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Impact of Obesity on Breast Cancer

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Abstract

Background: Obesity is linked with a high risk of breast cancer and affects prognosis as it is correlated with different molecular subtypes.

Method: All breast cancer patients referred to Kasr Alainy Oncology Center of Clinical Oncology and Nuclear Medicine (NEMROCK) from 2004 to2014 were recruited in this retrospective study. They were divided into three groups according to body mass index (BMI): non-obese (BMI < 30), obese (BMI= 30-34.9) and severely obese (BMI ≥ 35).

Results: There were 950 breast cancer patients with a median follow-up of 4.2 years. The mean age was 50.1 years, and BMI was assessed in 760 cases. Obesity was observed in 63.29% of the cases (23.82% obese and 39.47% severely obese). There was a statistically significant difference between non-obese and severely obese patients as regards age (52 vs. 48 years, $P < 0.001$), menopausal status (31.3 vs. 46.9%, $P < 0.001$), molecular types (non- luminal; 25 vs. 50%, $P < 0.011$), Her2 status (44.4 vs. 27.2%, $P = 0.014$), and hormonal therapy (Tamoxifen alone, 44.3 vs. 30.4%, $P = 0.001$). High BMI >30 had a worse mean overall survival (OS) (80, 88, and 102.5 months in obese, severely obese, and non-obese patients, respectively, $P=0.019$); however, this did not affect the disease-free survival ($P = 0.40$). In multivariate analysis, the factors that also had a significant effect on OS were lymph node stage ($P <0.001$; odds ratio (OR): 1; 95% confidence interval (CI): 0.07-0.46), BMI ($P = 0.001$; odds ratio (OR): 1; 95% CI: 0.14-0.61), and hormonal treatment (tamoxifen alone, $P = 0.001$; OR: 1; 95% CI: 1.4-16.4).

Conclusion: Severe obesity (BMI >35) had a poor OS with no influence on disease-free survival.

Keywords: Body mass index, Obesity, Breast cancer, Prognostic factors, Overall survival

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Introduction

Breast cancer (BC) is the most prevalent invasive neoplasm in women. The newly diagnosed female patients reached 2.1 million in 2018. This accounts for almost 1 in 4 cancer cases among women.[1] Among others, the prevalence of obesity is increasing worldwide.[2] In the United States of America, obesity is considered as an epidemic affecting 39.6% of adults aged 20 years and older.[3]

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In an Iranian study, obesity was high in pre- and post-menopausal female. However, it was associated with higher incidence of BC only in the pre-menopausal women.[4] This may be attributed to dietary habits in this population.[5]

Obesity is well known as a risk factor for BC. It is associated with poor outcome.[6] The increase in the prevalence of both obesity and BC has become a major issue. The excess of adipose tissue may induce more aggressive tumors with a high incidence of recurrence, poor survival, and high mortality.[7] This correlation is of interest because modifying the lifestyle by exercise or medication may influence the disease course. Nevertheless, this is influenced by various molecular subtypes, treatment modalities, and morbidity associated with obesity.[8]

The incidence of obesity and its impact on BC is not well studied in Egypt. The objective of this study was to investigate the prognostic effect of body mass index (BMI) on disease-free survival (DFS) and overall survival (OS). The correlation of obesity with various molecular subtypes and different treatment outcomes (hormonal therapy and chemotherapy) was further analyzed.

Patients and Methods

This retrospective study included 950 breast cancer patients presenting at Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) from January 2004 to December 2014. The study was approved by the ethics committees of the clinical oncology department and the Faculty of Medicine Cairo University (Code 12-10-19). The patients were considered eligible, if they were above ≥18 years of age and had a confirmed breast cancer by pathology. Those with incomplete medical data were excluded. All demographic and pathological data were collected.

The data retrieved included the histopathology. The patients' state at presentation was either adjuvant, neo-adjuvant, or metastatic. All TNM staging for pathological tumor size T1, 2, 3 or 4, pathological lymph node 1, 2, or N3, and immunophenotyping (Estrogen receptor (ER), Progesterone receptor (PR), Ki67, and Her2neu) were collected.

Molecular subtypes were considered as luminal subtype, which was defined as ER positive, PR positive, but not Her2 nor ki67. Luminal A subtype was defined as ER positive, PR positive, HER2 negative, and low ki67. Luminal B subtype was defined as ER positive, PR positive, HER2 negative, and high ki67 OR ER positive and/or PR positive, HER2 positive. Non-luminal subtype was defined as ER negative, PR negative, but cannot be assessed as either Her2 or ki67. HER 2 enriched subtype was defined as ER negative, PR negative, and HER 2 Positive. Triple negative subtype was defined as ER negative, PR negative, and Her2 negative. Patients were excluded, only if they had incomplete medical data. The extent of obesity in relation to all these data was analyzed to determine its impact on OS and DFS.

The patients were divided into three groups according to BMI. Using 30 kg/m^2 as the cut-off point, they were classified as non-obese (BMI <30 kg/m^2), obese (BMI=30- 34.9 kg/m^2), and severely obese (BMI 35 kg/m^2). BMI was calculated by dividing the weight in kilogram (Kg) by the height in square meter (m^2).[9]

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate. The comparison of numerical variables was done using student's t-test for independent samples for comparing two groups of normally distributed data; Mann Whitney U test was used for independent samples to compare data that were not normally distributed. For the comparison of categorical data, chi square test was performed. Exact test was used when the expected frequency was less than 5. Survival analysis was done for different outcome measures using Kaplan-Maier method, and the mean and median survival time were calculated for each group with their 95% confidence interval (CI) and the corresponding survival graphs.

A probability value (*P*-value) less than 0.05 was considered as significant. The statistical calculations were performed using computer programs Microsoft Excel version 2010 and SPSS (statistical package for the social sciences)

statistical programs version 15.0.

Results

Among the study population (950), the median age was 50 years (23-90). Most patients were in the adjuvant state (76.9%), while 11.7 % were neo-adjuvants, and 9.7% was metastasis. Post-menopausal patients represented the majority (52.6%) followed by premenopausal (46.6%), and male patients (0.8%).

Obesity was seen in 63.29% with BMI class I (30-34.9), which was the most common (23.82%), followed by class II (35-39.9) and morbid class III (20.66% and 18.81%, respectively). Only 13.95% of the cases had a normal weight with very few being underweight (0.79%). Overweightness was also common in this cohort (21.97%). Regarding histological types, almost all patients (87.05%) had infiltrating duct carcinoma, while infiltrating lobular carcinoma was only detected in 5.88%. The majority of the patients had pathological tumor T2 (56.91%) and were node positive (72.09%), grade II (87.8%), ER positive (73%), and PR positive (67.68%) (Table 1).

Association of BMI with patient and tumor characteristics

The distribution of 760 patients was studied according to BMI. The rest of the patients (190 patients) had missing data. For the sole purpose of simplifying the sample description here, we categorized the BMI into three different categories. Using 30 kg/m^2 as the cut-off point, the subjects were classified into non-obese (279, 36.7%), obese (181, 23.8%), severely obese (300, 39.5%) (Table 2).

Our study population showed significant correlations among different BMI groups and both age and menopausal status. The median age was 48, 49, and 52 years in the non-obese, obese, and severely obese, respectively ($P < 0.001$). Most of the premenopausal women (42.9%) were non-obese whereas severely obese patients were more likely to be postmenopausal (46.9%).

Regarding the disease extent, severely obese subjects were more associated with the characteristics of a poor prognosis, such as a large tumor size, grade 3 cancer, and more positive nodes compared to the non-obese group with non-significant *P*-value. Pathologic T4 disease was

Table 1. The demographic and pathological characteristics of 950 breast cancer patients

Item	Number (950)	Percentage (%)
Age (years)		
Median	50	
Mean ±SD	51.1± 11.5	
Range	23-90	
Menopausal state		
Pre-menopause	443	46.6%
Post-menopause	499	52.6%
Male	8	0.8%
State at diagnosis		
Adjuvant	731	76.9%
Neo- adjuvant	111	11.7%
Metastatic	92	9.7%
BMI groups	760	100%
Underweight <18.5	6	0.79%
Normal weight18.5-24.9	106	13.95%
Over weight 25-29.9	167	21.97%
Obese	481	63.29%
Obese class I 30-34.9	181	23.82%
Obese class II 35-39.9	157	20.66%
Obese class III >40	143	18.81%
Histological type		
IDC	827	87.05%
ILC	56	5.88%
Mixed IDC&ILC	40	4.24%
Other	27	2.83%
Pathological Tumor (pT)		
PT1	132	13.93%
PT2	541	56.91%
PT3	166	17.47%
PT4	111	11.69%
Pathological N (pN)		
PN0	275	28.91%
PN1	251	26.42%
PN2	219	23.05%
PN3	205	21.57%
Estrogen receptor (ER) status		
Positive	694	73%
Negative	256	27%
Progestin receptor (PR) status		
Positive	643	67.68%
Negative	307	32.31%
Her2 score		
0	428	45%
1	201	21.16%
2	61	6.43%
3	260	27.38%

BMI: Body mass index, IDC: Invasive duct carcinoma, ILC: Invasive lobular carcinoma, pT: pathological tumor size, pN: Pathological nodal status; SD: Standard deviation

Table 2. Distribution of variables by BMI category of 760 patients

		BMI (kg/m^2)			*P*-value
		BMI <30 Non-obese 279, 36.7% (%)	**BMI 30-34.9 Obese 181, 23.8% (%)**	**BMI ≥35 Severely obese 300, 39.5% (%)**	
Age (years)	Median	48	49	52	≤0.001*
	Mean ± SD	48.9±12.4	49±11	53.06 ±10.1	
Menopause	premenopausal	42%	26.2%	31.8%	≤0.001*
	postmenopausal	31.3%	21.8%	46.9%	
	male	62%	12.5%	25%	
Histological type					
	IDC	36.6%	24.3%	39.1%	0.272
	ILC	43.2%	13.6%	43.2%	
	Mixed	29.4%	20.6%	50%	
	others	34.8%	39.1%	26.1%	
Histological grading					
	Grade 1	16.7%	16.7%	66.7%	0.658
	Grade 2	37.6%	23.7%	38.7%	
	Grade 3	33.3%	26.3%	40.4%	
	Unknown	23	16	30	
Pathologic primary tumor size (pT)					
	pT1	26.6%	28.7%	44.7%	0.062
	pT2	36.8%	25.4%	37.8%	
	pT3	42.7%	19.7%	37.6%	
	pT4	32.5%	16.3%	51.2%	
Nodal stage (pN)					
	pN0	39%	22.4%	38.6%	0.761
	pN1	32%	23.3%	44.8%	
	pN2	36.3%	25.5%	38.2%	
	pN3	33.8%	26.2%	40%	
Molecular subtypes					
	Luminal	38.7%	24.4%	36.9%	0.011*
	Luminal A	18.5%	23.1%	58.5%	
	Luminal B	25.8%	19.3	45%	
	Non-luminal	25%	25%	50%	
	HER2	44.4%	28.4%	27.2%	
	TNBC	32.1%	22.6%	45.3%	
Estrogen receptor (ER) status					
	Positive	35.4%	22.9%	41.7%	0.562
	Negative	36.5%	25.9%	37.6%	
	Unknown	31	16	18	
Progesterone receptor (PR) status					
	Positive	35.6%	24%	40.4%	0.999
	Negative	35.7%	24%	40.3%	
HER2 status					
	Positive	38.8%	24%	37.2%	0.228
	Negative	32.1%	23.8%	44.1%	
Anti-hormone therapy					
	TAM	44.3%	25.4%	30.4%	0.001*
	AI	22%	19.5%	58.5%	
	TAM+AI	33.3%	15%	51.7%	
Chemotherapy					
	Anthracycline	39.6%	24.6%	35.8%	0.250
	Taxanes	29.4%	14.7%	55.9%	
	Anthracycline+Taxanes	33.2%	25.2%	41.6%	
	CMF	32%	20%	48%	
Radiotherapy					
	No	34.5%	25.2%	40.3%	0.766
	Yes	38%	24%	38%	

*Statistically significant, IDC: Invasive duct carcinoma, ILC: Invasive lobular carcinoma, pT: pathological tumor size, pN: Pathological nodal status, TAM: Tamoxifen, AI: Aromatase inhibitors, CMF: Cyclophosphamide, methotrexate, flurouracil; BMI: Body mass index; SD: Standard deviation

Table 3. Overall survival multivariate analysis

Variable	Overall survival multivariate analysis	
	OR (95% CI)	*P* value
Menopausal state		
Premenopausal	1 (0.097 – 8.03)	0.911
Post-menopausal	1 (0.062- 5.24)	0.621
Male	2	0.393
	Ref 2	Ref 0.393
Pathological tumor stage		
pT1	1(0.16 – 2.08)	0.46
pT2	1(0.27 – 1.3)	0.19
pT3	1(0.31- 1.9)	0.62
pT4	3	0.57
	Ref 3	Ref 0.57
Pathological nodal stage		
pN0	3	**0.001**
pN1	1(0.07 – 0.46)	**≤ 0.001**
pN2	1(0.16 - 0.77)	**0.01**
pN3	1 (0.34 – 1.3)	0.28
	Ref 3	Ref 0.001
BMI groups		
Non-obese	1 (0.14 – 0.61)	**0.001**
Obese	1 (0.35 – 1.37)	0.298
Severely obese	2	0.004
	Ref 2	Ref 0.004
Hormonal treatment		
TAM	1 (1.9 – 16.4)	0.001
AI	1 (0.63 – 16.4)	0.156
TAM+AI	2	0.005
	Ref 2	Ref 0.005

pT: Pathological tumor size, pN: Pathological nodal status, TAM: Tamoxifen, AI: Aromatase inhibitors, Ref: Reference; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index

more frequent in the severely obese group than in the non-obese one (51.2% vs. 32.5% $P = 0.062$), followed by pathologic N1 disease (44.8% vs. 32%, $P = 0.76$) and grade 3 tumor (40.4% vs. 33.3% $P = 0.658$).

ER positivity (41.7 % vs. 35.4%, $P = 0.56$) and PR positivity (40.4% vs. 35.6%, $P = 0.99$) were more frequent in severely obese patients with non-significant distribution among BMI groups.

Moreover, a significant correlation was found between BMI groups and molecular subtypes ($P = 0.011$); we noted that luminal type was more frequent in non-obese compared with obese and severely obese groups (38.7% vs. 24.4%, 36.9%), while non-luminal type was frequent in severely obese compared with non-obese patients (50% vs. 25%). Her2 positivity (score +3) was more frequent in non-obese patients compared with obese and severely obese (40% vs. 24%, 35.8%), and TNBC was more often observed in severely obese than non-obese subjects (45.3% vs. 32%).

Regarding hormonal treatment, there was a significant correlation among different BMI groups. Most non-obese patients received tamoxifen (44.3%); whereas, severely obese patients received aromatase inhibitors either alone or in combination (58.5% and 51.7%, respectively, $P = 0.001$). No difference was observed between the BMI groups concerning the distribution of chemotherapy and radiotherapy.

Association between BMI and OS

Median OS was 26.7 months for the study population. Mean OS was significantly better in non-obese groups compared with the obese and severely obese patients (102.5, 80, 88 months, $P = 0.019$), with no impact on DFS ($P = 0.40$) (Figures 1-3).

Association of BMI with DFS

Univariate analysis showed no significant difference among BMI groups in terms of the mean DFS: 74, 62, and 72 months in non-obese, obese, and severely obese subjects respectively (P= 0.40, Figure 3).

The effect of BMI on the outcomes according to pathological lymph node staging (pN)

Univariate analyses of mean OS according to lymph node status showed the significant effect of BMI on outcomes only for patients with pathological lymph node 1(pN1) with a mean OS of 103, 76, and 60 months in non-obese, obese, and severely obese patients, respectively (P = 0.036).

BMI had no significant effect on patients with node negative (N0) and pathological lymph node stages 2 and 3 (P = 0.929, 0.246, and 0.553, respectively).

Pathological lymph node positivity was found to be an independent prognostic factor. The OS was significantly longer in node negative compared with heavily infiltrated N3 (103 and 63 months, P < 0.001) (Figure 4).

Association of BMI with hormonal type

OS was significantly lower in severely obese and obese than in non-obese patients receiving tamoxifen (TAM) alone (P = 0.052). The survival of patients who received aromatase inhibitor alone or in combination was not affected by the BMI (P = 0.499 and 0.349, respectively) (Figure 5).

Association between BMI and chemotherapy

Severely obese and obese patients had poorer survival rates with Anthracyclin in comparison with non-obese patients with P = 0.016. Patients receiving either Taxanes or CMF were not affected by BMI (P = 0.944 and 0.185, respectively).

OS multivariate analysis

In multivariate analysis, pathological nodal stage (P < 0.001; OR: 1; 95% CI: 0.07- 0.46), BMI (P < 0.001; OR: 1; 95% CI: 0.14-0.61) and hormonal treatment (P = 0.001; OR: 1; 95% CI: 1.9-16.4) remained as significantly associated with OS (Table 3).

Discussion

Among 950 patients (942 women and 8 men), obesity (BMI ≥ 30 kg/m^2) was observed in 63.29%

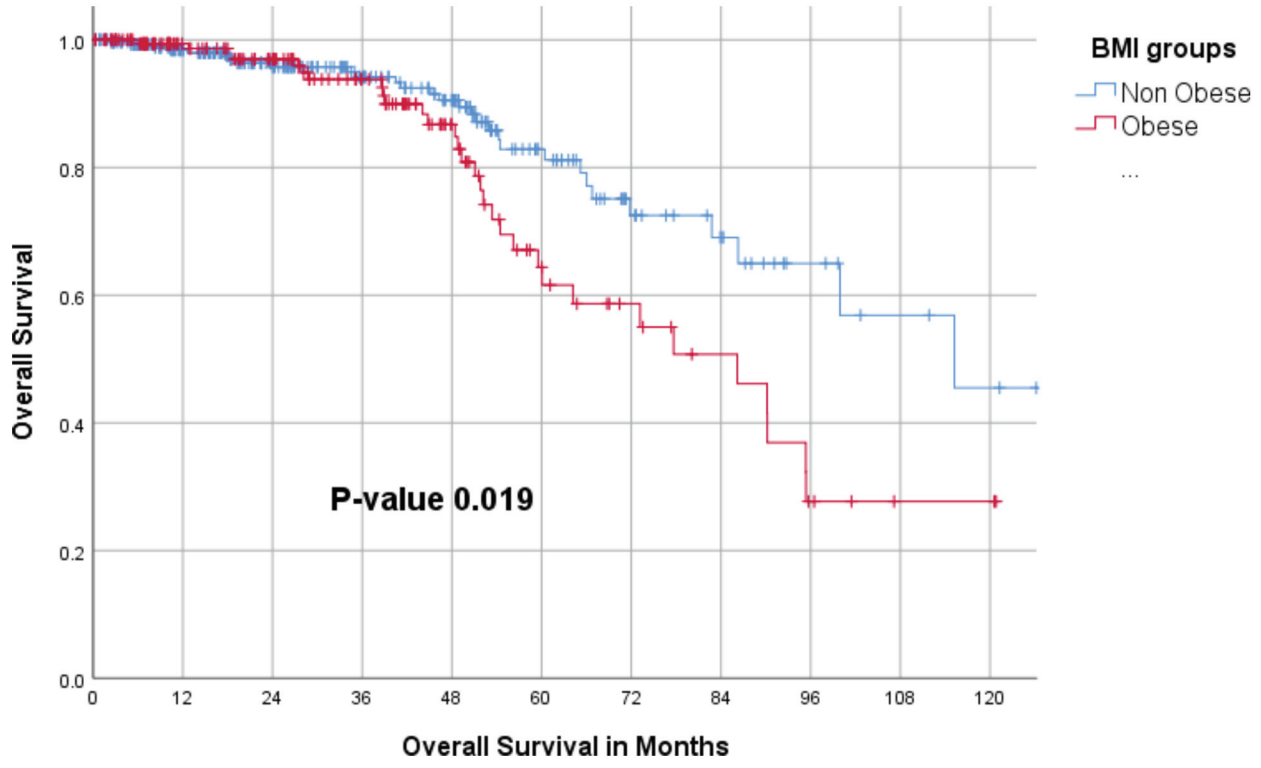

Figure 1. This figure shows the Kaplan–Meier plot of overall survival according to body mass index (BMI) in non-obese and obese groups.

and severe obesity (BMI ≥ 35) in 39.47%. BMI was significantly correlated with age and menopausal status ($P < 0.001$). The median age was 50 years (23-90), which was lower in non-obese and obese than in severely obese patients with BMI ≥35 (48, 49, 52, respectively). Most premenopausal patients (42.2%) were non-obese, while postmenopausal ones were more likely to be severely obese (46.9%).

Most premenopausal subjects had BMI <30 (42%), while the majority of the premenopausal patients were ≥35 (46.9%). Widschwendter et al. (2015) performed the SUCCESS-A trial on 3754 patients with high-risk early breast cancer. Their underweight and normal weight patients were younger on average (median age 50 years) and more often premenopausal (53%) compared with overweight or obese patients (mean age 54 years or older; fewer than 34 % premenopausal), which is consistent with the present study.[10]

Regarding the disease extent, the severely obese group was more likely associated with a large tumor size (T4 was 51.2% vs. 32.5%, $P = 0.062$), positive nodes N1 (45% vs.32%, $P = 0.76$), and grade 3 cancer cells (40.4% vs. 33.3%, $P = 0.658$), which was also reported by Boivin et al. (2017). Obese women more frequently had inflammatory presentations ($P = 0.006$), larger tumor sizes ($P = 0.038$), and axillary lymph node involvement ($P = 0.03$) with much more positive lymph nodes ($P = 0.02$).[11] This is also in agreement with Alarcón Rojas et al. (2019); they found that obesity was associated with more advanced stages, metastatic lymph nodes, and histologic grade 2 or 3.[12]

In the current study, severely obese patients were more frequently ERs (41.7 % vs. 35.4%, $P = 0.56$) and PR positive (40.4% vs. 35.6%, $P = 0.99$), which is in line with Gershuni et al. (2016).[13] The luminal type was more frequent in non-obese BMI <30 (38.7%), while non-luminal was frequent in severely obese BMI ≥35 (50%). These findings are in accordance with those obtained by Sahin et al. (2017) who reported that patients with BMI ≥30 kg/m^2 had less common luminal-like subtype.[14] Similarly, Verdial et al. (2018) conducted a study in the University of Washington, showing that women with luminal

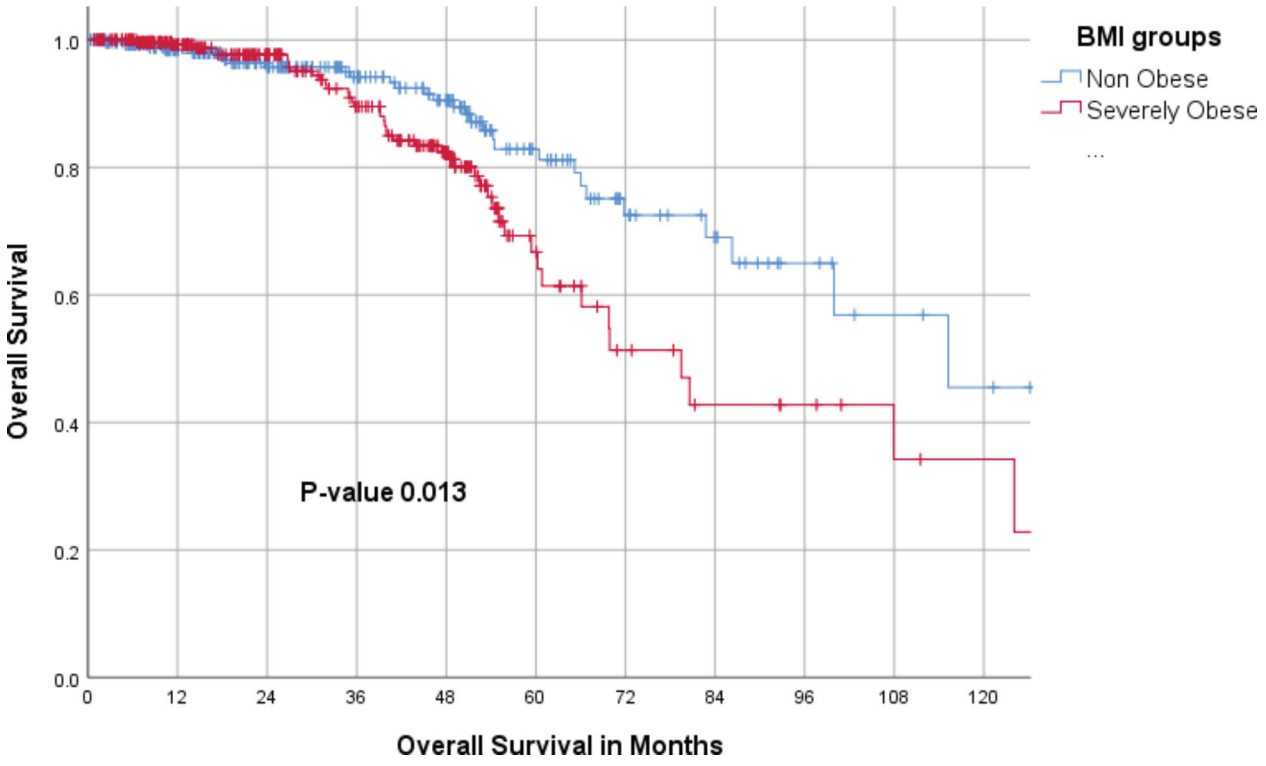

Figure 2. This is a Kaplan–Meier plot of overall survival according to body mass index (BMI) in non-obese and severely obese groups.

B tumors were more likely to have a BMI <25 kg/m^2.[15] In the present study, TNBC was more often observed in severely obese patients BMI ≥35 (45.3%), whereas the amplified Her2 status (score +3) was more frequent in non-obese subjects (40%). This is in agreement with Gershuni et al. (2017) who reported that obese women were more likely to present with TNBC, and normal weight patients were Her2 positive.[16] Also, Sahin et al. (2017) revealed the presence of TNBC in obese women.[14]

In hormone receptor positive BC, BMI groups affected the treatment outcome only for patients receiving tamoxifen alone with no impact on the subjects administered with AI alone or in combination. On the contrary, Ewertz et al. (2012) investigated 4760 patients receiving adjuvant endocrine treatment using AIs (and/or TAM), and normal weight subjects (BMI<25 kg/m^2) showed no significant difference in either OS or DFS with obese women (BMI≥30 kg/m^2).[17] Another study, however, found a poorer response to AIs in overweight and obese women, suggesting the inadequate suppression of circulating estrogen due to ineffective aromatase inhibition.[18] In a recent study on metastatic BC patients treated with either fulvestrant or AIs, there was no significant difference among normal weight, overweight, and obese patients in terms of time to progression or objective response rate.[19] The effect of tamoxifen on the prognosis is a reflection of the nature of the population, being mostly obese. The response of aromatase inhibitor was not superior due to the presence of more adipose tissues compared with normal weight individuals.

Under-dosing of chemotherapy in obese and overweight cancer patients may have a negative impact on survival. The American Society of Clinical Oncology (ASCO) has recommended appropriate dosing for these patients.[20] The data on chemotherapy dosing were not available in the current study. The potential impact on patients' prognosis could be investigated only for the type of chemotherapy. BMI ≥30 group was associated with poor survival in patients receiving anthracyclin-based chemotherapy (P = 0.016), and there was no significant effect on those receiving either Taxanes or CMF. The effect of

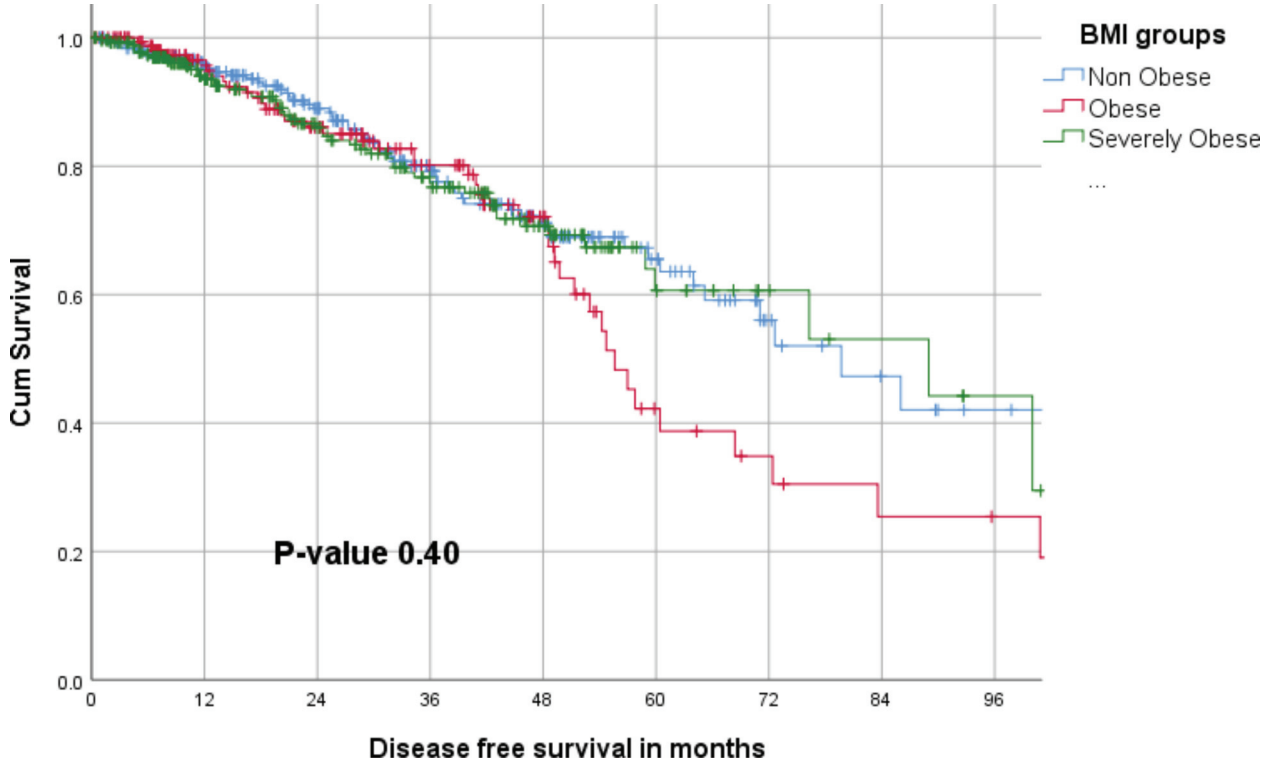

Figure 3. This is a Kaplan–Meier plot of disease-free survival according to body mass Index (BMI) in all groups.

neither anthracycline-based nor taxane-based chemotherapy regimen affected DFS or OS, which is consistent with the results shown in the primary analysis of the ADEBAR trial.[21]

The mean OS was by far better for non-obese patients (BMI < 30) compared with obese ones (102.5 months vs. 80 and 88) with no effect on the DFS. Similar results were shown in an analysis by Jackisch et al. (2015) who evaluated the impact of BMI on DFS and OS according to breast cancer subtypes in 8872 patients with primary BC treated with neoadjuvant chemotherapy. Their study found that obese (BMI 30 to < 40) and very obese patients (BMI ≥ 40) had shorter DFS and OS in comparison with normal weight patients (BMI =18.5 to < 25).[22, 23] In contrast to our study, a recent investigation showed more advanced staging in obese patients, but no significant effects were found on survival.[12] In addition, obese patients had a significantly improved progression free survival in a study restricted to women receiving chemotherapy.[24] On the contrary, research has shown that BMI has no effect on DFS or OS. This was evident in a study conducted in New Zealand on women with BC with 35% of the patients having a high BMI ≥30. There was no association between BMI and BC survival or DFS regardless of the treatment received.[25] This is consistent with the HERA trial in HER2-positive metastatic BC and a study done in Louisiana on 523 patients in which 55% were obese (BMI > 30).[26, 27] Moreover, an analysis of 489 patients in three randomized trials of chemotherapy for metastatic breast cancer, showed no correlation between BMI and progression-free or OS.[28]

To our knowledge, the present study is the most comprehensive analysis of obesity as a prognostic factor in BC in the Middle Eastern Arab countries. However, the present work was limited as it was retrospective with a relatively short period of follow-up.

Conclusion

In conclusion, the present study showed shorter

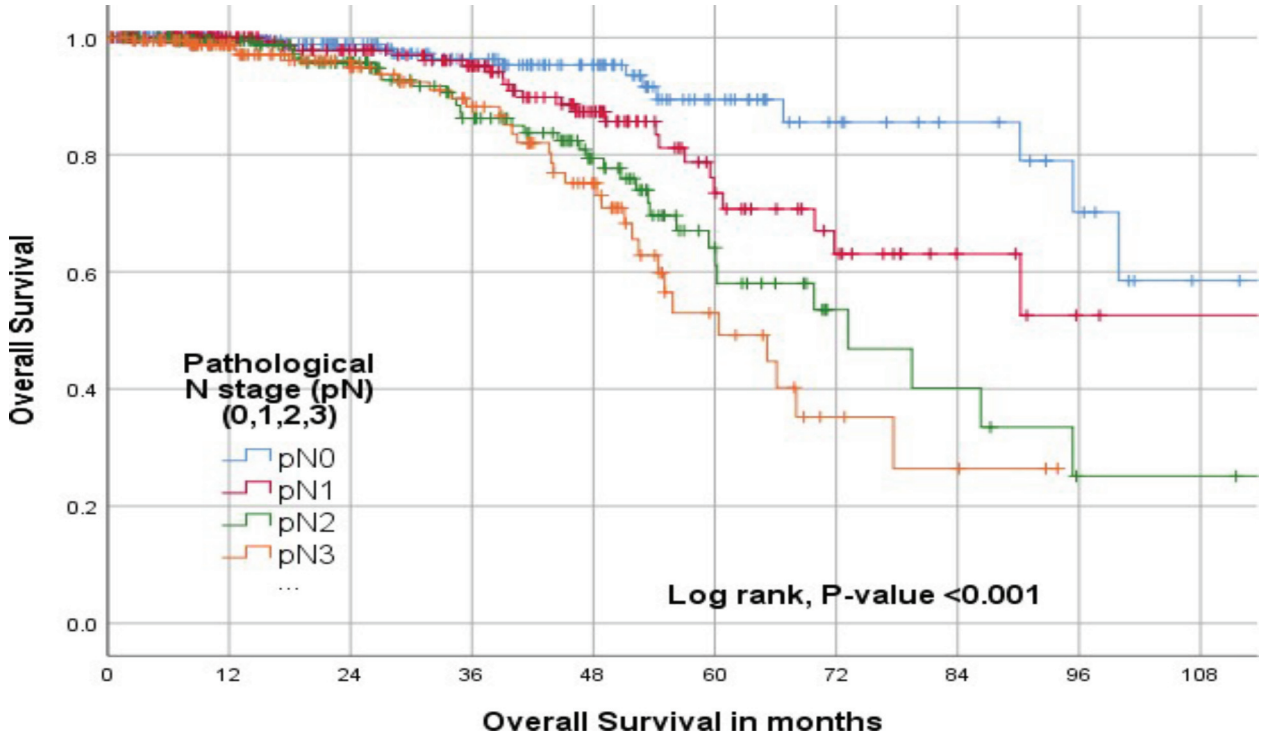

Figure 4. This is a Kaplan–Meier plot of disease-free survival according to lymph node stages N0, N1, N2 and N3.

OS in obese (BMI = 30-34.9) and severely obese patients (BMI ≥35), when compared with the non-obese (BMI <30) group (*P*= 0.019) without affecting DFS (*P*= 0.40).

Acknowledgement

We are thankful to our medical colleagues and cancer registry employees for helping us to collect the cases as well as the medical data.

Conflict of Interest

None declared.

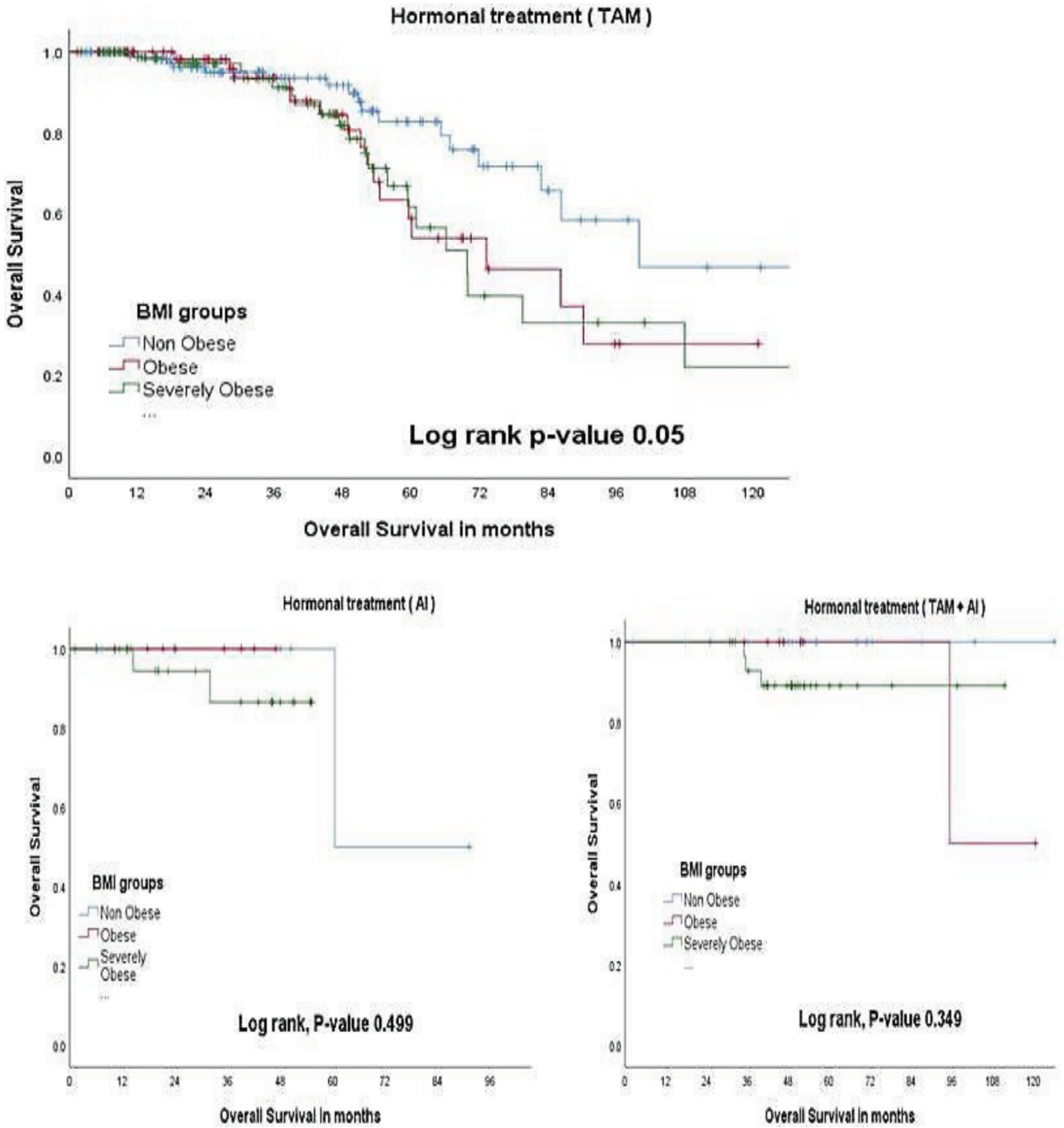

Figure 5. This figure shows the Kaplan–Meier plots of overall survival (OS) according to body mass index (BMI) group (non-obese, obese, and severely obese) in patients received tamoxifen (TAM), aromatase inhibitors (AI), or both.

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