: 0.69–1.53, p = 0.865) (Figure 1A). Also, there were no significant OS differences. In underweight/normal patients, the median OS was 22.1 months (95% CI: 11.1-33.1) compared to 21.3 months (95% CI: 13.8-28.8) in overweight/obese patients (HR 1.02, 95% CI: (0.67-1.57), p = 0.898) (Figure 1B). We also examined the impact of BMI on ORR. The ORR was 39.6% in underweight/normal patients and 40.3% in overweight/obese patients (p = 0.942).

Table 1 Baseline characteristics of patients according to BMI
We performed a subgroup analysis by excluding the underweight patients, both due to their small proportion in the total population (only 6 patients) and compared the overweight and obese patients to the normal-weight patients. There were no significant differences between these three groups. Table 2 shows the association between BMI, OS, and PFS in these groups. Normal-weight patients had a median PFS of 7.3 months (95% CI: 5.3–9.3), overweight patients had a median PFS of 8.1 months (95% CI: 3.5–12.7), and obese patients had a median PFS of 13.2 months (95% CI: 5.5–20.8) (p = 0.962). For OS, the median OS was 18.3 months (95% CI: 8.3-28.3) for normal-weight patients, 18.7 months (95% CI: 13.0-24.4) for overweight patients, and 23.5 months (95% CI: 15.0-32.1) for obese patients (p = 0.609). Figures 2A and B show Kaplan-Meier curves for these three groups. Normal-weight, overweight, and obese patients had ORR rates of 40.4%, 42.6%, and 34.4%, respectively (p = 0.815).

**Table 2** Association between BMI and OS and PFS (excluding underweight patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N (%)</th>
<th>BMI &lt;25 N (%)</th>
<th>BMI ≥25 N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong> (Total 130)</td>
<td>53 (40.7)</td>
<td>77 (59.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>23-91</td>
<td>23-91</td>
<td>34-77</td>
<td>0.953</td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
<td>63</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (16.2)</td>
<td>11 (20.8)</td>
<td>10 (13)</td>
<td>0.237</td>
</tr>
<tr>
<td>Male</td>
<td>109 (83.8)</td>
<td>42 (29.2)</td>
<td>67 (29)</td>
<td></td>
</tr>
<tr>
<td><strong>Metastatic site</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.126</td>
</tr>
<tr>
<td>≤ 2</td>
<td>62 (47.7)</td>
<td>21 (39.6)</td>
<td>41 (53.2)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2</td>
<td>68 (52.3)</td>
<td>32 (60.4)</td>
<td>36 (46.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>71 (54.6)</td>
<td>30 (56.6)</td>
<td>41 (53.2)</td>
<td></td>
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<tr>
<td>RCC</td>
<td>21 (16.2)</td>
<td>6 (11.3)</td>
<td>15 (19.5)</td>
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</tr>
<tr>
<td>Bladder</td>
<td>18 (13.8)</td>
<td>7 (13.2)</td>
<td>11 (14.3)</td>
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<tr>
<td>Gastric</td>
<td>14 (10.8)</td>
<td>9 (17.0)</td>
<td>5 (6.5)</td>
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</tr>
<tr>
<td>CRC</td>
<td>6 (4.6)</td>
<td>1 (1.9)</td>
<td>5 (6.5)</td>
<td>0.197</td>
</tr>
<tr>
<td><strong>Type of therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>61 (46.9)</td>
<td>30 (56.6)</td>
<td>31 (40.3)</td>
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</tr>
<tr>
<td>Anti-PD-L1</td>
<td>47 (36.2)</td>
<td>17 (32.1)</td>
<td>30 (39)</td>
<td></td>
</tr>
<tr>
<td>Anti-PD-(L)1+Targeted Therapy</td>
<td>22 (16.9)</td>
<td>6 (11.3)</td>
<td>16 (20.8)</td>
<td>0.145</td>
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<td><strong>Previous ChT</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>81 (62.3)</td>
<td>31 (58.5)</td>
<td>50 (64.9)</td>
<td>0.456</td>
</tr>
<tr>
<td>Yes</td>
<td>49 (37.7)</td>
<td>22 (41.5)</td>
<td>27 (35.1)</td>
<td></td>
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</table>
Table 1. HR (95% CI) and P value for Progression-free survival and Overall survival.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Progression-free survival</strong></td>
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<tr>
<td>18.5-24.9</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>0.98 (0.63-1.52)</td>
<td>0.938</td>
</tr>
<tr>
<td>≥ 30</td>
<td>0.92 (0.53-1.60)</td>
<td>0.783</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>25-29.9</td>
<td>1.09 (0.68-1.76)</td>
<td>0.706</td>
</tr>
<tr>
<td>≥ 30</td>
<td>0.80 (0.43-1.49)</td>
<td>0.498</td>
</tr>
</tbody>
</table>

Lastly, we compared the PFS and OS in males and females separately using a BMI binominal cutoff 25. In 21 female patients, the median weight was 62 kg (range 37-95) and the median BMI was 24.8 kg (range 15.8–37.6). 11 (52.4%) female patients had a BMI < 25, while 10 (47.6%) patients had a BMI ≥ 25. There were no significant differences in PFS (p = 0.168) or OS (p = 0.288) between underweight/normal-weight, and overweight/obese female patients. In 109 male patients, the median weight was 75 kg (range 45.2-118), and the median BMI was 25.9 (16.4-46.4). 42 (38.5%) male patients had a BMI < 25, and 67 (61.5%) male patients had a BMI ≥ 25. The PFS (p = 0.470) and OS (p = 0.635) were not significantly different between underweight/normal weight, and overweight/obese male patients.

**Discussion**

In recent years, BMI has emerged as a potential predictor of ICIs response, alongside steroid and antibiotic use, the presence of irAEs, and tumor characteristics such as mismatch repair deficiency (dMMR) and PD-L1 expression. There have been inconsistent results concerning BMI and response to ICIs. Several studies have demonstrated a positive correlation between BMI and ICI response (10, 11, 15, 17, 18), while others observed no correlation between BMI and response (16, 19–22). In our study, we did not find any statistically significant correlation between BMI and response to ICIs. In addition, after excluding underweight patients, we also found no correlation between response and being overweight or obese.

There may be a number of reasons why there is so much discordance between studies when we analyze the causes. ICIs have been approved for use as fixed-dose for many years. A recent study showed that weight-based dosing significantly improved PFS and OS in overweight patients (BMI ≥ 25) when compared with the BMI < 25 group. In the same study, it was also observed that patients with BMI < 25 tended to have improved outcomes with fixed-dose ICIs (23). The ICIs were administered in fixed doses to all patients in our study. In another study, patients with NSCLC who responded to nivolumab had a higher nivolumab mean trough concentrations than those who progressed, indicating a potential exposure-response relationship (24). In a study on the administration of monoclonal antibodies, it was found that
the effect of body weight on the pharmacokinetics has a significant impact on the variability of exposure. While the use of a fixed dose causes overexposure in underweight patients, it can result in underexposure in overweight patients, whereas body weight-based dosing can have the opposite effect (25). It is also controversial to what extent studies in which fixed dose regimens were assigned reflect regional patient characteristics; for instance, in our study, overweight patients comprised the majority of the cohort (59.3%). Consequently, further pharmacokinetic, pharmacodynamic, and dosing studies should be conducted in specific patient populations to clarify this situation.

It has been considered that the better response of obese and overweight individuals is due to greater T cell exhaustion, which is rapidly reversed by PD-L1 blockade and is associated with a positive response (15). However, it is unknown whether this situation is static or dynamic; T cell exhaustion may become irreversible over time, thereby nullifying the initial advantage in response. Further studies utilizing valid methodologies should determine the levels of inflammation at various clinical points and evaluate whether a high BMI has this impact. In addition, the BMI index of the patients fluctuates over the course of treatment, so it is unknown how long the benefits of excess weight last. It has been shown that a decrease in BMI prior to ICI treatment was associated with decreased response rates, whereas BMI at baseline was not significantly associated with treatment outcomes (20). This situation should be clarified by studies that account for responses at various clinical time points and the dynamic changes in BMI.

Although previous research found a correlation between BMI and the clinical efficacy of ICI in male patients only, we found no correlation between gender and BMI (18, 23, 26). Nonetheless, inconsistent outcomes are still observed in this instance. In a meta-analysis, obesity was found to be associated with a favorable response in cancer patients treated with ICI; however, this benefit was independent of gender (27). In a study involving patients with NSCLC, there was no difference between the ICI responses of obese female and male patients (14).

Regarding the effect of BMI on the ICI response, when all the results are considered, they are remarkably inconsistent. A number of studies yielded varied results at various endpoints. Takada et al. observed a positive correlation between a high BMI and ORR, instead no effect on PFS and OS (28). In the study conducted by Di Giorgi et al. on RCC patients receiving nivolumab, there was no correlation between BMI and ORR, but there was a correlation between BMI and OS (29). In contrast, our research produced self-consistent results. We found no difference in PFS, OS, or ORR when we divided the patients into two groups based on the BMI cut-off 25 or when we investigated the effect of overweight and obesity by excluding the underweight patients. These findings suggest that there is no direct correlation between BMI and ICIs response, that there is a complex relationship between adipose tissue, tumor cells, and immune cells, and that further preclinical and clinical research is necessary to elucidate this context.

Our study has several limitations, including the retrospective nature of our analysis with the risk of selection bias. Our patient cohort comprised a variety of tumor types, and not all treatments were identical. Additionally, we only evaluated baseline BMI, without taking into account longitudinal changes
during treatment. As our study included patients from a particular geographical region, the BMI distribution reflected regional characteristics.

In conclusion, we found no associations between outcomes and BMI in this study. Our results suggest that it should be reconsidered that BMI is a predictor of the responses of ICIs. Additional clinical and translational studies are needed to elucidate the ‘obesity paradox.’

**Declarations**

**Funding**

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

**Competing Interests**

The authors have no relevant financial or non-financial interests to disclose.

**Author Contributions**

GAŞ: Conceptualization, data curation, writing-original draft preparation. NSÖ: Visualization, investigation. ED: Writing, data curation. GAŞ, MG: Methodology, software. HT: Supervision, editing. MÖ: Reviewing and editing.

**Data Availability**

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval**

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İstanbul University Cerrahpaşa (Date 25.4.2023/No E-83045809-604.01.01-672007).

**References**


Figure 1

**A**

Median PFS
BMI <25: 7.7
BMI ≥25: 8.7
HR (95% CI), 1.03 (0.69-1.53)
*P* = 0.865

**B**

Median OS
BMI <25: 22.1
BMI ≥25: 21.3
HR (95% CI), 1.02 (0.67-1.57)
*P* = 0.898
Progression-free survival (PFS) (A) and overall survival (OS) (B) in patients with BMI<25 and BMI≥25.

Figure 2

Progression-free survival (PFS) (A) and overall survival (OS) (B) in patients with normal weight, overweight and obesity.