ALLRED SCORE DIRECTLY ASSOCIATED TO BODY MASS INDEX IN KURDISH PREMENOPAUSAL WOMEN WITH BREAST CANCER

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ABSTRACT

Background

Obesity has been documented as an important prognostic factor and increased mortality with each successive increase in body mass index (BMI). It is unclear whether these associations differ among breast cancer subtypes.

Objectives

To know the association of the Allred score which has both predictive and prognostic value, with the body mass index in Kurdish Premenopausal women with breast cancer.

Patients and Methods

This study carried out at Hiwa hematology/oncology hospital of Sulaimani between June 2007 to December of 2015. Age, menopausal status, hormone receptor, Her-2 neu status height, weight, and body mass index were studied. Allred score by immunohistochemistry of all breast cancer patients was retrospectively analyzed.

Results

We conducted a population-based case-case study consisting of 519 women diagnosed with invasive breast cancer. Mean age of the studied group was 47.3±9.2 years. Mean menopausal age was 51±3 years; almost two-thirds of whom were premenopausal. Mean BMI of breast cancer patients was 30.1±5.6 kg/m2; 47% were obese. There was a strong association between high BMI and breast cancer in the age period of 40 to 49 years (p=0.03). The obese patient had a high tumor grade, ki67 and stage III disease. Strong expression of both Estrogen and progesterone receptors were observed in obese premenopausal patients.

Conclusion

Obese women usually presented with an increased risk of breast cancer in premenopausal women, advanced stage, and the majority of them had positive hormonal receptor status (ER/PR) Estrogen Receptor /Progesterone Receptor. Fortunately, obese linked to high Allred score with good response to hormonal therapy and better survival.

Keywords: *Breast Cancer, Body Mass Index, Obesity, Estrogen Receptor, Allred Score.*

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INTRODUCTION

A meta-analysis estimated that there is a 3% increase in risk per 1 kg/m^2 increase in BMI (Body Mass Index) [1].Obesity has further been linked to breast cancer recurrence and poorer survival in pre- and post-menopausal breast cancer [2-5].

Obesity dramatically modifies the adipose tissue microenvironment in numerous ways, including induction of fibrosis and angiogenesis, increased stem cell abundance, and expansion of proinflammatory immune cells. As many of these changes also resemble shifts observed within the tumor microenvironment, proximity to the adipose tissue may present a hospitable environment to developing tumors, providing a critical link between adiposity and tumorigenesis [6].

Multiple studies have revealed that the degree of Estrogen Receptor positivity is directly related to tumor responsiveness to antiestrogen therapy. In the earlier Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Overview analysis, women with tumors that had 2+ ER staining derived a significantly larger reduction in the risk of death from 5 years of tamoxifen compared to those with 1+ staining. Similarly, patients who had tumors with an Allred score of 6 and above —Allred score is calculated as the sum of an intensity score (range, 1–3) and a frequency score (range, 0–5) of ER and PR staining—are most likely to respond to treatment [7].

The biosynthesis of estrogens differs between premenopausal and postmenopausal women [8]. The qualitative expression (absent/present) of ER and PR is predictive for treatment response and prognostic for the outcome but to a different extent for each receptor [9]. Identifying predictors of endocrine responsiveness is, therefore, important to avoid unnecessary toxicities and to promote the selection of alternative treatment strategies for patients with endocrine-resistant tumors

PATIENTS AND METHODS

This retrospective-prospective study conducted at Hiwa Hematology/Oncology Teaching Hospital in Sulaimani. It covered a period of nearly seven years from 2007 to 2015. Data were collected from 519 cases concerning(age, sex, weight, height, body mass index) and clinicopathological assessment (such as tumor size, histological type, lymph node status), TNM(tumor,lymph node,metastasis) staging, histology grade, ER/PR ,(Herceptin Receptor) HER2 status and all red score).

Information obtained via patient database provided in their files in the registry unit at the hospital. Completion of the full questionnaire for each patient was done during their requested visits to the hospital, either for receiving treatments, follow up sessions or merely for this study. Male patients, dead patients data and non-compliant and uncooperative patients were excluded from the study.

Body mass index was calculated as weight in kilograms divided by height in meters squared and rounded to the nearest tenth. Following current recommendations, normal weight was defined as a BMI of 18.5-24.9; overweight as BMI of 25.0 to 29.9, and obesity as a BMI of 30.0 or higher.

Statistical analysis: All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 17 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fisher's exact test was used when expected variables were less than 5) One way ANOVA analysis was used to compare between more than two means. In all statistical analysis, level of significance (p-value) set at ≤ 0.05 and the result presented as tables and/or graphs. Statistical analysis of the study was done by the community medicine specialist.

RESULT

A total of 519 breast cancer women were included in the present study. Mean age of breast cancer patients at diagnosis was 47.3±9.2 years; 71% of them were between 40-59 years at diagnosis(Table 1). Both obesity and overweight, with increasing age, lead to an increase in the number of breast cancer patient to reach the peak between 40-49 years (p=0.03).

Almost two thirds (64%) of our patients were premenopausal. Mean age of menopause was 51±3 years.No significant differences were observed among breast cancer patients with different BMI categories regarding menopausal (p>0.05). Data are shown in Table 2.

More than half of the obese patient had a high-grade tumor and low-grade tumor reported in an only

minority of obese patient had a low-grade tumor but this was statistically not significant pvalue= 0.17 (Table 3).

Strong correlation documented between high proliferative index Ki67% and obesity in Kurdish premenopausal women 50.1% with P- value <0.001 (Table 4).

Majority of the obese patient in our study diagnosed with locally advanced disease stage III(48.8%), versus (32.9%) of patients with normal BMI (Table 5).

Table 1. Age Distribution According to BMI Categories.

Variable		Normal		Overweight		Obese		χ^2	P
		No.	%	No.	%	No.	%		
AGE	No.								
20-29 years	11	3	4.4	5	3.2	3	1.3		
30-39 years	76	11	16.2	29	18.7	36	15.5		
40-49 years	177	23	33.8	63	40.6	91	39.1	19.4*	0.03
50-59 years	148	22	32.4	45	29.0	81	34.8		
60-69 years	38	5	7.4	11	7.1	22	9.4		
≥ 70 years	6	4	5.9	2	1.3	0	-		

Table 2. Relation between BMI and menopausal status of the patient.

Variable	Normal		Overweight		Obese		χ^2	P
	No.	%	No.	%	No.	%		
Menopause								
Premenopausal	54	64.2	129	67.9	148	60.4	2.6	0.2
Postmenopausal	30	35.8	61	32.1	97	39.6		

Table 3. Relation between BMI and Grade of the Tumor.

Grade	Normal	Overweight	Obese	Total
Low Grade	6 (25%)	6 (25%)	12 (50%)	24
Intermediate grade	7 (5.2%)	59 (43.7%)	69 (51.1%)	135
High grade	20 (11.6%)	47 (27.3%)	105 (61%)	172

Table 4. Relation between BMI and ki67 of the Tumor.

BMI groups	Ki67% in Premenopausal Patients					
	<10%		10-20%		>20%	
	N	%	N	%	N	%
Normal	0	-	9	16.4	12	19.3
Overweight	5	62.5	18	32.7	28	33.7
Obese	3	37.5	28	50.9	43	51.8
Total	9	100	55	100	83	100

P value <0.001

Table 5. Effect of BMI on the stage of cancer.

Variable	Normal		Overweight		Obese		χ^2
	No.	%	No.	%	No.	%	
TNM staging							
0	0	-	3	1.6	0	-	
I	10	16.5	18	14.3	23	14.5	26.3*
II	21	38.8	43	34.9	50	28.5	
III	20	32.9	50	40.2	75	48.8	
IV	6	10.6	7	5.8	8	5.4	

No significant association was observed between premenopausal breast cancer patients with different BMI groups regarding molecular subtypes (p=0.3). Table 6.

A significant association was observed between obesity and Allred scores of PR among breast cancer patients (p=0.02). There was a significant association between obesity and Allred scores of ER among breast cancer patients (p=0.03) See Figure 1.

There was a significant association between premenopausal breast cancer patients with strong Allred score and obesity (p=0.03). No significant difference was observed between postmenopausal breast cancer patients with different Allred scores regarding BMI (p=0.4), Table 7.

Table 6. Distribution of BMI According to Molecular Subtypes.

Molecular subtypes	Premenopausal BMI						
	Normal		Overweight		Obese		Total
	N	%	N	%	N	%	
HR+/Her-	29	53.7	63	48.8	83	56.1	175
HR+/Her+	7	13.0	23	17.8	20	13.5	50
HR-/Her+	7	13.0	28	21.7	22	14.9	57
HR-/Her-	11	20.4	15	11.6	23	15.5	49

χ^2=6.3, P=0.3

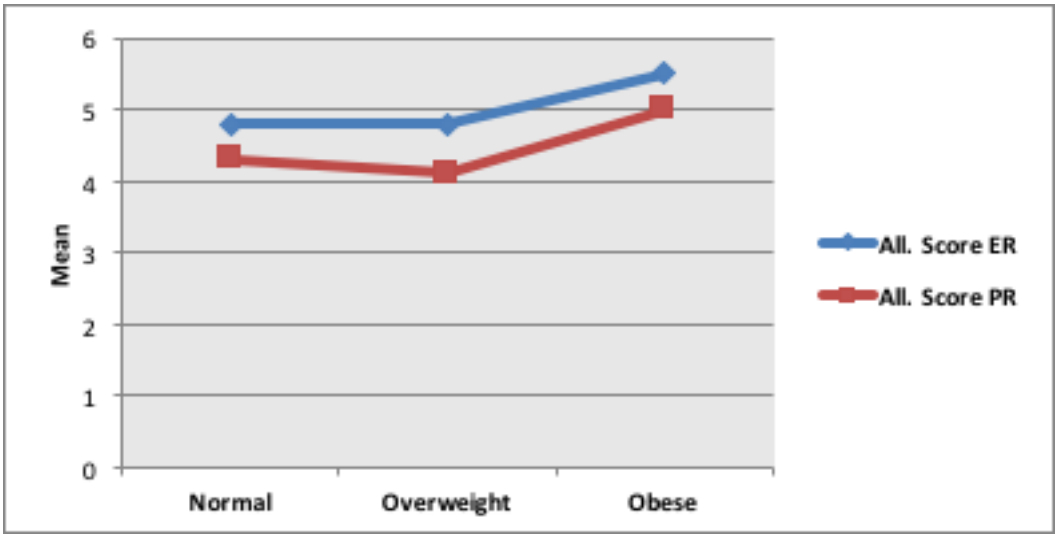

Fig 1. Distribution of Menopausal Age, Allred Scores for ER and PR Means According to BMI Categories.

Table 7. Distribution of Allred Scores According BMI for Menopausal and Postmenopausal Breast Cancer Patients.

BMI groups	Premenopausal Allred scores						Postmenopausal Allred scores					
	Weak		Moderate		Strong		Weak		Moderate		Strong	
	N	%	N	%	N	%	N	%	N	%	N	%
Normal	6	35.3	4	10.3	29	17.1	2	28.6	5	20.0	10	10.1
Overweight	8	47.1	20	51.3	59	34.7	1	14.3	8	32.0	29	29.3
Obese	3	17.6	15	38.5	82	48.2	4	57.1	12	48.0	60	60.6
Statistical test	χ^2=10.5, P=0.03						Fishers exact test=0.4					

DISCUSSION

The percentage of overweight and obesity has been steadily increasing over the last two decades. Obesity is an established risk factor for the development of postmenopausal breast cancer [10]. Obesity has emerged as an important prognostic factor in breast cancer. A prospective study of over 500,000 women revealed a stepwise increase in worsening prognosis and increased mortality with each successive increase in BMI [11].

Our study revealed that the percentage of obesity and overweight among breast cancer patients were 47.2% and 36.4%, respectively. These findings are close to another study done in Sulaimani [12]. Of our findings are similar to results of a study done in Baghdad Medical City which reported obesity and overweight prevalent among breast cancer patients around 47% and 36% respectively [13].

Our results showed that mean age at diagnosis for breast cancer patients was 47 ± 9 years; lower than mean age reported by a study done in Iraq as 49.7 years [13]. This result was similar to another study done in Sulaimani which reported the mean age of 47.4 ± 11 [14]. These small differences might be attributed to the difference in inclusion and exclusion criteria between these studies.

An association was observed between the number of breast cancer patients with age to reach the peak at 40-49 years, in both overweight and obese patients (p=0.03). This is in disagreement with a study reported a peak cancer incidence at 50-59 years among obese post-menopausal patients in Arab women [15]. Mean age at menopause for breast cancer women in the current study was 50.6 years; 36.3% of them were postmenopausal. These findings are similar to results of the previous study done in Iraq [14,15].

The relationship between obesity and specific breast cancer characteristics, such as hormone receptor status and molecular subtype, is less clear [16]. Positive HR were the prevalent subtype (69.6%), while HER2 positive represented only 28.4% % of the patients, this is similar to studies done in Iraq and Turkey [14, 17]. There was no significant association between breast cancer patients with positive HR .this is not compatible with the results of multiple clinical trails concerning the postmenopausal obese patient.

A meta-analysis conducted on the associations between obesity and the risk of breast cancer subtypes defined by ER and PR. They reported that obese women had 22% lower risk of premenopausal ER-positive (ER+)/PR+ breast cancer than premenopausal women with BMI lower than 25 kg/m2 and 39% higher risk of postmenopausal ER+/PR+ breast cancer than postmenopausal women with BMI lower than 25 kg/m^2 (summary risk ratio=1.39, 95% CI =1.14–1.70). In the same study, obesity was not associated with the risk of ER-negative (ER–)/PR– breast cancer in either premenopausal women or postmenopausal women [18].

In our study no link observed between obesity and triple-negative cancer this also explained by another study that showed patients with high BMI are most clearly associated with hormone receptor-positive tumors and suggest that triple-negative tumors may have distinct etiology [19, 20] .

There was a significant association between Allred score for both ER and PR and obesity (p=0.03 and p=0.02 respectively), as shown in Figure 1. This relation is mainly seen in premenopausal breast cancer patients with a strong Allred score for both ER and PR receptors (p=0.03) in the obese patient, as shown in Table 7. Unfortunately, there is no known study explains the relationship between Allred score and BMI.the high level of hormone receptor expression indicate a better response to endocrine therapy and better disease control.

In conclusion, obese women usually presented with an increased risk of breast cancer in premenopausal women. Obesity associated with adverse prognostic factors like an advanced stage, high KI67 and majority of them had positive hormonal receptor status (ER/PR). fortunately, obesity in premenopausal female linked to high Allred score with good response to hormonal therapy and better survival.

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