

Body mass index and type 2 diabetes mellitus as metabolic determinants of immune checkpoint inhibitors response in melanoma

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ABSTRACT

Background Immune checkpoint inhibitors (ICIs) have improved survival outcomes in melanoma. Studies exploring the correlations between body mass index (BMI), type 2 diabetes (T2DM) and the outcomes of ICI treatment have yielded inconsistent results. In this study, we aim to investigate the effects of BMI and T2DM on survival outcomes of patients with melanoma receiving ICIs.

Methods A retrospective multicenter cohort of patients with melanoma treated with ICIs was analyzed. Overall survival was evaluated with Kaplan-Meier survival analysis, univariate Cox and multivariate Cox proportional hazards model. Propensity-score matching (1:1) analysis between overweight and non-overweight groups was done and survival analyses and Cox analyses were performed again. Subgroup analyses and secondary analyses stratifying patients with different weights and T2DM statuses were also performed.

Results A total of 2,078 patients were included, of whom 1,412 were overweight (BMI \geq 25 kg/m²) and 666 were non-overweight (BMI<25 kg/m²). Overweight patients had better overall survival compared with non-overweight (median 71.7 vs 36.7 months, $p<0.001$). Patients with T2DM had worse overall survival compared with patients without T2DM (median 28.5 vs 67.3 months, $p<0.001$). After propensity-score matching (666 overweight were matched to 666 non-overweight), overweight patients remained to have better overall survival compared with non-overweight (median 67.7 vs 36.7 months, $p<0.001$). Patients with T2DM had worse survival in univariate Cox (HR 1.71, (95% CI: 1.20 to 2.43)) and multivariate Cox (HR 1.58, (95% CI: 1.08 to 2.31)) analyses. Overweight patients without T2DM had the best survival outcomes compared with other weight and T2DM combinations.

Conclusion In patients with melanoma treated with ICIs, being overweight had better survival outcomes compared with non-overweight. Having T2DM was associated with worse survival compared with those without T2DM. Further studies are needed to investigate the underlying mechanisms of these associations.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment in recent years and have significantly improved survival

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Metabolic factors such as body mass index and type 2 diabetes mellitus (T2DM) have been found to influence the outcomes of patients with melanoma receiving immune checkpoint inhibitors. However, the effects of these metabolic factors on patient outcomes have been inconsistent across studies.

WHAT THIS STUDY ADDS

⇒ In this large propensity score-matched cohort study evaluating patients with melanoma treated with immune checkpoint inhibitors, being overweight had better survival outcomes compared with non-overweight. Having T2DM was associated with worse survival compared with those without T2DM. Being overweight and without T2DM was associated with the best overall survival among all subgroups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Metabolic factors such as body mass index and T2DM may be used to predict the outcomes of patients with melanoma receiving immune checkpoint inhibitors. Further studies are needed to elucidate the complex relationships between body composition, T2DM, and the responses to immune checkpoint inhibitors.

outcomes in multiple malignancies, including melanoma.^{1–10} However, the treatment response of ICIs has remained heterogeneous among different patient cohorts, highlighting the importance of discovering predictive biomarkers.¹¹ Metabolic factors such as body mass index (BMI, defined as weight divided by the square of height¹² and type 2 diabetes mellitus (T2DM) have been investigated for their association with treatment outcomes for patients with cancer who received ICIs.^{13–30} In melanoma, several studies have investigated the association between being overweight or obese (defined as BMI \geq 25 kg/m² and BMI \geq 30 kg/m², respectively,¹² and treatment



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outcomes of ICIs.^{13–21} While most studies have shown possible positive survival outcomes in overweight/obese patients treated with ICIs (compared with patients with BMI < 25 kg/m²),^{13–20} a recent meta-analysis study showed no significant survival benefit in overweight/obese patient groups.²¹

On the other hand, the relationship between T2DM and ICI treatment outcomes remains complicated. Recent reports have shown that patients with cancer with T2DM might have a negative survival outcome when treated with ICIs compared with patients without T2DM.^{29–30} However, when investigating the effect of glucose-lowering medications, especially metformin, on ICI survival outcomes, there are mixed reports with both positive and negative associations.^{29–32} In melanoma specifically, additional studies are needed to investigate the relationship between T2DM and ICI treatment outcomes.

In recent years, a new phenotype of obesity has been proposed, termed “metabolically healthy obesity (MHO)”, which describes a subgroup of obese individuals that lack cardiometabolic comorbidities.^{33–37} Studies have shown that MHO patients might have more favorable mortality outcomes compared with patients with metabolically unhealthy obesity (MUO), including cancer mortalities.^{33–38} This phenomenon should also be considered when elucidating the heterogeneous effect of different metabolic derangements on ICI treatment outcomes.

In this study, we aimed to investigate the impact of different metabolic factors such as overweight/obesity and T2DM on the survival outcomes of patients with melanoma treated with ICIs with a large real-world multicenter cohort.

METHODS

Study design, setting, and population

This was a multicenter, retrospective cohort study with propensity-score matching analysis.³⁹ The database was constructed using a protocol approved by institutional review boards at the Mass General Brigham (MGB), detailing electronic medical records access in patients with diagnosis of metastatic or non-metastatic melanoma who have received ICIs including anti-programmed cell death protein 1 (anti-PD-1, eg, pembrolizumab, nivolumab), anti-programmed cell death-ligand 1 (anti-PD-L1, eg, atezolizumab), anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4, eg, ipilimumab) and anti-lymphocyte-activation gene-3 (eg, relatlimab) therapies between January 2014 and December 2022 within the hospitals in the MGB network. The index date was determined as the date of the first ICI administration after the diagnosis of melanoma. Patients who had unknown data for the ICI therapy, multiple cancer diagnoses and incomplete records were excluded from the study. Patients were classified into overweight (BMI ≥ 25 kg/m²) or non-overweight (BMI < 25 kg/m²) based on the WHO definitions.¹²

Covariates and outcomes

We extracted clinical characteristics including patient demographics, baseline glucose level, underlying comorbidities (defined by International Classification of Diseases (ICD) codes), and medication usage at the time of starting ICI treatment from the MGB Research Patient Data Registry (RPDR) and Severe Immunotherapy Complications (SIC) registry. Oncology-specific data including the specific type of ICI, date of ICI initiation, and the presence of metastatic disease were also collected from the RPDR and SIC registry. The primary endpoint was all-cause mortality in overweight and non-overweight patients.

Statistical analysis

Patient characteristics were compared between overweight and non-overweight groups with appropriate statistical tests: t-test for continuous variables, and χ^2 for discrete variables. We performed Kaplan-Meier analysis to evaluate time of survival between the BMI groups (overweight or non-overweight) and T2DM status (with T2DM and without T2DM). Time of survival was calculated from the index date to the date of death or date of last follow-up, which censoring would occur. Univariate and multivariate Cox proportional hazards model was used to evaluate the association between baseline characteristic variables and overall survival. The proportional HR assumption was assessed using the Schoenfeld residuals. In the multivariate Cox proportional hazards analysis, we incorporated variables including age, sex, metastatic disease, different ICI types and underlying comorbidities to further adjust for baseline differences.

We later performed a 1:1 propensity-score matching³⁹ to minimize the baseline differences between the overweight and non-overweight cohorts. The propensity score was constructed using the following predetermined variables: age, sex, metastatic disease, ICI type, underlying comorbidities including hypertension, T2DM, hyperlipidemia, ischemic heart disease, chronic obstructive pulmonary disease, and statin use. We selected these variables because they predict the likelihood of the exposure (ie, overweight or non-overweight), are potential confounders, or are related to the primary outcome. The selection of such variables has been shown to provide optimal propensity-score matching models.⁴⁰ We used a nearest neighbor matching approach, with a caliper set at 0.2 of the SD of the logit of the propensity score. After matching, we compared the differences in clinical characteristics between patients who were overweight and non-overweight using standardized mean differences (SMD). A covariate with less than 10% SMD is considered adequately matched.

After propensity-score matching, Kaplan-Meier analysis was used to evaluate the time of survival between the BMI groups (overweight or non-overweight) of the new cohort. We subsequently analyzed the new cohort using the univariate and multivariate Cox proportional hazards model as described previously. Similarly, we incorporated

variables including age, sex, metastatic disease, different ICI types, and underlying comorbidities to adjust for baseline differences in the multivariate model. In subgroup analyses, we assessed the effects of BMI on overall survival in prespecified subgroups including age, sex, metastatic disease, different ICI types, and underlying comorbidities. We also performed Kaplan-Meier analyses to evaluate the effect of BMI in both male and female subgroups.

In secondary analyses, we compared the survival of patients across four different combination groups: BMI \geq 25 kg/m² with or without diabetes mellitus and BMI $<$ 25 kg/m² with or without diabetes mellitus. We also compared the survival of patients across five different BMI (kg/m²) groups: underweight (BMI $<$ 18.5), healthy weight (18.5 \leq BMI $<$ 25), overweight (25 \leq BMI $<$ 30), obese (30 \leq BMI $<$ 35), and severely obese (BMI \geq 35). In addition, Kaplan-Meier analyses comparing patients with or without baseline hyperglycemia (glucose level \geq 126 mg/dL) and their BMI groups and DM status were also performed.

A *p* value $<$ 0.05 for a two-sided test was used to indicate statistical significance. The analyses were conducted using Stata V.16.0 (StataCorp LLC, College Station, Texas, USA) and R statistical software V.4.3 (<http://www.r-project.org/>).

RESULTS

Patient demographics

We identified 2,254 patients with melanoma who were treated with ICIs between January 2014 and December 2022 cross referencing the MGB RPDR database and SIC registry. After excluding patients with unknown data for the ICI therapy, multiple cancer diagnosis and incomplete records, 2,078 patients remained eligible for analysis (online supplemental figure 1). Baseline characteristics were shown in table 1. Among the 2,078 patients, 1,412 patients were overweight and 666 patients were non-overweight. Among all patients, 43% received pembrolizumab, 31% received ipilimumab and nivolumab combination, 15% received nivolumab, 9.4% received ipilimumab, 1% received nivolumab and relatlimab combination and 1% received atezolizumab. Patients who were overweight had a higher proportion of underlying comorbidities including hypertension, T2DM and hyperlipidemia. Overweight patients were also more commonly prescribed cardiovascular and metabolic medications than non-overweight patients.

Analysis for the overall cohort

Kaplan-Meier analysis showed that overweight patients (BMI \geq 25 kg/m²) had a longer overall survival compared with non-overweight patients (BMI $<$ 25 kg/m²) (log-rank, *p* $<$ 0.001; median 71.7 months vs 36.7 months) (figure 1A). When comparing patients with T2DM versus without T2DM, Kaplan-Meier analysis showed patients with T2DM had worse survival (log-rank, *p* $<$ 0.001; median 28.5 months vs 67.3 months) (figure 1B). Univariate and multivariate Cox regression analyses of overall survival

were performed and shown in online supplemental table 1. In the univariate Cox proportional hazard model, BMI \geq 25 kg/m² was associated with an approximately 30% reduction in the risk of mortality (HR, 0.68 (95% CI: 0.60 to 0.79), *p* $<$ 0.001). In the multivariate Cox proportional hazard model, BMI \geq 25 kg/m² remained associated with a reduction in the risk of mortality after adjusting for the variables including age, sex, metastatic disease, different ICI type and underlying comorbidities (HR, 0.69 (95% CI: 0.60 to 0.80), *p* $<$ 0.001). In univariate Cox analysis, T2DM was associated with a 46% increased risk of mortality (HR, 1.46 (95% CI: 1.19 to 1.80), *p* $<$ 0.001) and similarly so after adjusting for the variables in multivariate Cox analysis (HR, 1.44 (95% CI: 1.14 to 1.81), *p*=0.002).

In addition, in univariate Cox analysis, other comorbidities such as hypertension, heart failure and chronic kidney disease showed statistically significant association with increased risk of mortality. However, only heart failure remained with a statistically significant association in the multivariate Cox analysis (HR, 1.39 (95% CI: 1.02 to 1.90), *p*=0.036). Furthermore, hyperlipidemia did not show a significant association with mortality in univariate Cox analysis, but it showed a statistically significant association with decreased risk of mortality in the multivariate Cox model (HR, 0.83 (95% CI: 0.70 to 0.99), *p*=0.035).

Propensity-score matching analysis

A total of 666 overweight patients were matched to 666 non-overweight patients. After propensity-score matching, all covariates including underlying comorbidities were well balanced between the two groups (table 2 and online supplemental figure 2).

During a median follow-up period of 17.3 (IQR: 6.6–43.7) months, 235 (35%) and 303 (45%) patients died in the overweight and non-overweight groups, respectively. Kaplan-Meier analysis of the propensity-score matched cohort showed that overweight patients (BMI \geq 25 kg/m²) had higher overall survival compared with non-overweight patients (BMI $<$ 25 kg/m²) (log-rank, *p* $<$ 0.001; median 67.7 months vs 36.7 months) (figure 2). Univariate and multivariate Cox analyses of the overall survival of the propensity-score matched cohort were shown in table 3. In univariate Cox analysis, BMI \geq 25 kg/m² was significantly associated with a 29% reduction in the risk of mortality (HR, 0.71 (95% CI: 0.60 to 0.84), *p* $<$ 0.001). In multivariate Cox analysis, BMI \geq 25 kg/m² remained significantly associated with a reduction in the risk of mortality after adjusting for the variables listed (HR, 0.71 (95% CI: 0.60 to 0.84), *p* $<$ 0.001). In the univariate Cox proportional hazard model, T2DM was associated with a 71% increased risk of mortality (HR, 1.71 (95% CI: 1.20 to 2.43), *p*=0.003) and remained associated with an increased risk after adjusting for the variables in multivariate analysis (HR, 1.58 (95% CI: 1.08 to 2.31), *p*=0.019).

Other comorbidities such as hypertension, heart failure and chronic kidney disease still showed statistically significant association with increased risk of all-cause mortality

Table 1 Patient baseline characteristics

	Total N=2,078	BMI \geq 25 (overweight) N=1,412	BMI<25 (non-overweight) N=666	P value
Age	67 (57–75)	66 (57–75)	67 (56–76)	0.66
Male	1283 (62%)	949 (67%)	334 (50%)	<0.001
Metastatic disease	1180 (57%)	785 (56%)	395 (59%)	0.11
Glucose on ICI initiation, median	106 (95–124)	108 (97–127)	103 (91–118)	<0.001
ICI type				
Atezolizumab	18 (1%)	13 (1%)	5 (1%)	0.22
Ipilimumab	195 (9%)	121 (9%)	74 (11%)	
Ipilimumab and nivolumab	635 (31%)	422 (30%)	213 (32%)	
Nivolumab	305 (15%)	220 (16%)	85 (13%)	
Nivolumab and relatlimab	30 (1%)	19 (1%)	11 (2%)	
Pembrolizumab	895 (43%)	617 (44%)	278 (42%)	
Targeted therapy				
MEK inhibitors	23 (1%)	13 (1%)	10 (2%)	0.24
BRAF inhibitors	29 (1%)	16 (1%)	13 (2%)	0.14
Underlying comorbidities				
T2DM	215 (10%)	184 (13%)	31 (5%)	<0.001
Hypertension	875 (42%)	666 (47%)	209 (31%)	<0.001
Hyperlipidemia	734 (35%)	558 (40%)	176 (26%)	<0.001
Heart failure	99 (5%)	76 (5%)	23 (3%)	0.054
Ischemic heart disease	11 (1%)	9 (1%)	2 (0%)	0.32
Chronic kidney disease	124 (6%)	91 (6%)	33 (5%)	0.18
COPD	103 (5%)	75 (5%)	28 (4%)	0.28
Cardiovascular and metabolic medications				
Beta-blocker	461 (22%)	342 (24%)	119 (18%)	0.001
Diuretics	191 (9%)	136 (10%)	55 (8%)	0.31
Calcium channel blocker	261 (13%)	192 (14%)	69 (10%)	0.038
Aspirin	249 (12%)	177 (13%)	72 (11%)	0.26
Renin-angiotensin system inhibitor	384 (18%)	300 (21%)	84 (13%)	<0.001
Metformin	121 (6%)	102 (7%)	19 (3%)	<0.001
Insulin	87 (4%)	76 (5%)	11 (2%)	<0.001
Statin	452 (22%)	343 (24%)	109 (16%)	<0.001

BMI unit: kg/m².

Glucose unit: mg/dL.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICI, immune checkpoint inhibitor; T2DM, type 2 diabetes mellitus.

in univariate Cox analysis, however, none of these comorbidities showed statistically significant association in the multivariate Cox analysis. On the other hand, hyperlipidemia also did not show a significant association with all-cause mortality in both univariate and multivariate Cox analysis.

Subgroup analysis

In our subgroup analysis of the propensity-score matched cohort, overweight (BMI \geq 25 kg/m²) was mostly associated with a reduction or a trend towards

a lower risk of all-cause mortality across different subgroups including age, sex, presence of metastatic disease and underlying comorbidities (online supplemental figure 3). In the analysis of different ICI regimens, overweight appeared to be associated with a statistically significant reduction in mortality in patients receiving anti-PD-1/PD-L1 therapy (HR, 0.64 (95% CI: 0.51 to 0.80)); however, overweight did not appear to have statistical significance in reduction in mortality in patients receiving anti-CTLA-4 (HR, 0.70 (95% CI: 0.43

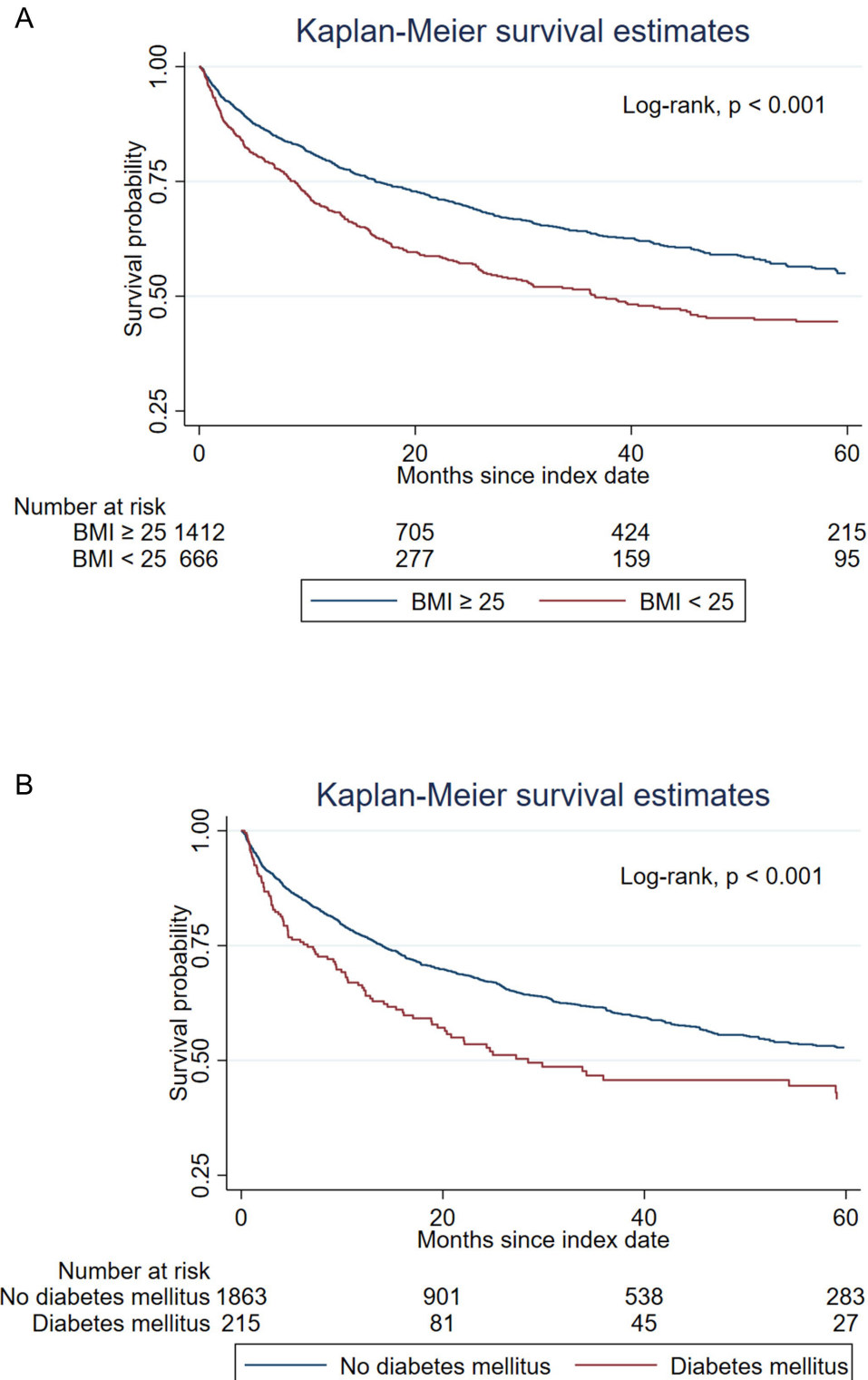


Figure 1 Kaplan-Meier survival analysis comparing overall survival between patients with (A) BMI ≥ 25 kg/m² and BMI < 25 kg/m² (median survival 71.7 (IQR: 16.3 to not reached) months vs 36.7 (IQR: 8.8 to not reached) months), and (B) with and without type 2 diabetes mellitus (median survival 28.5 (IQR: 6.6 to not reached) months vs 67.3 (IQR: 14.0 to not reached) months). BMI, body mass index.

to 1.14) or anti-PD-1/anti-CTLA-4 combination (HR, 0.87 (95% CI: 0.63 to 1.19)).

Additional Kaplan-Meier analysis comparing overweight and non-overweight in male patients (online supplemental figure 4A). Log-rank, ($p=0.001$; median 67.7

months vs 36.6 months) and in female patients (online supplemental figure 4B). Log-rank, ($p=0.012$; median survival 67.7 months vs 36.3 months) were also performed, which showed consistent favorable survival outcomes of overweight among both male and female patients. We also

Table 2 Patient baseline characteristics after propensity-score matching

	Total N=1,332	BMI≥25 (overweight) N=666	BMI<25 (non-overweight) N=666	P value
Age	67 (57–76)	67 (57–75)	67 (56–76)	0.75
Male	669 (50%)	335 (50%)	334 (50%)	0.96
Metastatic disease	780 (59%)	385 (58%)	395 (59%)	0.58
Glucose on ICI initiation, median	104 (93–121)	105 (94–123)	103 (91–118)	<0.001
ICI type				
Atezolizumab	10 (1%)	5 (1%)	5 (1%)	0.3
Ipilimumab	137 (10%)	63 (9%)	74 (11%)	
Ipilimumab and nivolumab	409 (31%)	196 (29%)	213 (32%)	
Nivolumab	198 (15%)	113 (17%)	85 (13%)	
Nivolumab and relatlimab	19 (1%)	8 (1%)	11 (2%)	
Pembrolizumab	559 (42%)	281 (42%)	278 (42%)	
Targeted therapy				
MEK inhibitors	18 (1%)	8 (1%)	10 (2%)	0.64
BRAF inhibitors	19 (1%)	6 (1%)	13 (2%)	0.11
Underlying comorbidities				
T2DM	62 (5%)	31 (5%)	31 (5%)	1
Hypertension	412 (31%)	203 (30%)	209 (31%)	0.72
Hyperlipidemia	352 (26%)	176 (26%)	176 (26%)	1
Heart failure	51 (4%)	28 (4%)	23 (3%)	0.48
Ischemic heart disease	5 (0%)	3 (0%)	2 (0%)	0.65
Chronic kidney disease	56 (4%)	23 (3%)	33 (5%)	0.17
COPD	57 (4%)	29 (4%)	28 (4%)	0.89
Cardiovascular and metabolic medications				
Beta-blocker	234 (18%)	115 (17%)	119 (18%)	0.77
Diuretics	109 (8%)	54 (8%)	55 (8%)	0.92
Calcium channel blocker	129 (10%)	60 (9%)	69 (10%)	0.4
Aspirin	136 (10%)	64 (10%)	72 (11%)	0.47
Renin-angiotensin system inhibitor	185 (14%)	101 (15%)	84 (13%)	0.18
Metformin	46 (3%)	27 (4%)	19 (3%)	0.23
Insulin	22 (2%)	11 (2%)	11 (2%)	1.00
Statin	208 (16%)	99 (15%)	109 (16%)	0.45

BMI unit: kg/m².

Glucose unit: mg/dL.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICI, immune checkpoint inhibitor; T2DM, type 2 diabetes mellitus.

Secondary analyses

Furthermore, we compared the survival of patients in the following four subgroups: Patients with BMI≥25 kg/m² with or without T2DM, and patients with BMI<25 kg/m² with or without T2DM. Kaplan-Meier analysis showed that patients with BMI≥25 kg/m² and without T2DM had the highest median overall survival (median 67.7 months) among the four subgroups, followed by patients who had BMI≥25 kg/m² with T2DM (median 38.6 months), and followed by BMI<25 kg/m² without T2DM (median 27.3 months). Patients who had a BMI<25 kg/m² and

with T2DM had the worse overall survival (median 12.0 months). Log-rank p value<0.001 (figure 3A).

We also performed Kaplan-Meier analysis in five different BMI groups (underweight (BMI<18.5 kg/m²), healthy weight (18.5 kg/m²≤BMI<25 kg/m²), overweight (25 kg/m²≤BMI<30 kg/m²), obese (30 kg/m²≤BMI<35 kg/m²), and severely obese (BMI≥35 kg/m²)). Results showed that patients who were overweight (median 67.7 months), obese (median not reached months), or severely obese (median 59.0 months) had higher overall survival compared with patients who were underweight (median

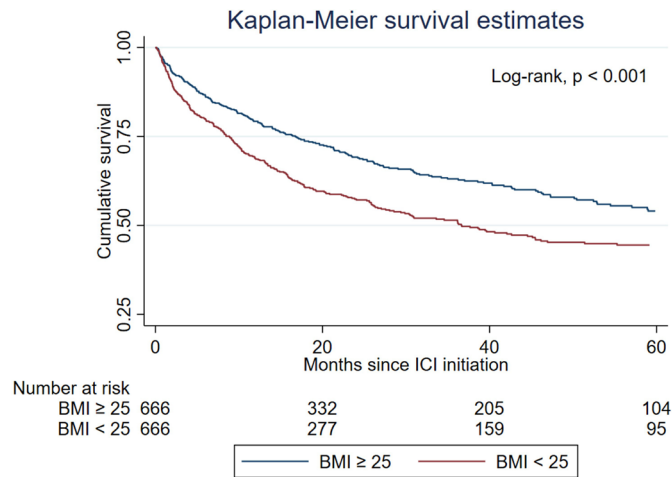


Figure 2 Kaplan-Meier survival analysis comparing overall survival between BMI ≥ 25 kg/m² and BMI < 25 kg/m² after propensity-score matching. Median survival 67.7 (IQR: 16.7 to not reached) months versus 36.7 (IQR: 8.8 to not reached) months. BMI, body mass index.

11.2 months) or healthy weight (median 38.6 months). Log-rank p value < 0.001 (figure 3B).

In addition, Kaplan-Meier analyses comparing patients with or without baseline hyperglycemia (glucose level ≥ 126 mg/dL) and their BMI groups (online supplemental figure 5) as well as their DM status (online supplemental figure 6) were performed. Patients with baseline hyperglycemia experienced worse overall survival in the respective BMI groups and DM groups.

DISCUSSION

In this large retrospective cohort study with propensity-score matching analysis, we found that being overweight (BMI ≥ 25 kg/m²) was associated with improved overall

survival among patients with melanoma undergoing ICI therapy, while patients with T2DM were associated with worse overall survival. Furthermore, patients with BMI ≥ 25 kg/m² without T2DM had the highest median overall survival compared with other groups of BMI/T2DM combinations. Among all patients with BMI ≥ 25 kg/m², there were no significant differences between those who were overweight, obese, and severely obese. To the best of our knowledge, this was the largest retrospective cohort study to date to investigate the association between BMI, T2DM, and survival outcomes in patients with melanoma undergoing ICI therapy.

There have been several studies investigating the association between BMI and survival among patients with melanoma receiving ICI therapy, but the results have been inconsistent.²¹ In a multicenter cohort study conducted by McQuade *et al*, obesity (BMI ≥ 30 kg/m²) was associated with improved progression-free survival and overall survival among male patients receiving anti-CTLA-4 or anti-PD-1/PD-L1 inhibitors.¹⁴ Similarly, in another cohort study performed by Naik *et al*, overweight to obese (25 kg/m² ≤ BMI < 35 kg/m²) male patients receiving anti-PD-1 monotherapy or combination ICI therapy also experienced improved survival compared with normal-weight patients.¹⁵ Nevertheless, many studies did not find an association between BMI and survival outcomes.¹⁶⁻¹⁸ For example, in a multicenter cohort study performed by Di Filippo *et al*, a higher BMI was not associated with an improved progression-free survival or overall survival among patients receiving an anti-PD-1 monotherapy or combination ICI therapy.¹⁸ In our study, we found an improved overall survival among overweight patients compared with those who were non-overweight. The results remained consistent in propensity-score matched analysis. Furthermore, these survival benefits

Table 3 Cox regression analysis comparing all-cause mortality after-propensity-score matching

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CHR)	P value
Age	1.02 (1.01 to 1.03)	<0.001	1.02 (1.01 to 1.03)	<0.001
Sex	1.00 (0.85 to 1.19)	0.96	0.87 (0.73 to 1.04)	0.125
Metastatic disease	1.24 (1.04 to 1.48)	0.017	1.24 (1.04 to 1.48)	0.018
ICI type	0.99 (0.95 to 1.02)	0.49	0.96 (0.93 to 1.00)	0.045
BMI ≥ 25	0.71 (0.60 to 0.84)	<0.001	0.71 (0.60 to 0.84)	<0.001
T2DM	1.71 (1.20 to 2.43)	0.003	1.58 (1.08 to 2.31)	0.019
Hypertension	1.26 (1.05 to 1.51)	0.011	0.91 (0.73 to 1.14)	0.42
Heart failure	2.10 (1.45 to 3.04)	<0.001	1.30 (0.85 to 1.98)	0.22
Hyperlipidemia	1.13 (0.93 to 1.37)	0.21	0.85 (0.68 to 1.07)	0.162
Chronic kidney disease	2.00 (1.41 to 2.85)	<0.001	1.35 (0.91 to 1.99)	0.135
COPD	1.27 (0.85 to 1.90)	0.24	1.05 (0.69 to 1.60)	0.81
Ischemic heart disease	0.76 (0.19 to 3.06)	0.70	0.52 (0.12 to 2.20)	0.37

BMI unit: kg/m².
COPD, chronic obstructive pulmonary disease; ICI, immune checkpoint inhibitor; T2DM, type 2 diabetes mellitus.

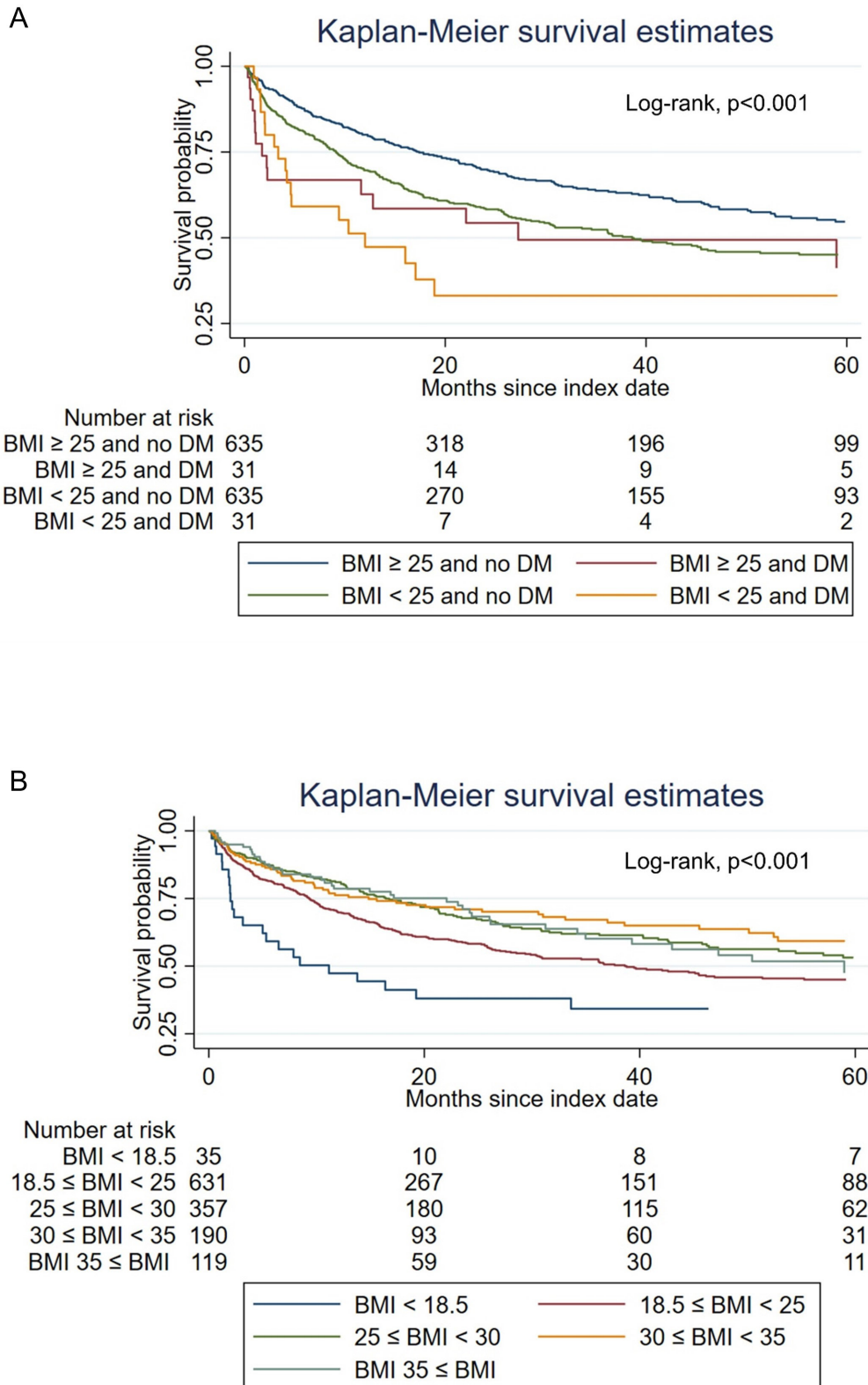


Figure 3 Kaplan-Meier survival analysis comparing overall survival (A) between BMI ≥ 25 kg/m² with T2DM (median 38.6 (IQR: 9.1 to not reached) months) and without T2DM (median 67.7 (IQR: 17.4 to not reached) months), and BMI < 25 kg/m² with T2DM (median 12.0 (IQR: 3.4 to not reached) months) and without T2DM (median 27.3 (IQR: 1.7 to not reached) months), and (B) between five different BMI groups (underweight: median 11.2 (IQR: 2.0 to 64.6) months; healthy weight: median 38.6 (IQR: 9.3 to not reached) months; overweight: median 67.7 (IQR: 16.4 to 103.4) months; obese: median not reached (IQR: 14.8 to not reached) months; severely obese; median 59.0 (IQR: 22.1 to not reached) months) (BMI unit kg/m²). BMI, body mass index; T2DM, type 2 diabetes mellitus.

were observed consistently across the overweight, obese, and severely obese categories. In our subgroup analysis, the survival benefit of overweight remained consistent in both male and female patients. Interestingly, when looking into treatment types, although patients with $\text{BMI} \geq 25 \text{ kg/m}^2$ had favorable survival outcomes when receiving anti-PD-1/PD-L1 monotherapy, anti-CTLA-4 monotherapy and anti-CTLA-4 with anti-PD-1 combination therapies, only anti-PD-1/PD-L1 group had statistical significance in HR. It was unclear why there had been such a discordance among the published literature. However, factors such as differences in study population including cohort size, underlying comorbidities, cancer stages, ICI regimen, and differences in analysis such as adjustments for potential confounders, could all have contributed to the discrepancies in the reported results.

The mechanism underlying this observation, coined the “obesity paradox”, has not been fully elucidated. However, preclinical studies have shown that adipose tissues, which are increased in patients with higher BMIs, may exert immunomodulatory effects via the production of various cytokines and hormones that can activate antitumor immune responses.⁴¹ Furthermore, patients with higher BMIs have increased tumor-infiltrating cytotoxic T-lymphocytes in the tumor microenvironment and hence may be primed to provide a more efficacious response to ICIs.⁴²

Previously, there were few studies investigating pre-existing T2DM affecting patients with cancer undergoing ICI treatment.^{29–30} Cortellini *et al* previously reported an association between diabetes, use of glucose-lowering medications, and poorer outcomes in patients treated with ICIs in a mixed cancer cohort of 1,395 patients, among which 345 were patients with melanoma.³⁰ To our knowledge, no dedicated melanoma study has established this association. Our study found that patients with melanoma with T2DM at baseline had worse overall survival compared with patients without T2DM when receiving ICI therapies. Furthermore, we found that overweight patients without T2DM experienced the best overall survival compared with overweight patients with T2DM and non-overweight patients with or without T2DM. Not surprisingly, non-overweight patients with T2DM experienced the worst overall survival. We also found that patients with baseline hyperglycemia experienced worse overall survival in the respective BMI groups and DM groups. Furthermore, patients with baseline hyperglycemia and no DM experienced similar survival outcomes compared with patients with DM. Our findings could be a possible validation of potential health benefits in the recently proposed concept of “metabolically healthy obesity (MHO)” status.^{33–37} Previously, Calori *et al*³⁸ had shown that obese subjects with insulin resistance (ie, MUO) had higher cancer mortality compared with non-obese insulin-sensitive subjects. No significant mortality difference was found comparing obese insulin-sensitive (ie, MHO) subjects with non-obese insulin-sensitive subjects. Our results support the hypothesis that patients

with MHO cancer will have potentially favorable outcomes when treated with ICIs. Further studies are needed to further elucidate this complex interaction.

We also had additional observations that patients with heart failure at the time of starting ICI therapy had a higher risk of all-cause mortality in multivariate Cox analyses in the overall cohort but not in the propensity-score matched cohort. Previous studies have shown that patients with pre-existing cardiac conditions such as heart failure may be prone to developing ICI-mediated cardiotoxicity and related immune-related adverse events when treated with ICIs.^{43–47} Heart failure was also a risk factor for developing major adverse cardiovascular events for patients with cancer treated with ICIs.⁴⁸ These phenomena could potentially explain our observations of less favorable outcomes in the overall patient cohort. However, this association might be due to a confounding effect as we did not have the same observation in the propensity-score-matched cohort. Our study was also limited by a lack of cause of death annotation, therefore we were not able to distinguish cardiovascular-related mortality including ICI-toxicity from other causes of death. Additional research exploring the effect of pre-existing heart failure on patients with melanoma treated with ICIs is needed.

Another observation that we made was that patients with hyperlipidemia showed a statistically significant association with decreased risk of all-cause mortality in the multivariate Cox model in the overall patient cohort but not in the propensity-score matched cohort. There were recent studies showing that higher blood cholesterol level was associated with better outcomes in patients with cancer treated with ICIs.^{49–52} While our observation in the overall patient cohort is consistent with previous studies, we did not see the same association in the propensity-score-matched cohort. This could also be due to the possible confounding effect between high BMI and hyperlipidemia. By performing propensity-score matching, we removed this effect and showed that hyperlipidemia alone was not associated with a reduced risk of mortality. Further clinical and mechanistic studies are needed to understand the complicated interaction between obesity, hyperlipidemia and its effect on ICI treatment.

One major strength of our study was that we used propensity-score matching and subsequently multivariate analyses to minimize the baseline differences and potential confounders between patients who were overweight and non-overweight. The large sample size allowed us to explore possible effect modifiers in different subgroups of patients. Nevertheless, there were several limitations that need to be acknowledged. This was an observational study and despite the use of propensity-score matching and multivariate analyses, there were likely residual confounders that were not included in the models. We did not have data on the causes of death, ICI toxicity, and tumor-based endpoints such as relapse-free or progression-free survival and response to treatment. Therefore, we could not be entirely certain that



the survival benefits associated with a higher BMI were attributed to an improved response to ICI therapy or other non-oncologic mechanisms. The different lines of melanoma therapy might affect our survival analysis as well. In both cohorts, about 1–2% of patients had received BRAF/MEK inhibitors prior to ICI. Also, although we used the first ICI encounter in the system as the patients' ICI start date, we could not exclude a small number of patients who might have received ICIs in different institutions prior to the encounter. Although this was a multicenter study, the hospitals are in the same healthcare system in the New England area which may limit its generalizability. The identification of most comorbidities and conditions relied on physician diagnoses and ICD coding, which could potentially introduce some degree of inaccuracy or incompleteness of the data. Lastly, we only had the data on BMI, which may not be a representative surrogate for body composition as it does not differentiate between skeletal muscle and adipose tissue.⁵³

CONCLUSION

In this large retrospective cohort study with propensity-score matching analysis, overweight patients with melanoma had better overall survival compared with non-overweight patients when treated with ICIs, particularly those undergoing anti-PD-1 therapy. Patients with T2DM were associated with worse overall survival compared with patients without T2DM. Overweight patients without T2DM experienced the best overall survival compared with other groups. Further prospective randomized trials and molecular mechanistic studies are needed to further investigate the relationships between BMI, T2DM and patients with melanoma treated with ICIs.

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