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Original article

Impact of body mass index on the clinical outcomes of patients with HER2-positive metastatic breast cancer

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ABSTRACT

Background: Overweight and obesity are associated with an increased risk of developing many types of cancer, including breast cancer. Moreover, increased body mass index (BMI) seems to be associated with a worse prognosis in patients with HER2-positive early breast cancer. However, little is known about the impact of BMI on the clinical outcomes of HER2-positive metastatic breast cancer (MBC).

Methods: This was a multicenter retrospective cohort study including 329 consecutive patients with HER2-positive MBC treated with first-line trastuzumab-based regimens. BMI at the time of MBC diagnosis was collected. World Health Organization BMI categories were used: underweight <18.5, normal 18.5–24.9 Kg/m^2, overweight 25–29.9 Kg/m^2, and obese ≥30 Kg/m^2. The analyses were conducted using two categories: BMI < 25.0 (normal/underweight) and BMI ≥ 25 (overweight/obese). Progression-free survival (PFS) and overall survival (OS) rates were estimated using Kaplan-Meier method. Univariate and multivariate survival analyses were performed using the Cox's proportional hazards model. Disease response to therapy was analyzed using univariate and multivariate logistic regression.

Results: Overall, 176 (53.5%) patients were normal/underweight and 153 (46.5%) overweight/obese. Median PFS was 14.8 months in BMI < 25 group and 15.7 months in BMI ≥ 25 group (adjusted-HR 0.88; 95% CI 0.66–1.17; p = 0.387). Median OS was 58.6 months in BMI < 25 group and 52.6 in BMI ≥ 25 group (adjusted-HR 0.88; 95% CI 0.59–1.31; p = 0.525). Overall response rate was 71.7% and 65.9% (p = 0.296) and clinical benefit rate was 82.1% and 83.3% (p = 0.781) in BMI < 25 and BMI ≥ 25 groups, respectively.

Conclusions: BMI does not seem to be associated with clinical outcomes in HER2-positive MBC patients.

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1. Introduction

Body mass index (BMI) is a weight-for-height ratio that has been

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used for decades by the World Health Organization (WHO) to assess quantitatively a person's relative body fatness [1]. It categorizes individuals into four groups: underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9) and obese (≥30.0). Despite its limitations, this standardized measure is now commonly used worldwide. Epidemiological studies including more than 68.5 million participants in 195 countries showed that the prevalence of obesity is 12.0% among adults worldwide [2]. Projections are alarming as it is estimated that by 2025 the prevalence of obesity will reach 18% and 21% in men and women respectively [3]. Obesity has been associated with an increased risk of developing many types of cancer including breast cancer [4]. In addition, pre- and postmenopausal breast cancer survivors appear to have an increased mortality risk if they are obese at time of diagnosis [5]. The limited data available in the metastatic setting suggest no impact of BMI on the outcome of patients treated with first line chemotherapy in unselected breast cancer patients [6].

Breast cancer is a heterogeneous disease composed of different subtypes [7]

hormone receptor status, number of metastatic sites, visceral involvement, and disease-free interval. Follow-up was calculated as the median follow-up time of censured patients. All tests were 2-sided and p values of <0.05 were considered statistically significant. All analyses were performed using Stata 13.1 (StataCorp LP).

3. Results

Between January 2000 and December 2013, 329 (79.1%) consecutive women diagnosed with recurrent HER2-positive MBC and treated with first-line trastuzumab-based therapy were included from the initial data set of 416 patients. Among included patients, 176 (59.5%) had a BMI < 25 and 153 (46.5%) had a BMI ≥ 25. Median follow up was 3.0 years (IQR 2.1–5.4).

Table 1
Patients' demographic and clinicopathologic characteristics according to BMI group.

Characteristics	BMI < 25 n = 176 (53.5)	BMI ≥ 25 n = 153 (46.5)	p-value
Age at diagnosis (years), n (%)			
<35	21 (11.9)	7 (4.6)	0.071
≥35 to <50	61 (34.7)	51 (33.3)	
≥50 to <70	76 (43.2)	72 (47.1)	
≥70	18 (10.2)	23 (15.0)	
Median	51.1	55.9	
(IQR)	(41.3–61.9)	(45.3–63.7)	
Menopausal status, n (%)			
Premenopausal	75 (42.6)	57 (37.3)	0.323
Postmenopausal	101 (57.4)	96 (62.8)	
AJCC stage at presentation, n (%)			
I	28 (15.9)	15 (9.8)	0.326
II	47 (26.7)	39 (25.5)	
III	54 (30.7)	55 (35.9)	
IV	43 (24.4)	43 (28.1)	
Unknown	4 (2.27)	1 (0.65)	
Hormonal status, n (%)			
ER or PR positive	100 (56.8)	95 (62.1)	0.452
ER and PR negative	74 (42.0)	62 (40.5)	0.658
Unknown	4 (2.27)	2 (1.31)	
Nuclear grade, n (%)			
G1	3 (1.70)	1 (0.65)	0.657
G2	47 (26.7)	39 (25.5)	
G3	90 (51.1)	64 (41.8)	
Unknown	36 (20.5)	48 (31.4)	
Histologic type, n (%)			
Ductal	159 (93.3)	36 (88.9)	0.429
Lobular	5 (2.8)	5 (3.3)	
Others	7 (4.0)	9 (5.9)	
Unknown	5 (2.8)	3 (2.0)	
Prior adjuvant chemotherapy (excludes *de novo metastatic disease*), n (%)			
Anthracycline plus taxane	31 (23.5)	33 (30.0)	0.086
Anthracycline alone	49 (37.1)	24 (21.8)	
Other	19 (14.4)	14 (12.7)	
None	33 (25.0)	39 (35.5)	
Prior adjuvant trastuzumab exposure (excludes *de novo metastatic disease*), n (%)			
Yes	40 (30.3)	42 (38.2)	0.197
No	92 (69.7)	68 (61.8)	
Prior adjuvant endocrine therapy, n (%)			
Tamoxifen	20 (15.2)	22 (20.0)	0.561
AI	24 (18.2)	17 (15.5)	
Tamoxifen + LHRHa	12 (9.1)	15 (13.6)	
Sequential tamoxifen − AI	7 (5.3)	3 (2.7)	
Other	2 (1.5)	2 (1.8)	
None	67 (50.8)	51 (46.4)	
First line treatment (in the metastatic setting), n (%)			
CT + trastuzumab	132 (75.0)	108 (70.6)	0.672
CT + trastuzumab + ET	27 (15.3)	25 (16.3)	
ET + trastuzumab	15 (8.5)	16 (10.5)	
Other	2 (1.1)	4 (2.6)	

Abbreviation: BMI, Body mass index; IQR, Interquartile range; AJCC, American Joint Committee on Cancer; ER, Estrogen receptor; PR, Progesterone receptor; G, Grade; AI, Aromatase inhibitor; LHRHa, Luteinizing-hormone-releasing hormone analogue; CT, Chemotherapy; ET, Endocrine therapy.

There was no significant difference in baseline demographic characteristics between the two BMI cohorts (Table 1). A total of 86 (26.5%) patients had *de novo* stage IV disease. Approximately half of the patients had hormone receptor-positive disease, (195, 56.2%), and grade 3 tumors (154, 46,8%). In the 242 (73.6%) patients with recurrent disease, 82 (33.9%) were previously treated with trastuzumab. First-line treatment consisted of chemotherapy plus trastuzumab, chemotherapy plus trastuzumab and endocrine therapy and endocrine therapy plus trastuzumab in 75.0%, 15.3% and 8.5% of patients, respectively.

The median number of metastatic sites at diagnosis was 2 (IQR 1–2) in both cohorts (Table 2). Visceral involvement as first site of distant metastasis represented the majority of patients (237, 72.0%) and the most frequent site of first metastasis was the liver (104, 31.6%). Compared to patients with a BMI ≥ 25, those with a BMI < 25 had significantly more non-visceral involvement if they were hormone receptor-negative (p = 0.029). Otherwise, there was no significant difference in first site of distant metastasis according to BMI and hormone receptor status (supplementary material; Table 1).

3.1. Tumor response to first-line trastuzumab-based therapy according to BMI

278 (84.5%) patients were evaluable for response (Fig. 1) of which 146 (83.0%) from the BMI < 25 cohort and 132 (86.3%) from the BMI ≥ 25 cohort (Table 3). In BMI < 25 and BMI ≥ 25 cohort, respectively, ORR to first-line trastuzumab-based regimen was 71.7% and 65.9% (adjusted odds ratio [OR], 0.60; 95% confidence interval [CI], 0.33–1.10; p = 0.296) and CBR was 82.1% and 83.3% (adjusted OR, 0.948; 95% CI, 0.44–2.05; p = 0.893).

3.2. Effectiveness in BMI < 25 and BMI ≥ 25

In the overall cohort, 279 (84.8%) progressions and 154 (47.1) deaths occurred, 155 (88.1%) and 90 (51.4%) in the BMI < 25 and 124 (81.1%) and 64 (42.1%) in BMI ≥ 25 group respectively (Fig. 1).

Median PFS was 14.8 months in BMI < 25 group and 15.7 months in BMI ≥ 25 group. Both the univariate (HR 0.95; 95% CI 0.75–1.20; p = 0.691) and multivariate (adjusted-HR 0.88; 95% CI 0.66–1.17; p = 0.387) comparison between BMI groups were not statistically different (Fig. 2).

Median OS was 58.6 months in BMI < 25 cohort and 52.6 months in BMI ≥ 25 cohort. Both the univariate (HR 0.95; 95% CI 0.69–1.31; p = 0.765) and multivariate (adjusted-HR 0.88; 95% CI 0.59–1.31; p = 0.525) comparison between groups were not statistically different (Fig. 3). Similar findings were documented when

Table 2
First site of distant metastasis according to BMI group.

	BMI < 25	BMI ≥ 25	p-value
First site of distant metastasis			
Brain	20 (11.4)	14 (9.2)	0.820
Liver	58 (33.0)	46 (30.1)	
Lung	37 (21.0)	31 (20.3)	
Bone	38 (21.6)	39 (25.5)	
Others	22 (12.5)	23 (15.0)	
Unknown	1 (0.6)	0 (0)	
First site of distant metastasis			
Non-visceral involvement	44 (25.0)	47 (30.7)	0.260
Visceral involvement	131 (74.4)	106 (69.3)	
	1 (0.6)	0 (0)	
No. of metastatic sites			
Median (IQR)	2 (1–2)	2 (1–2)	0.494
Min. − Max.	1–6	1–7	

Abbreviation: BMI, Body mass index; IQR, Interquartile range.

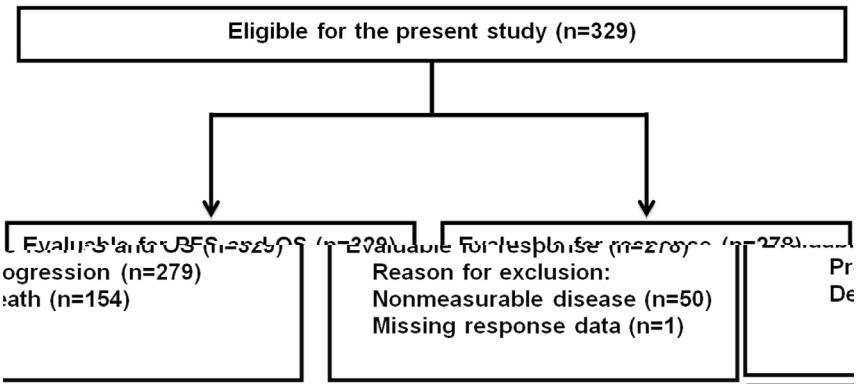

Fig. 1. Flow diagram of participants. Abbreviation: PFS, Progression-free survival; OS, Overall survival.

Table 3
Patients' response according to BMI group. Multivariate analysis adjusted for stage IV at diagnosis, disease-free interval, hormone receptor status and histologic grade.

	BMI < 25	BMI ≥ 25	p-value
Objective response rate (ORR), n (%)	104 (71.7)	87 (65.9)	0.296
Adjusted OR (95% CI)	0.60 (0.33–1.10)		0.100
Best objective response, n (%)			
Complete response	33 (22.8)	33 (25.0)	0.662
Partial response	71 (49.0)	54 (40.9)	0.178
Stable disease	20 (13.8)	28 (21.2)	0.103
Progressive disease	21 (14.5)	17 (12.9)	0.698
Clinical benefit rate (CBR), n (%)	119 (82.1)	110 (83.3)	0.781
Adjusted OR (95% CI)	0.948 (0.44–2.05)		0.893
Evaluable for response, n (%)	146 (83.0)	132 (86.3)	–

Abbreviation: BMI, Body mass index; ORR, Objective response rate; CBR, Clinical benefit rate.

analysing results according to hormone receptor status (supplementary material; Fig. 1).

4. Discussion

To our knowledge, this is the largest study that evaluated the impact of BMI on clinical outcomes of patients with HER2-positive MBC. In our analysis, BMI was not associated with PFS, OS and response rate (ORR and CBR). These results are in contrast with the findings of Parolin and colleagues [12]. This retrospective study evaluated the impact of BMI on outcomes in 155 patients with HER2-positive breast cancer patients treated with trastuzumab and chemotherapy in different settings of the disease. Of the 155 patients included, 52 had MBC and 48% were overweight/obese. Higher BMI was associated with worse outcomes in HER2-positive MBC: OS was 67, 54, 39 months ($p = 0.001$) for normal weight, overweight and obese patients, respectively. The limited number of patients in this study needs to be kept in mind in respect to considering generalizing those data [12].

The HER2 status is an important and well known prognostic marker that confers an aggressive behaviour to breast cancer tumors who are tested positive [16]. In molecular aggressive breast cancer subtypes like HER2-positive breast cancer, the prognostic impact of higher BMI, if one there is, may be overshadowed by the tumor biology. For example in the adjuvant setting, studies evaluating the impact of BMI in early triple-negative breast cancer, another aggressive breast cancer subtype, have failed to consistently show a relationship between BMI and outcomes [17,18]. In

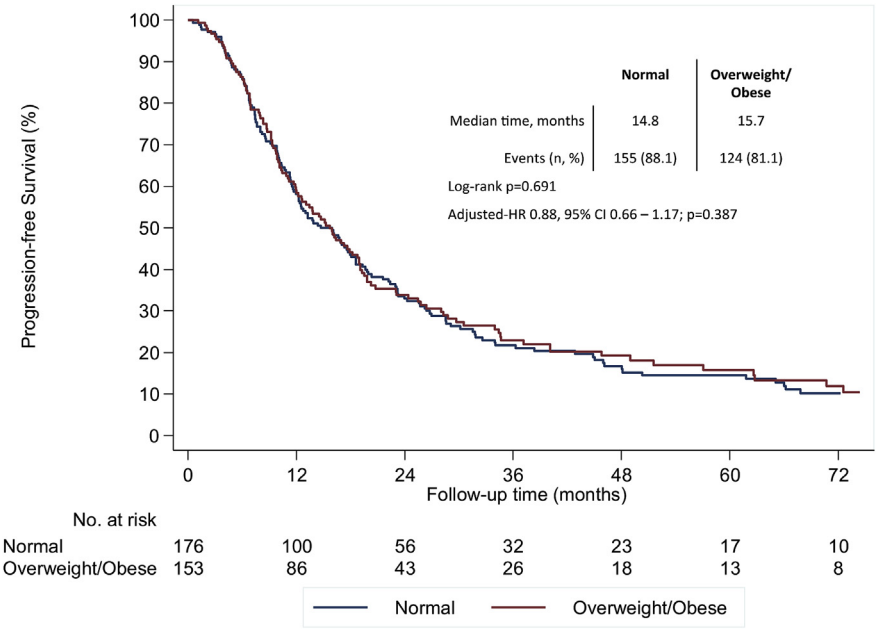

Fig. 2. Progression-Free Survival according to BMI. Abbreviation: BMI, Body mass index; HR, Hazard ratio; CI, Confidence interval.

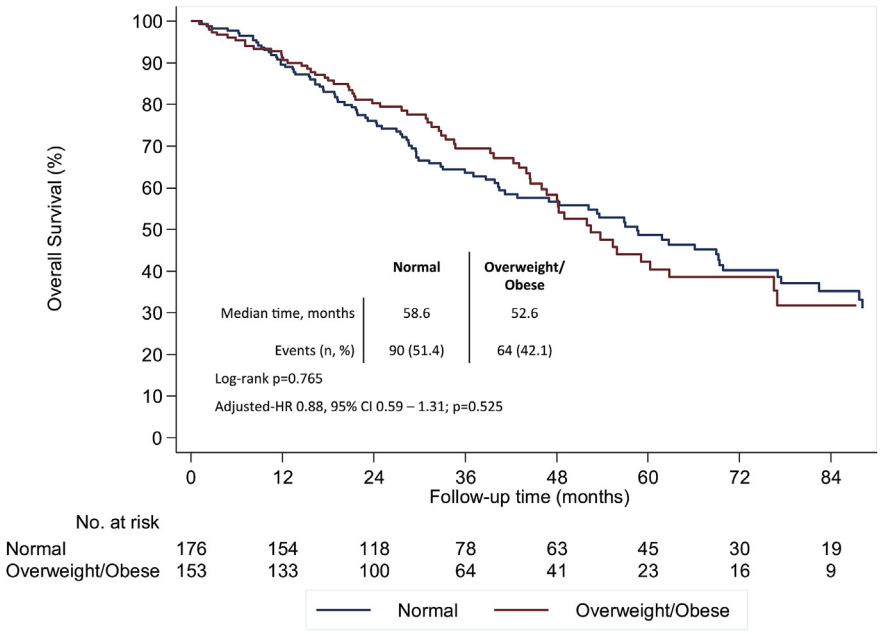

Fig. 3. Overall Survival according to BMI. Abbreviation: BMI, Body mass index; HR, Hazard ratio; CI, Confidence interval.

contrast, the negative impact of higher BMI on outcomes in hormone-receptor positive tumors are more consistent and seems to result from the increase in estrogens level associated with increase weight [19]. In the ATAC trial, women with a baseline BMI > 35 Kg/m^2 had more recurrences (including distant recurrences) than women with a BMI < 23 Kg/m^2 and this may be link to higher levels of circulating estrogen [20].

Our results contrasts with the general observation that an increased BMI at diagnosis is associated with worse outcomes which at least holds true in the adjuvant setting of unselected breast cancer subtypes as demonstrated in a substantial meta-analysis [5]. Great efforts have been made to better understand the underlying mechanisms explaining this association and, so far, the current accepted hypothesis are related to the chronic inflammation and the perturbations of multiple mediators related to carcinogenesis encountered in obese patients. Chronic inflammation secondary to obesity can induce alterations in the tissue microenvironment that then have pro-tumorigenic effects. Insulin resistance, increased levels of insulin and Insulin-like growth factors (IGF-1), higher level of leptin and decreased level of adiponectin associated to extra body fatness can have pro-tumorigenic effects. As it relates to HER2-positive disease, preclinical data have revealed the existence of a bidirectional crosstalk between leptin and IGF signalling that can lead to phosphorylation of HER2 and reduce sensitivity to anti-HER2 treatment and therefore rise the risk of recurrence [21,22]. Our results are hypothesis generating as they allow us to think that there may be a paradoxical effect of bodyweight in early versus advanced breast cancer setting. It is possible that a higher BMI favours carcinogenesis and affect prognosis in early setting and that in the advanced setting a higher BMI has only marginal effect [23].

Further studies with larger cohort of patients are needed to show if there is a real effect. In our study, the relative small sample size may have prevented us to observe a correlation. Moreover, we acknowledge that evaluation of body fatness using BMI has limitations, the main one being that it inaccurately assesses adiposity. Weight (used as a numerator in the formula) doesn't distinguish lean muscle from fat mass. So even though BMI have been extensively used, it is possible that this measure is not suitable to evaluate if it correlates with breast cancer outcomes [24]. Finally, the American Society of Clinical Oncology (ASCO) guidelines highlight the importance of recommending an appropriate chemotherapy dosing for adult obese patients with cancer [25]. Suboptimal chemotherapy dosing could have a negative impact on survival for overweight and obese patients. Moreover, it has been recently shown that higher BMI can be also associated with lower trastuzumab exposure [26]. However, information on chemotherapy dosing was not available in our study and its potential impact on patients' prognosis could not be investigated.

Nonetheless the here above findings, it is crucial to underscore that the benefits of having a normal BMI can go beyond the sole improvement of breast cancer outcomes. Despite absence of evidence to support its prognostic role in HER2-positive MBC, a correct lifestyle is advisable as it is likely to play a role in these patients that are now expected to live years rather than months. Obesity is a major health issue as it is associated not only to an increase in all-cause mortality but also to many morbid diseases (i.e. type II diabetes, coronary heart disease and stroke among others) that significantly contribute to decrease quality of life and the financial burden of medical care [27–29]. Moreover, there is a mounting proof that obesity often complicates treatment delivery [30,31]. Acknowledging the importance of obesity and its implications related to the oncology field, the ASCO Obesity Initiative has been created to inform and develop concrete actions to address this issue [32]. Oncologists are in a unique position to advise and counsel patients in regard to optimal weight targets.

5. Conclusion

In conclusion, our study did not demonstrate that BMI at the time of diagnosis of metastatic disease is negatively associated with clinical outcomes of HER2-positive MBC patients. Our study gives further insights on the complex relationship between BMI and tumor biology and reinforces the need to better understand how they may be intertwined in different settings of the same disease. Additional data are needed to clarify the uncertainties surrounding

the impact of BMI for HER2-positive MBC in order to better counsel patients in the future.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2017.11.004.

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