RESEARCH ARTICLE

Overweight: Is It a Prognostic Factor in Women with Triple-Negative Breast Cancer?

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Abstract

Background: Obesity is associated with poor outcomes in patients with breast cancer expressing hormone receptors, but this association is not well established for triple-negative breast cancer. In this study, we investigated the influence of body mass index (BMI) in triple-negative breast cancer outcomes. **Methods:** This is a descriptive and analytical retrospective cohort study at the Regional Oncology Center Hassan II-Oujda. We identified 115 patients with triple-negative breast cancer, met the criteria for inclusion, treated between January 2009 and December 2011. The clinicopathological characteristics were collected to assess the association between BMI and overall survival and disease-free survival at 5 years, using the Kaplan-Meier and Cox model. **Results:** Data analysis focused on 115 patients, 34 patients (28.7%) were normal weight (BMI < 25) and 82 patients (71.3%) were overweight (BMI ≥ 25). The rates of overall mortality and progression at 5 years were 37.4% and 69.6% respectively. After adjusting for clinicopathological variables and menopausal status, overweight was associated with OS (HR: 2.903, 95% CI: 1.551- 5.432, p = 0.001) and DFS (HR:1.899, 95% IC: 1.05 – 3.433, p=0.034) in all patients with triple-negative breast cancer. When stratified by menopausal status, overweight was associated with DFS and OS (HR : 3.242, 95% CI: 1.249 to 8.412, p = 0.016) and (HR : 2.752, 95% CI: 1.267 to 5.978, p = 0.011) respectively in pre-menopausal women. By cons, BMI was not associated with DFS or OS in postmenopausal women. **Conclusions:** Overweight is an independent prognostic factor for OS and DFS at 5 years in all patients with triple-negative breast cancer, and menopausal status may be a mitigating factor. Premenopausal women with overweight are at greater risk of death and progression than women with normal weight. Once validated, these results should be considered in the development of prevention programs.

Keywords: Body mass index- Triple-negative breast cancer- overweight- overall survival- disease free-survival

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Introduction

Breast cancer is now widely recognized that is a heterogeneous disease composed of different subtypes, characterized by their different clinico-pathological features, prognoses and responses to treatment (Perou et al., 2000; Sorlie et al., 2001). Triple-negative breast cancer (TNBC) is defined by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) expression. This molecular subtype is particularly aggressive, frequently seen in premenopausal women, and accounts for 10–15% of breast cancers in white women, with a higher prevalence among black women (Perou et al.,1999; Rais et al., 2012).

Obesity is associated with poorer outcomes in patients with hormone receptor-positive breast cancer, but this association is not well established for triple-negative breast cancer. Therefore, we retrospectively investigated the effects of BMI at the time of breast cancer diagnosis on outcomes in triple-negative breast cancer.

Materials and Methods

This descriptive and analytical retrospective cohort study included all female patients with triple-negative breast cancer who received treatment at the Regional Oncology Center Hassan II-Oujda, Morocco, between January 2009 and December 2011. Exclusion criteria included ER or PR positivity, HER2 overexpression/ amplification and male sex.

Information was available for all patients' age and menopausal status at diagnosis, height and weight at diagnosis (for BMI calculations), tumor size, number of lymph nodes removed, number of positive lymph nodes, histological type and grade, treatment regimen.

Associations between BMI and other characteristics were analyzed using the chi-square test. For the assessment of the influence of BMI on survival outcome (OS and DFS at 5 years), we adjusted for age at diagnosis, menopausal status, tumor size, nodal status, grade and systemic adjuvant therapy by multivariate Cox proportional hazards

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models. All P values were two-sided. Statistical analyses were performed using SPSS Statistics 21.0. P<0.05 was considered significant.

Results

Patients and follow up

The study included 115 women with TNBC, 34 (28.7%) of whom were a normal weight (BMI <25 kg/m^2) and 82 (71.3%) of whom were overweight (BMI ≥25 kg/m^2)

The normal weight group's median age was 47.1 years (range: 29–65 years). The overweight group's median age was 45.6 years (range: 26–87 years)

The overweight group had a significantly higher proportion of larger tumours (>3 cm; p=0.05) with vascular emboli (p=0.038) and included more premenopausal women (p<0.001). BMI was not associated with tumour grade, lymph node status and age (Table 1).

Mortality and disease progression

Rates of overall mortality and disease progression at 5 years were 37.4% and 69.6%, respectively.

The normal weight group's rates of overall mortality and disease progression at 5 years were 41.9% and 61.3%, respectively. The overweight group's rates of overall mortality and disease progression at 5 years were 66.7% and 81.6%, respectively.

After adjusting for clinico-pathological variables and menopausal status, overweight BMI was associated with a worse overall survival OS (p=0,002) and disease-free survival DFS (p=0,002) than underweight BMI in patients with TNBC (Figure 1).

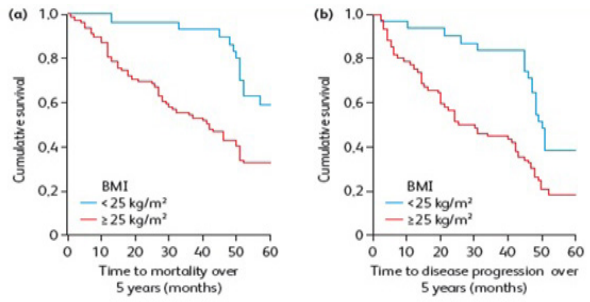

Figure 1. Kaplan- Meier Plots of Time to Mortality (a) and time to disease progression (b) in women with TNBC, according to BMI (<25 vs. ≥25 kg/m^2)

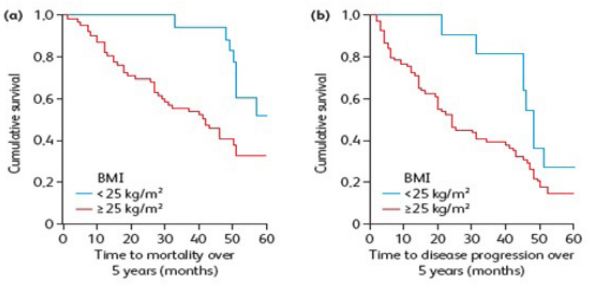

Figure 2. Kaplan- Meier Plots of Time to Mortality (a) and time to disease progression (b) in premenopausal women with TNBC, according to BMI (<25 vs. ≥25 kg/m^2)

In multivariable analysis, overweight was significantly with OS (hazard ratio [HR] for mortality 2.903, 95% CI: 1.551- 5.432, p=0.001, Table 3) and DFS (HR for progression 1.899, 95% CI: 1.05- 3.433, p=0.034, Table 2) after adjustment for clinicopathologic risk factors.

In stratification analysis, overweight was an independent prognostic factor for DFS (HR: 3.242, 95% CI: 1.249- 8.412, p=0.016, Table 2) and OS (HR: 2.752, 95% CI: 1.267- 5.978, p=0.011, Table 3).

Among postmenopausal women, BMI did not predict for DFS (HR: 1.345, 95% CI: 0.375–4.831, P = 0.648, Table 2) or OS (HR: 1.305, 95% CI: 0.276–6.172, p = 0.736, Table 3).

Discussion

Patients with this breast cancer phenotype tend to have a worse clinical outcome partly as a result of lacking a

Table 1. Baseline Characteristics of Patients

Characteristics	IMC < 25 N (%)	IMC ≥ 25 N (%)	p
Tumor size (cm)			
≤ 3	8 (23.5)	34 (42)	0.05
> 3	26 (76.5)	47 (58)	
Lymph node status			
N –	16 (47)	32 (39.5)	0.276
N +	18 (53)	49 (60.5)	
Tumor grade			
I – II	20 (58.8)	45 (55.5)	0.428
III	14 (41.2)	36 (44.5)	
Vascular emboli			
No	26 (76.5)	48 (59.3)	0.038
Yes	8 (23.5)	33 (40.7)	
Menopausal status			
Pre-	12 (35.3)	73 (90.2)	< 0.001
Post-	22 (64.7)	8 (9.8)	
Age (years)			
≤ 40	11 (32.3)	27 (33.3)	0.586
> 40	23 (67.7)	54 (66.7)	

Table 2. Univariate and Multivariate DFS Analysis of BMI in TNBC Patients According to Menopausal Status

Menopausal status / BMI	Univariate p	Multivariate p	HR	95% CI
Total	0.002	0.034		
BMI ≤ 25			1	-
BMI >25			1.899	1.05 – 3.433
Premenopausal patients	0.05	0.016		
BMI ≤ 25			1	-
BMI >25			3.242	1.249 – 8.412
Postmenopausal patients	0.642	0.736		
BMI ≤ 25			1	-
BMI >25			1.035	0.276 – 6.172

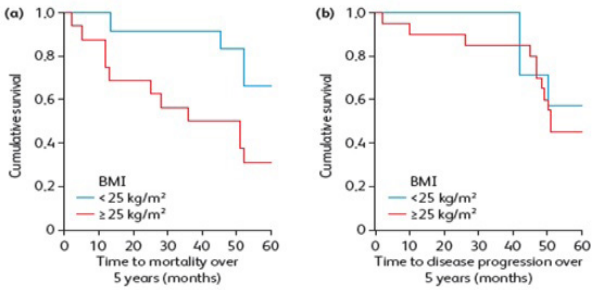

Figure 3. Kaplan- Meier Plots of Time to Mortality (a) and time to disease progression (b) in postmenopausal women with TNBC, according to BMI (<25 vs. ≥25 kg/m^2)

Table 3. Univariate and Multivariate OS Analysis of BMI in TNBC Patients According to Menopausal Status

Menopausal status / BMI	Univariate p	Multivariate p	HR	95% CI
Total	0.002	0.001		
BMI ≤ 25			1	-
BMI >25			2.903	1.551-5.432
Premenopausal patients	0.019	0.011		
BMI ≤ 25			1	-
BMI >25			2.752	1.267-5.978
Postmenopausal patients	0.036	0.648		
BMI ≤ 25			1	-
BMI >25			1.345	0.375-4.831

therapeutic target. Consequently, establishing a relation between modifiable factors that may portend an adverse outcome potentially may be beneficial to these patients (Ademuyiwa et al., 2011).

A number of studies (Dal Maso et al.,2008; Kroenke et al., 2005; Loi et al., 2005; Nichols et al, 2009) have evaluated the adverse prognostic effect of general obesity before breast cancer diagnosis or at the time of or shortly after a diagnosis of breast cancer, but very few studies have focused on BMI's prognostic role in specially TNBC, the results of which vary considerably (Tao et al, 2006; Majed et at, 2008; Dawood et al, 2008).

In the current study, we demonstrated that overweight has a negative influence on DFS and OS only in premenopausal patients with TNBC but not in postmenopausal ones. Our results agreed with several reports in the literature, which showed that increasing BMI is related to a poor outcomes and short survivorship.

In a large study that involved 8,872 women, Fontanella et al demonstrated that mean DFS and OS were shorter in obese and very obese compared with normal weight patients in TNBC after a median follow up of 42.7 months (Fontanella et al., 2015). In a single center study of 818 patients with TNBC, obesity was associated with worse DFS and OS for premenopausal patients with TNBC at a median follow-up of 29 months (Turkoz et al., 2013). Pajares et al., (2013) performed a retrospective analysis including 5,683 operable BC patients enrolled in four randomized clinical trials (GEICAM/9906, GEICAM/9805, GEICAM/2003-02, and BCIRG 001) to assess the prognostic effect of body mass index (BMI) on disease recurrence, breast cancer mortality (BCM), and overall mortality (OM). As a result, Severely obese patients present a worse prognosis regarding recurrence, BCM, and OM than patients with BMI < 25. The magnitude of the harmful effect of BMI on survival-related outcomes was similar across subtypes including TNBC. Shuang Hao et al investigated the prognostic effects of body mass index (BMI) on clinical outcomes in 1106 patients with TNBC. They identified Overweight as an independent prognostic factor of OS in all women with TNBC, and menopause status as mitigating factor (Hao et al., 2015). Premenoposaul women who are overwheight with TNBC are at a greater risk of poor prognosis than normal weight ones. On the other side, no significant relationship between obesity and outcomes in patients with TNBC after controlling for clinically significant factors was found either by Tait et al., (2014) or Ademuyiwa et al (Ademuyiwa et al., 2011). This is possibly because TNBC patients tend to receive cytotoxic chemotherapy which may neutralize potential detrimental effects of a higher BMI (Hao et al., 2015).

There are several hypotheses on the mechanisms that link increasing BMI to TNBC prognosis (Rose et al., 2009; Verreault et al.,1989; Foluso et al., 2011). Such as obesity associated comorbidities that interfere with optimal treatment (Hao et al., 2015). Metabolic syndrome, presents increased levels of insulin and insulin-like growth factor, hormones with potent mitogenic activity toward epithelial cells (Nelson et al., 2013; Renehan et al., 2006; Yu et al., 2000). Also paracrine secretion of interleukin-6 and tumor necrosis factor-alpha and the establishment of a pro-inflammatory micro-environment can induce the development of malignant phenotypes that are independent of hormonal secretion (Howe et al., 2013). Alternatively, the detrimental effect of obesity on TNBC prognosis might be linked to sub-therapeutic treatment. Drug dosing has traditionally been based on a patient's estimated body surface area (BSA) in adults (Chen et al., 2016). It's suggested elsewhere that the adipokines, which include leptin and vascular endothelial growth factor and heparin-binding epidermal growth factor- like growth factor, exert a stimulatory effect on ER-negative breast cancers, where estrogen action is not a factor, by hormonal, paracrine, and autocrine mechanisms (Zheng et al., 2013). Ishikawa et al., (2004) found that high leptin and leptin receptor expression in breast cancer tissue was associated with distant metastases. And Liu et al., (2011)reported that serum leptin concentrations were higher in patients with high-grade tumors and that a polymorphism in the leptin receptor gene at codon 109 (LEPRO-109RR genotype) was more frequent in patients who were overweight and those with triple-negative cancers. Leptin implicate stimulatory effects on breast cancer cell proliferation and invasion, but also possesses angiogenic activity (Niu et al., 2013).

It seems to be the first study to examine the relationships between obesity and TNBC survival outcomes in Moroccan patients, to our knowledge. Our

study established a relationship between overweight and TNBC which is beneficial for this aggressive subtype of breast cancer. These results will be taken into account in the programs of prevention and also in the medical management by using intensified treatments in patients with overweight. However, there were some potential limitations in our study. Firstly, due to the relatively proportion of underweight and obese patients, classification was measured in a binary scale. This classification did not allow to clearly distinguish between women who were obese and those who were overweight. Secondly, the retrospective nature of the study design and its relatively small sample size.

In conclusion, this retrospective cohort analysis showed that overweight BMI was an independent prognostic factor for OS and DFS at 5 years in women with TNBC. Our analysis indicated that menopausal status may be a mitigating factor, with overweight premenopausal women at greater risk of death and progression than women with a normal weight. Clearly, the relationships between outcome and obesity in triple-negative breast cancer are an important topic for further study. Once validated, these results could be considered in the clinical management of breast cancer and in the development of targeted preventive programs.

List of abbreviations

BMI, Body Mass Index
OS, Overall Survival
HR, Hazard Ratio
CI, Confident Interval
DFS, Disease Free Survival
DNA, Deoxy-Ribonucleic Acid
ER, Oestrogen Receptor
PR, Progesteron Receptor
HER 2, Human Epidermal growth factor Receptor 2

Declarations section

Ethics approval and consent the study was performed according to the ethical principles and informed patient consent for using data was obtained.

Standards of reporting

Reporting guidelines "STIPOD".

Consent of publication

The patients provided consent for publication.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Al jarroudi performed data collection, analysis and interpretation and drafted the article. Seddik and Brahmi participated in the collection of data. Abda participated in the statistical analysis and interpretation of results. Said Afqir contributed in the article's drafting and performed a critical revision of the article. All authors read and approved the final manuscript.

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