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RESEARCH ARTICLE

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Obesity is not associated with disease-free interval, melanoma-specific survival, or overall survival in patients with clinical stage IB-II melanoma after SLNB

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Abstract

Background and Objectives: Clinicopathologic characteristics have prognostic value in clinical stage IB-II patients with melanoma. Little is known about the prognostic value of obesity that has been associated with an increased risk for several cancer types and worsened prognosis after diagnosis. This study aims to examine effects of obesity on outcome in patients with clinical stage IB-II melanoma.

Methods: Prospectively recorded data of patients with clinical stage IB-II melanoma who underwent sentinel lymph node biopsy (SLNB) between 1995 and 2018 at the University Medical Center of Groningen were collected from medical files and retrospectively analyzed. Cox-regression analyses were used to determine associations between obesity (body mass index> 30), tumor (location, histology, Breslow-thickness, ulceration, mitotic rate, SLN-status) and patient-related variables (gender, age, and social-economic-status [SES]) and disease-free interval (DFI), melanoma-specific survival (MSS), and overall survival (OS).

Results: Of the 715 patients, 355 (49.7%) were women, median age was 55 (range 18.6-89) years, 149 (20.8%) were obese. Obesity did not significantly affect DFI (adjusted hazard ratio [HR] = 1.40; 95% confidence interval [CI] = 0.98–2.00; $p = 0.06$), MSS (adjusted HR = 1.48;95%CI = 0.97–2.25; $p = 0.07$), and OS (adjusted HR = 1.25; 95% CI = 0.85–1.85; $p = 0.25$). Increased age, arm location, increased Breslow-thickness, ulceration, increased mitotic rate, and positive SLN-status were significantly associated with decreased DFI, MSS, and OS. Histology, sex, and SES were not associated.

Conclusion: Obesity was not associated with DFI, MSS, or OS in patients with clinical stage IB-II melanoma who underwent SLNB.

KEYWORDS
melanoma, melanoma-related associations, obesity, recurrence, sociodemographic, survival

1 | INTRODUCTION

In the Netherlands, the annual incidence of melanoma doubled from 3604 to 7127 new cases between 2005 and 2019. Notably, the incidence specifically increased among people ≥45 years of age, while remaining stable among individuals of less than 45 years old.[1] The rising melanoma incidence is mainly attributed to the increased ageing of our population; ozone layer depletion that has amplified the intensity of ultraviolet radiation; and lifestyle changes, such as sun-seeking behavior and tanning bed use.[2,3] There have also been changes in the distribution and stage of melanoma at diagnosis, with a higher percentage of thin melanomas diagnosed, further increasing the prevalence of melanoma diagnosis.[1,4]

Among patients with clinical stage IB-II melanoma, prognosis is based on and well-defined for several tumor and clinicopathologic factors, including primary tumor site; Breslow thickness; mitotic rate, ulceration; regression; histopathologic subtype; sentinel lymph node status; and patient characteristics, such as age and sex.[5–9] For patients with localized melanoma, the most important predictor of outcome is the presence of regional lymph node metastases.[9]

Modern lifestyle changes have led to significantly increased obesity rates. Obesity develops gradually and is commonly associated with high-fat and high-sugar diets, and a physically inactive lifestyle. The prevalence of obesity has doubled since 1980.[10] Worldwide in 2016, among adults over 18 years of age, 39% were overweight, and 13% were obese.[11] In 2018 in the Netherlands, 50% percent of adults were overweight and 15% were obese.[12]

Obesity constitutes a serious public health problem, potentially increasing the risks of many health issues, including diabetes, cardiovascular disease, and musculoskeletal disorders. Obesity is an established endogenous risk and progression factor associated with significantly higher all-cause mortality,[11] and is an important risk factor for the development of various types of cancer—specifically breast, ovary, colorectal, uterine corpus, esophagus (adenocarcinoma), pancreatic, kidney (renal cell), liver, stomach (gastric cardia), gallbladder, thyroid, multiple myeloma, and brain (meningioma) cancers.[13] In the USA, 5% of all new cancers in men and 11% in women are attributable to obesity.[14] While obesity is clearly a risk factor for the development of various cancers, its effects on survival seem to be more complex. According to the obesity paradox, although obesity is associated with an increased risk of cancer compared to normal weight, once cancer is diagnosed, patients with cancer and with a moderately increased body mass index (BMI) exhibit improved outcomes compared to those of normal weight, while patients with morbid obesity and cancer have worse outcomes.[15]

The association between obesity and melanoma risk and outcome remains unclear.[16] A meta-analysis identified an elevated melanoma risk with increasing BMI among men, whereas a pooled case-control study among women demonstrated a null association between BMI and melanoma risk.[17,18] Discrepant results have also been reported regarding outcomes, for example, disease progression and survival. Some studies have found associations between elevated BMI and worse melanoma outcome,[19] while others report no association between BMI and melanoma survival.[20] Additionally, one study found improved outcomes in male obese patients with metastatic melanoma who were treated with immune or targeted therapy, but no significant associations between obesity and outcomes among women or in patients receiving chemotherapy.[21]

Obesity is more prevalent among people with lower socioeconomic status (SES) compared to those with higher SES.[22] Moreover, obesity reportedly shows a negative association with SES among patients with melanoma.[23] Additionally, among patients with melanoma, those with a lower SES (measured as lower median household income) more commonly presented with advanced stages of melanoma and exhibited shorter survival.[24,25]

In the current study, we aimed to investigate the impact of obesity at diagnosis on disease-free interval (DFI), melanoma-specific survival (MSS), and overall survival (OS) among patients with clinical stage IB-II melanoma who underwent sentinel lymph node biopsy (SLNB). Our analyses included adjustment for potential tumor and patient-related confounders, including primary tumor site, histology, Breslow thickness, ulceration, mitosis, sentinel node status, age, gender, and SES. Our hypothesis was that obesity (body mass index [BMI] ≥ 30 kg/m^2) would negatively affect DFI, MSS, and OS.

2 | MATERIALS AND METHODS

2.1 | Patients and procedure

This study, which was approved by the University Medical Center of Groningen (UMCG) Medical Ethics Committee, included all patients with clinical stage IB-II melanoma who underwent SLNB, were ≥18 years of age, and were treated between 1995 and 2018 at the Department of Surgical Oncology of the UMCG. Patients were excluded if their BMI could not be calculated because height and/or weight had not been recorded at diagnosis.

All patients were offered SLNB as standard procedure, with no exclusion criteria. Informed consent was required. The same SLNB procedure was used for all patients, including lymphoscintigraphy with ^{99}mTc nanocolloid and blue dye technique, with an identification rate of 99%, as previously described.[26] No changes were made to the lymphoscintigraphy technique (e.g., SPECT/CT) during the study time period.

The institutional guidelines applicable during the study period (1995–2018) prescribed that SLNB-positive patients, including those with isolated tumor cells in the sentinel lymph node, should undergo completion lymph node dissection (CLND). Patients who participated in the MSLT-II study did not undergo CLND, but rather received follow-up with ultrasound. Among the patients with a positive sentinel lymph node in the present study, none received adjuvant systemic treatment (interferon, drug targeted therapy, or immunotherapy).

From the patients' hospital files, we retrieved prospectively collected relevant data regarding tumor and clinicopathologic characteristics, such as primary tumor site, histology, Breslow

TABLE 1 Patient' and melanoma characteristics of the study group, and of nonobese (BMI < 30) and obese patients (BMI ≥ 30) at diagnosis, and comparisons between groups

Characteristic		Total, *n* = 715	Low BMI < 30, *n* = 566 (79.2%)	High BMI ≥ 30, *n* = 149 (20.8%)	*p* value
Sex	Female	355 (49.7)	277 (48.9)	78 (52.3)	0.46
	Male	360 (50.3)	289 (51.1)	71 (47.7)	
Age	Median (range)	55.0 (18.6-89.0)	53.7 (18.6-89.0)	58.6 (22.9-82.8)	0.008
SES	Low (1)	241 (35.2)	186 (34.4)	55 (38.5)	0.61
	2	167 (24.4)	138 (25.5)	29 (20.3)	
	3	121 (17.7)	92 (17.0)	29 (20.3)	
	4	68 (9.9)	55 (10.2)	13 (9.1)	
	High (5)	87 (12.7)	70 (12.9)	17 (11.9)	
Location	Head/neck	105 (14.7)	85 (15.0)	20 (13.4)	0.37
	Trunk	281 (39.3)	227 (40.1)	54 (36.2)	
	Arm	99 (13.8)	72 (12.7)	27 (18.1)	
	Leg	230 (32.2)	182 (32.2)	48 (32.2)	
Histology	SSM	463 (64.7)	367 (64.8)	96 (64.4)	0.99
	Nodular	189 (26.4)	149 (26.3)	40 (26.8)	
	Other	63 (8.8)	50 (8.8)	13 (8.7)	
Breslow	≤1.0	57 (8.0)	46 (8.1)	11 (7.4)	0.72
	1.1–2.0	288 (40.3)	231 (40.8)	57 (38.3)	
	2.1–4.0	257 (35.9)	204 (36.0)	53 (35.6)	
	>4.0	113 (15.8)	85 (15.0)	28 (18.8)	
Ulceration	No	473 (67.1)	385 (68.9)	88 (60.3)	0.049
	Yes	232 (32.9)	174 (31.1)	58 (39.7)	
Mitotic rate	0–1	282 (43.9)	218 (42.9)	64 (47.8)	0.42
	2–4	171 (26.7)	141 ((27.8)	30 (22.4)	
	5 or higher	189 (29.4)	149 (29.3)	40 (29.8)	
SLNB positive	No	511 (71.5)	409 (72.3)	102 (68.5)	0.36
	Yes	204 (28.5)	157 (27.7)	47 (31.5)	

Abbreviations: BMI, body mass index; SES, social-economic-status; SSM, shifting standards model.

thickness (mm), ulceration, mitosis (number of mitoses per mm^2), and sentinel node status, as well as patient characteristics, including gender, date of birth, body weight, and height.

BMI was calculated as weight (kg) divided by the squared height (m^2) at the time of the primary diagnosis. According to the standard WHO definitions, patients were categorized into two groups: obese (≥30 kg/m^2) or nonobese (<30 kg/m^2).

SES scores are assigned to different postal code areas by the Netherlands Institute for Social Research (SCP), based on information regarding income, employment, and education level.[27] These calculated scores provide an estimated SES for the particular postal code area in which a patient resides, and range from 1 (low SES) to 5 (high SES).

2.2 | Statistical analysis

Statistical analyses were performed using STATA/SE 12.0. Patient characteristics were described, and obese and nonobese patients were compared using χ^2 tests for categorical variables, and a nonparametric test for the equality of medians for age. Cox proportional-hazards models were used to examine associations of clinicopathologic and patient characteristics with DFI, MSS, and OS. We calculated the five-year rates of DFI, MSS, and OS, and assessed the univariable and multivariable hazard ratios (HR) with corresponding 95% confidence intervals (CIs) for the entire follow-up period. DFI was defined as the time from wide excision until recurrence or death due to melanoma, MSS as the time from wide excision until death

due to melanoma, and OS as the time from wide excision until death from any cause. Among the surviving patients, follow-up time was calculated as the time from wide excision until the last outpatient visit. The multivariable model included all variables with $p < 0.05$ in univariable analyses, and obesity, since this was the variable of interest. Survival curves were generated using the Kaplan–Meier method. In addition to using obesity as a categorical variable, we also performed univariable and multivariable analyses with obesity included as a continuous variable with a 1 or 10 units increase. p values of ≤0.05 were considered statistically significant.

3 | RESULTS

3.1 | Patients

SLNB staging was performed in 776 patients of ≥18 years old, at the UMCG, between 1995 and 2018. For 61 patients, the BMI could not be calculated due to a lack of information regarding weight and/or height. Thus, our analyses included 715 patients. Among these patients, 355 (49.7%) were women and 360 men, the median age was 55 years (range, 18.6–89 years), 566 (79.2%) were nonobese, and 149 (20.8%) were obese. The obese and nonobese groups did not significantly differ in patient and clinicopathologic characteristics, except for age and ulceration. Compared to patients with obesity, nonobese patients were significantly younger ($p = 0.008$) and fewer had ulceration ($p = 0.049$) (Table 1). Of the 204 SLNB-positive patients, 171 (84%) underwent CLND. Among the 33 SLNB-positive patients who did not undergo CLND, 24 (12%) were participating in the MSLT-II study and received follow-up with ultrasound, while the records of 9 patients (4%) did not specify why CLND was not performed.

3.2 | Disease-free interval, melanoma-specific survival, and overall survival

Among the 715 patients, 215 (30.1%) exhibited disease recurrence (median follow-up, 4.4 years; range, 0–16.8 years; inter quartile range [IQR], 1.7–8.7 years), 149 (20.8%) died of melanoma (median follow-up, 5.3 years; range, 0–17.9 years; IQR, 2.6–9.4 years), and an additional 45 patients died of other causes (total number of deceased patients, 194 (27.1%); median follow-up, 5.3 years; range, 0–17.9 years; IQR, 2.6–9.4 years). In the present cohort, we observed no melanoma-related mortality in patients with melanoma of ≤1.0 mm. Thus, for survival analyses, we divided Breslow thickness into two groups: ≤2 mm (combining ≤1.0 and 1.1–2.0) and >2 mm (combining 2.1–4 and >4.0).

Univariable analyses revealed no significant associations between obesity and DFI ($p = 0.16$), MSS ($p = 0.08$), or OS ($p = 0.21$), or between SES and DFI, MSS, or OS. We also found no significant association between histology and MSS (Tables 2–4; Figure 1A–C). The other analyzed variables were significantly associated with DFI, MSS, and OS (Tables 2–4). Among all patients, the five-year DFI, MSS, and OS rates were 72.1%, 82.2%, and 78.6%, respectively. Supplementary univariable analyses using obesity as a continuous variable with 1 and 10 units increase showed that obesity was significantly associated with MSS ($p = 0.03$), but not with DFI or OS (Supplementary Table).

Cox proportional-hazards multivariable analyses revealed that obesity did not significantly affect DFI ($p = 0.06$; HR, 1.40; 95% CI, 0.98–2.00), MSS ($p = 0.07$; HR, 1.48; 95% CI, 0.97–2.25), or OS ($p = 0.25$; HR, 1.25; 95% CI, 0.85–1.85), although trends towards significance were found for DFI and MSS (Tables 2–4). Supplementary Cox proportional-hazards multivariable analyses using obesity as a continuous variable with 1 and 10 units increase showed that obesity did not significantly affect MSS, DFI, or OS (Supplementary Table).

Cox multivariable analyses further indicated that gender and histology did not significantly affect DFI, MSS, or OS. On the other hand, age, tumor location, Breslow thickness, ulceration, mitotic rate, and SLNB status impacted all outcomes, except that Breslow thickness did not affect OS. Compared to their counterparts, worse outcomes were observed among patients who were older, or had melanoma on the arm, melanoma thicker than 2.0 mm, ulceration, a mitotic rate of ≥5, or a positive SLNB status (Tables 2–4).

4 | DISCUSSION

The current study showed that DFI, MSS and OS in patients with clinical stage IB-II melanoma who underwent SLNB were not significantly associated with obesity, defined as BMI ≥ 30 kg/m^2. These finding were supported by supplementary analyses including obesity as a continuous variable rather than a categorical variable. Multivariate analyses showed that DFI, and MSS, and OS were significantly associated with tumor location, Breslow thickness, ulceration, mitotic rate, and SLNB status, but not with histology. Among the analyzed patient characteristics, age was negatively associated with all three outcomes, while no significant associations were found for sex or SES. Thus, our results reject the hypothesis that obesity would be associated with decreased DFI, MSS, and OS in patients with clinical stage IB-II melanoma who underwent SLNB.

Our present results are in line with the findings of an earlier study that showed no association between high BMI and melanoma mortality,[20] but in contrast with a report that elevated BMI was associated with worse outcomes in patients with melanoma, after adjustment for sex, age, and stage.[19] Our present findings are also in contrast to a report showing improved outcomes in obese male patients with metastatic melanoma who received targeted therapy or immunotherapy.[21] Moreover, the current findings do not support the obesity paradox—a phenomenon that has previously been criticized. The contradictory reports regarding the existence of an obesity paradox may be explained by methodological issues (e.g., BMI being a suboptimal measure; confounding, selection, and detection biases; and reverse causality) and/or clinical issues (e.g., tumor aggressiveness and treatment responses).[15]

TABLE 2 Disease-free interval (DFI) (univariable and multivariable analyses) according to patient and tumor characteristics

Characteristic		5 years DFI	HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Sex	Female	79.8 (74.8–83.9)	Reference		Reference	
	Male	64.5 (58.7–69.6)	1.76 (1.34–2.33)	<0.001	1.36 (0.97–1.92)	0.08
Age			1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	0.002
Obesity	No	73.1 (68.9–76.9)	Reference		Reference	
	Yes	68.3 (59.4–75.7)	1.25 (0.92–1.72)	0.16	1.40 (0.98–2.00)	0.06
SES	1	73.4 (66.7–79.0)	Reference			
	2	76.6 (68.8–82.6)	0.85 (0.58–1.23)	0.39		
	3	66.5 (56.4–74.8)	1.18 (0.80–1.73)	0.41		
	4	61.3 (46.8–72.8)	1.42 (0.90–2.25)	0.13		
	5	72.0 (60.1–80.9)	0.86 (0.54–1.37)	0.53		
Localization	Head/neck	61.3 (49.9–70.8)	Reference		Reference	
	Trunk	69.2 (62.8–74.7)	0.75 (0.51–1.10)	0.15	0.62 (0.39–0.98)	0.04
	Arm	87.4 (78.3–92.9)	0.34 (0.19–0.61)	<0.001	0.25 (0.13–0.49)	<0.001
	Leg	73.7 (67.0–79.2)	0.69 (0.46–1.02)	0.07	0.64 (0.39–1.04)	0.07
Histology	SSM	77.4 (72.8–81.3)	Reference		Reference	
	Nodular	62.5 (54.8–69.2)	1.68 (1.26–2.26)	<0.001	1.16 (0.82–1.63)	0.40
	Other	63.9 (49.1–75.4)	1.68 (1.06–2.62)	0.02	1.57 (0.94–2.63)	0.09
Breslow	≤2.0	87.5 (83.0–90.9)	Reference		Reference	
	>2.0	58.5 (52.9–63.7)	2.96 (2.18–4.03)	<0.001	1.46 (0.99–2.13)	0.05
Ulceration	No	81.8 (77.5–85.3)	Reference		Reference	
	Yes	53.6 (46.5–60.2)	2.75 (2.09–3.63)	<0.001	2.11 (1.52–2.93)	<0.001
Mitotic rate	0–1	84.9 (79.5–89.0)	Reference		Reference	
	2–4	77.6 (70.4–83.3)	1.43 (0.96–2.16)	0.08	1.34 (0.87–2.05)	0.19
	5 or higher	56.7 (49.0–63.7)	2.67 (1.86–3.83)	<0.001	1.62 (1.07–2.44)	0.02
SLNB	Negative	80.7 (76.6–84.2)	Reference		Reference	
	Positive	51.3 (43.7–58.3)	3.08 (2.35–4.04)	<0.001	2.90 (2.13–3.96)	<0.001

Abbreviations: CI, confidence interval; HR, hazards ratio; SES, social-economic-status; SLNB, sentinel lymph node biopsy; SSM, shifting standards model.

Obesity induces immune suppression via inflammation, and accelerates tumor growth.[28] When melanoma invades deeper layers of the skin, papillary, reticular dermis, or the subcutis, the melanoma cells reportedly interact with adipose tissue, which secretes both soluble factors and exosomes, thus supporting melanoma proliferation, invasiveness, and metastatic potential,[29,30] This may explain the finding that ulceration was more common in patients with obesity compared to nonobese patients. The effects of obesity on melanoma growth patterns, and on immune responses both in general and in cancer immunotherapy, are poorly understood.[16] A recent study documented a positive correlation between overweight status and the efficacy of immune checkpoint inhibitors in metastatic melanoma and other malignancies.[30] Experiments in a melanoma mouse model showed that obesity promotes tumor progression and immune dysfunction, particularly through PD-1 upregulation.[28] This could be an explanation for the improved response to PD-1/PD-L1 inhibition treatment, rather than the previously proposed obesity paradox.[15,28,30,31]

Our present study included patients with clinical stage IB-II melanoma who underwent SLNB, but not patients with advanced stage melanoma. It is possible that associations between obesity and melanoma progression and survival are different in advanced stage disease than in patients with early stage melanoma, as previously reported.[19,21]

The present results suggested a trend towards associations between obesity and DFI and MSS—indicating that patients with obesity may have worse outcomes. It can even be argued that there were strong trends towards obesity being significantly associated with DFI and MSS, considering the number of obese patients and events in the study, the determined HR and *p* values, and the fact

TABLE 3 Melanoma-specific survival (MSS) (univariable and multivariable analyses) according to patient and tumor characteristics

Characteristic		5 years MSS	HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Sex	Female	88.3 (83.9–91.5)	Reference		Reference	
	Male	76.2 (70.7–80.7)	1.88 (1.34–2.63)	<0.001	1.35 (0.88–2.05)	0.16
Age			1.02 (1.01-1.03)	<0.001	1.02 (1.01–1.03)	0.002
Obesity	No	82.7 (78.9–85.9)	Reference		Reference	
	Yes	80.4 (72.0–86.5)	1.39 (0.96–2.01)	0.08	1.48 (0.97–2.25)	0.07
SES	1	84.8 (78.9–89.2)	Reference			
	2	83.1 (75.6–88.5)	0.95 (0.60–1.51)	0.84		
	3	78.7 (69.0–85.6)	1.37 (0.87–2.18)	0.17		
	4	77.6 (63.8–86.7)	1.75 (1.01–3.03)	0.05		
	5	82.0 (70.3–89.4)	1.06 (0.61–1.84)	0.82		
Location	Head/neck	74.4 (62.6–83.0)	Reference		Reference	
	Trunk	79.0 (73.1–83.8)	0.81 (0.51–1.29)	0.39	0.57 (0.33–0.96)	0.04
	Arm	90.3 (81.5–95.1)	0.40 (0.20–0.80)	0.009	0.27 (0.13–0.58)	0.001
	Leg	85.6 (79.8–89.9)	0.67 (0.42–1.10)	0.11	0.50 (0.27–0.90)	0.02
Histology	SSM	86.2 (82.1–89.5)	Reference			
	Nodular	75.4 (68.0–81.3)	1.40 (0.98–1.99)	0.06		
	Other	74.6 (60.2–84.5)	1.55 (0.92–2.62)	0.09		
Breslow	≤2.0	93.0 (89.0–95.5)	Reference		Reference	
	>2.0	72.8 (67.4–77.4)	2.85 (1.96–4.13)	<0.001	1.64 (1.06–2.54)	0.03
Ulceration	No	89.4 (85.6–92.1)	Reference		Reference	
	Yes	68.3 (61.2–74.3)	2.69 (1.94–3.73)	<0.001	2.06 (1.39–3.02)	<0.001
Mitotic rate	0–1	91.0 (85.9–94.3)	Reference		Reference	
	2–4	86.1 (79.6–90.6)	1.42 (0.85–2.36)	0.18	1.29 (0.75–2.19)	0.35
	5 or higher	70.8 (63.4–77.0)	2.93 (1.81–4.44)	<0.001	1.83 (1.12–3.00)	0.02
SLNB	Negative	88.5 (85.1–91.4)	Reference		Reference	
	Positive	66.8 (59.0–73.4)	2.93 (2.12–4.05)	<0.001	2.65 (1.84–3.81)	<0.001

Abbreviations: CI, confidence interval; HR, hazards ratio; SES, social-economic-status; SLNB, sentinel lymph node biopsy; SSM, shifting standards model.

that the present results are hypothesis generating. It is possible that significant associations between obesity and DFI and MSS would be found in analyses including a larger number of patients. A larger study group would also likely include more patients with obesity. Therefore, the present analyses should be repeated in a large multicenter study of clinical stage IB-II melanoma patients, with efforts to ensure that the groups are comparable in terms of relevant clinicopathologic and patient characteristics.

There are a number of potential explanations for the present findings. Compared to most other malignancies, melanoma is generally diagnosed at an earlier age and lower stage,[32] and the tumor biology and host immunity differ among patients with melanoma at different ages.[33] The treatment of clinical stage IB-II melanoma comprises surgical (re-) excision of the tumor and SLNB under local, regional, or general anesthesia.[8] Therefore, the only factors that may affect the immune system are gender and age.[34] In accordance with the literature, our present study showed that age was an independent predictor of melanoma progression, MSS, and OS.

Also in accordance with the literature, male patients with melanoma were found to have worse outcomes compared to female patients in univariate analyses.[35,36] However, in multivariate analyses, these differences were no longer significant, indicating that other variables included in the analyses played a greater role than gender in determining disease progression and survival.

In the Netherlands, people with lower SES are more commonly overweight and obese.[37] The Dutch Cancer Registry showed that low SES was associated with advanced melanoma.[38] However, our present study found that SES was not associated with DFI, MSS, or OS among clinical stage IB-II melanoma patients who underwent SLNB. It is reassuring to find that SES does not influence these disease outcomes

TABLE 4 Overall survival (OS) (univariable and multivariable analyses) according to patient and tumor characteristics

Characteristic		5 years OS	HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Sex	Female	85.9 (81.3-89.5)	Reference		Reference	
	Male	71.5 (66.0-76.3)	1.97 (1.46-2.64)	<0.001	1.34 (0.92-1.94)	0.12
Age			1.04 (1.03-1.05)	<0.001	1.03 (1.02-1.05)	<0.001
Obesity	No	78.9 (75.0-82.4)	Reference		Reference	
	Yes	77.3 (68.8-83.8)	1.24 (0.89-1.73)	0.21	1.25 (0.85-1.85)	0.25
SES	1	80.3 (74.1-85.1)	Reference			
	2	78.9 (70.9-84.9)	1.04 (0.70-1.53)	0.85		
	3	75.0 (65.1-82.4)	1.21 (0.80-1.82)	0.37		
	4	73.3 (58.9-83.4)	1.48 (0.89-2.46)	0.13		
	5	81.0 (69.3-88.5)	1.12 (0.70-1.79)	0.63		
Location	Head/neck	68.5 (56.5-77.9)	Reference		Reference	
	Trunk	75.3 (69.1-80.3)	0.79 (0.53-1.19)	0.26	0.66 (0.41-1.08)	0.10
	Arm	87.7 (78.4-93.2)	0.45 (0.29-0.80)	0.006	0.36 (0.19-0.68)	0.002
	Leg	82.7 (76.6-87.3)	0.60 (0.39-0.92)	0.02	0.53 (0.31-0.90)	0.02
Histology	SSM	83.5 (79.2-87.0)	Reference		Reference	
	Nodular	70.1 (62.7-76.4)	1.52 (1.12-2.06)	0.008	1.03 (0.71-1.47)	0.88
	Other	70.8 (56.2-81.3)	1.54 (0.96-2.47)	0.07	1.44 (0.82-2.54)	0.20
Breslow	≤2.0	90.0 (85.5-93.1)	Reference		Reference	
	>2.0	68.8 (63.4-73.6)	2.60 (1.88-3.58)	<0.001	1.47 (0.99-2.20)	0.06
Ulceration	No	86.2 (82.2-89.3)	Reference		Reference	
	Yes	65.0 (58.0-71.2)	2.33 (1.74-3.11)	<0.001	1.72 (1.22-2.42)	0.002
Mitotic rate	0 – 1	88.2 (82.8-92.0)	Reference		Reference	
	2 – 4	83.1 (76.4-88.1)	1.41 (0.91-2.20)	0.12	1.43 (0.90-2.28)	0.13
	5 or higher	66.9 (59.5-73.3)	2.66 (1.80-3.93)	<0.001	1.96 (1.26-3.05)	0.003
SLNB	Negative	85.3 (81.4-88.4)	Reference		Reference	
	Positive	62.6 (55.1-69.5)	2.53 (1.91-3.37)	<0.001	2.38 (1.72-3.30)	<0.001

Abbreviations: CI, confidence interval; HR, hazards ratio; SES, social-economic-status; SLNB, sentinel lymph node biopsy; SSM, shifting standards model.

following diagnosis with clinically stage IB-II melanoma. This suggests that the medical treatment and financial resources of patients with early stage melanoma are independent of SES level in the Netherlands.[39]

The percentage of obese (BMI ≥ 30 kg/m^2) patients found in the current study (20.8%) is higher than the rate found in the general population in the Netherlands in 2018 (15%).[40] However, the latter percentage is based on self-report, while the BMI in the present study was objectively measured using recorded body height and weight from the time of diagnosis.

A strength of the current study is that it included a large cohort with prospectively collected baseline data on several potential confounders in the relationships between BMI and DFI, MSS, and OS. Additionally, BMI was calculated using objectively measured body weight and height at the time of primary diagnosis. Questionnaire-based self-report is more prone to error.

A limitation of this study is that obesity was determined using only BMI, and not measures like fat mass and fat-free mass index, which may be more sensitive.[41] A second limitation is that we could not examine how changes in adiposity levels before and after diagnosis may have influenced oncological endpoints. It has been shown that changes in adiposity levels affect disease and outcomes in several types of malignancies.[42–44] It may be argued that obesity levels would not be likely to change during the early development of a melanoma, or following the not so aggressive treatment, namely a surgical intervention of early stage melanoma. A third limitation is that the results may have been affected by a selection bias, as the study included only patients who were SLNB staged. This is particularly relevant since we identified trends of associations between obesity and DFI ($p = 0.06$) and MSS ($p = 0.07$). It is possible that significant associations would have been found if our analyses had included all clinical stage IB-II patients with melanoma, which

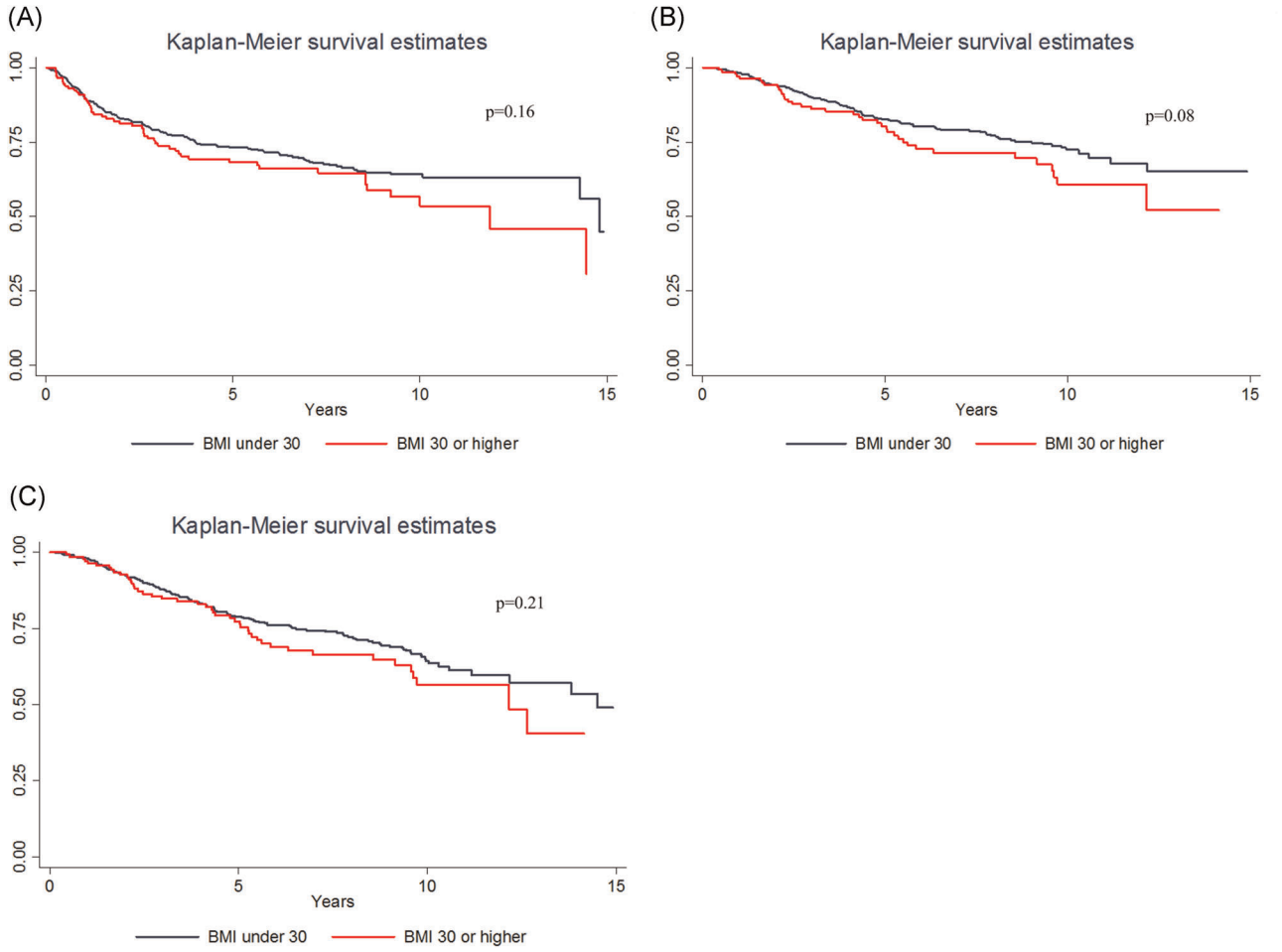

FIGURE 1 Kaplan–Meier curves according to BMI (obese ≥ 30 kg/m^2, non–obese < 30 kg/m^2) and (A) DFI, (B) MSS, and (C) OS. BMI, body mass index; DFI, disease-free interval; MSS, melanoma-specific survival; OS, overall survival

would have been a larger study group, likely including a greater number of patients with obesity. A fourth limitation is that the metastatic tumor burden in the sentinel lymph node was not systematically recorded in the patients' files during the study period. It may be possible that the lymph node metastases, on average, were larger among patients with obesity. However, we were unable to control for this variable.

In our present analyses, we adjusted for a number of clinicopathological and patient characteristics known to affect melanoma progression and survival. Other variables have also been reported to be associated with cancer outcomes, including biomarkers (LDH, S-100B), tumor immune response-related cytokines/chemokines, inflammatory markers (C-reactive protein), and smoking behavior.[19,45–48] A relationship has been identified between smoking and SLN metastasis in stage IB-II melanoma, which is independent of tumor thickness and ulceration.[46] Additionally, links have been described between obesity, inflammation, and immune response, and the impacts on the metastatic potential of malignancies and on disease outcome.[19–21,49] The linkage between immune response and obesity has also been identified in coronavirus diaease 2019 infection, as obesity is a risk factor for higher severity and worse prognosis.[50,51] Unfortunately, in the present study, we were unable to investigate relationships between all of these variables, and obesity and disease outcome. Future studies should include such variables in analyses.

5 | CONCLUSION

The present study showed that obesity (BMI ≥ 30 kg/m^2) was not significantly associated with DFI, MSS, or OS in patients with clinical stage IB-II melanoma who underwent SLNB. Among these patients, increased age was associated with decreased DFI, MSS, and OS. Outcomes were not significantly associated with gender or SES in our cohort. Compared to their counterparts, patients with melanoma on the arm, thicker melanoma, ulceration, a mitotic rate of ≥5/mm^2, and/or a positive sentinel lymph node status exhibited decreased DFI, MSS, and OS.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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