RESEARCH ARTICLE

Editorial Process: Submission:05/07/2022 Acceptance:09/04/2022

The Association between Abdominal Obesity, Metabolic Syndrome and Survival Outcomes in Patients with Breast Cancer

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Abstract

Background: Obesity and metabolic syndrome (MetS) have been linked to the risk of developing certain cancers. This study aimed to analyze the association between obesity markers, MetS and survival outcomes of patients with breast cancer. **Methods:** This study retrospectively investigated patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-), nonmetastatic breast cancer diagnosed between January 2010 and December 2019. Data on clinical conditions, body mass index (BMI), waist-to-hip ratio (WHR), MetS, time of metastasis and death were collected. **Results:** A total of 223 breast cancer patient records were eligible for analysis. Obesity (BMI ≥ 25) was found in 38.1% of cases. Abdominal obesity measured as WHR ≥ 0.85 was found in 48.9%. Metabolic syndrome was detected in 56.1% of patients and was associated with older age (OR = 2.196, p = 0.005), postmenopausal status (OR = 2.585, p = 0.001), obesity (OR = 5.684, p = 0.001) and abdominal obesity (OR = 2.612, p = 0.001). Obesity was not associated with poor disease-free survival (DFS) or overall survival (OS), while abdominal obesity was modestly associated with poor DFS (HR = 1.539, p = 0.083) and OS (HR = 3.117; p = 0.019). Multivariate analysis revealed that WHR ≥ 0.85 was independently associated with unfavorable DFS (HR = 1.907, p = 0.027). Patients with MetS had a similar survival rate to those with normal metabolism. **Conclusion:** In Indonesian women with HR+/HER2- breast cancers, obesity and MetS were not associated with poor survival outcomes. The abdominal obesity marker (WHR) was more accurate in predicting unfavorable DFS.

Keywords: Abdominal obesity- breast neoplasm- estrogen receptor- metabolic syndrome- prognosis

Asian Pac J Cancer Prev, **23 (9)**, 3157-3165

Introduction

Obesity and metabolic syndrome (MetS) are significantly associated with breast cancer incidence, although their association with the incidence of other tumors remains unclear (Bitzur et al., 2016). In women with breast cancer, obesity increases the risk for recurrence and death, especially in the estrogen receptor (ER)-positive subtype (Jilarerspong et al., 2016). In another study, obesity became a poor prognostic factor for women in the treatment of triple-negative breast cancer (Chen et al., 2016). MetS is characterized by hypertension, increased waist circumference, high triglycerides, low high-density lipoprotein cholesterol (HDL-C), and increased blood glucose levels. In estrogen receptor-negative breast cancer, MetS was associated with an increased recurrence rate (Oh et al., 2011), possibly related to insulin resistance or mediated by adipokines. One previous study involving a large number of patients with breast cancer reported that MetS was associated with recurrence and distant metastasis (Berrino et al., 2014).

Recent studies showed that receiving chemotherapy as well as hormonal therapy for breast cancer treatment was associated with developing MetS (Dieli-Conwright et al., 2016; Sarici et al., 2020). It is presently unclear whether MetS and obesity, especially abdominal obesity, affect the recurrence and survival of patients diagnosed with hormone receptor (HR)-positive breast cancer who receive

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hormonal treatment. This current controversy needs to be explored further. This study aimed to determine the association between obesity, especially abdominal obesity, and MetS with recurrence and survival of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) subtypes, nonmetastatic breast cancer who had received hormonal treatment.

Materials and Methods

Study design and participants

This retrospective, observational study received approval from the Institutional Review Board of the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada (Ref: KE/FK/0793/EC/2019).

We investigated women with breast cancer who were diagnosed and treated between January 2010 and December 2019 in our hospital. The inclusion criteria for the selection of patients were age > 18 years, invasive ductal carcinoma histology type, HR+/HER2- subtype, and nonmetastatic stage. Patients had received adjuvant selective estrogen receptor modulator (SERM), e.g., tamoxifen (Tam), or aromatase inhibitors (AI) for at least 6 months before inclusion, with or without previous chemotherapy treatment. Clinical data, including age, TNM stage, histology type, hormone receptor expression, anthropometric and metabolic profiles, such as body mass index (BMI), waist circumference (WC), hip circumference, waist-to-hip ratio (WHR), serum triglyceride level, serum HDL-C, hyperglycemia, and hypertension at the initial visit (post breast cancer diagnosis), were collected. Metabolic syndrome was defined by the Modified National Cholesterol Education Program Adults Treatment Panel III (NCEP ATP III) for Asians.

Patients who had incomplete clinical, anthropometric, or metabolic data or incomplete regular follow-up visits and surveillance as well as patients with documented severe comorbidities (congestive heart failure, chronic kidney disease on hemodialysis, active tuberculosis or chronic obstructive pulmonary disease, systemic autoimmune disease or Eastern Cooperative Oncology Group (ECOG) performance status > 2) or multiple malignancies were excluded from selection.

Definitions

The presence of any three of five metabolic criteria was defined as MetS. The five criteria were as follows: 1) increased WC (male > 90 cm, female > 80 cm); 2) elevated triglycerides or use of medication for hypertriglyceridemia (triglyceride ≥ 150 mg/dL); 3) low HDL-C (male ≤ 40 mg/dL, female ≤ 50 mg/dL); 4) hyperglycemia (fasting glucose ≥ 100 mg/dL); and 5) hypertension or use of medication for hypertension (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg). Obesity was defined by BMI ≥ 25 according to the Asia-Pacific guidelines (Pan et al., 2008; WHO, 2000).

Disease-free survival (DFS) was calculated from the date of the pathology result of the primary tumor until the date of the earliest documented recurrence or metastasis, death from any cause, or the end of follow-up. Overall survival (OS) was defined as the time from the date of pathology result of primary tumor until the date of death or until the end of follow up. Survival follow-up ended on December 31st, 2020.

Measurements

Body mass index was calculated by dividing body weight in kilograms units by the square of a person's height in meters. BMI < 18.5 was considered underweight, 18.5 - 22.9 was considered normal, ≥ 23 was considered overweight, ≥ 25 was considered obese I, and ≥ 30 was considered obese II (WHO, 2000).

Waist circumference was measured as waist circumference at the umbilical level in centimeters by a tape meter line (Lemoncito et al., 2010). Hip circumference was the largest part of the hip around the buttock. The WHR was determined by dividing waist measurement by hip measurement. Abdominal obesity was defined as WHR > 0.85.

Resting blood pressure was measured as the average value of two measurements with a digital tensimeter in the sitting position as a standard procedure in our hospital. Triglyceride, HDL-C, and fasting glucose levels were measured by a standard laboratory protocol in our hospital. All clinical, anthropometric, and metabolic data at the initial visit after breast cancer diagnosis were extracted from medical records.

Recurrence and survival data were assessed every six months by clinical examination, breast, and abdominal sonography and yearly by chest X-ray, mammography and bone survey as routinely mandated by local clinical guidelines in our hospital.

Sample size calculation

Sample size was calculated using a sample size calculator for designing clinical research (sample-size.net/sample-size-survival-analysis) UCSF. Type I error $\alpha = 0.05$; type II error $\beta = 0.2$. If the proportion of MetS in breast cancer patients was 0.32 and the relative hazard group MetS for survival was 2; $Z\alpha = 1.9600$; $Z\beta = 0.8416$, then the total events needed were 75 events. Based on calculated events within 100 months of observation time and a baseline event rate of 30 events in the group without risk, a total of 213 breast cancer patients were needed for analyses.

Statistical Analysis

Patient characteristics were described using descriptive statistics. Normally distributed variables are shown as the mean ± standard deviation. Nonnormally distributed variables are shown as medians with ranges of minimum and maximum values. Independent T tests and X^2 tests were used to compare continuous and categorical data. A significant difference was considered if $p < 0.05$.

Kaplan–Meier estimation survival analysis and bivariate and multivariate Cox proportional hazard models (Cox regression) were implemented to show the association of obesity, WHR, and MetS with survival functions (DFS and OS). Hazard ratios (HRs) with 95%

confidence intervals (95% CIs) were calculated.

All statistical analyses were conducted using SPSS 23 (IBM Corp., Chicago).

Results

Clinical characteristics, obesity and metabolic syndrome in patients with HR+/HER2- breast cancer

There were 1,612 HR+/HER2-, breast cancer cases diagnosed and treated between 1 January 2010 and 31 December 2019. Ineligible cases were mostly due to incomplete metabolic parameters at the initial visit and surveillance data at certain points, as seen in the recruitment diagram in Figure 1. There were 223 HR+/HER2-, nonmetastatic breast cancer patients eligible for analysis. The median age at diagnosis was 49 years (ranging from 32 to 74 years old). Forty-seven patients were ER+/PR-, 174 were ER+/PR+ and 2 were ER-/PR+. Eighty-one (36.3%) patients were postmenopausal. All patients received tamoxifen (63.7%) or an aromatase inhibitor (36.8%). The clinical characteristics of the eligible patients are listed in Table 1.

Overweight and obesity, detected at diagnosis of breast cancer, were observed in 58.7% of women with HR+/HER2- breast cancer (Table 1). Obesity (BMI ≥ 25) was not associated with age (OR = 1.013; 95% CI 0.586 - 1.751; p = 0.962) or menopausal status (OR = 1.010; 95% CI 0.576 - 1.772; p = 0.971). Obesity was not associated with tumor size (OR = 0.952, 95% 0.554-1.635, p = 0.858), node involvement (OR = 1.128, 95% CI 0.548 – 2.317, p = 0.746), or histology grade (OR = 0.893, 95% CI 0.498 – 1.603, p = 0.705).

A waist-to-hip ratio ≥ 0.85 was observed in 48.9% of patients at the time of diagnosis and was not associated with age (OR = 1.405; 95% CI 0.851- 2.476; p = 0.170) and menopausal status (OR = 1.532; 95% CI 0.880-2.683; p = 0.132). There were no associations between WHR≥ 0.85 at diagnosis and tumor size (OR = 1.494, 95% CI 0.880 – 2.536, p = 0.137), node involvement (OR = 1.270, 95% CI 0.625 – 2.580, p = 0.508), or grade (OR = 1.237, 95% CI 0.700 – 2.187, p = 0.464).

A total of 125 out of the 223 (56.1%) patients were diagnosed with MetS at the time of breast cancer diagnosis. MetS was more common in postmenopausal women than in premenopausal women (70.4% vs. 40.9%, OR = 2.585, 95% CI 1.448-4.614, p = 0.001) and was associated with older age (OR = 2.196, 95% CI 1.265-3.812; p = 0.005), obesity (OR = 5.684, 95% CI 3.026 – 10.676, p = 0.001) and WHR ≥ 0.85 (OR = 2.612, 95% CI 1.513 – 4.508, p = 0.001). Metabolic syndrome was not associated with tumor size (OR = 0.986, 95% CI 0.580-1.677, p = 0.959), node involvement (OR = 1.165, 95% CI 0.568 – 2.388, p = 0.677) or histological grade (OR = 1.029, 95% CI 0.270-2.273, p = 0.402).

Association between obesity, visceral obesity and MetS with survival outcome of patients with HR+/HER2- breast cancer

The median duration of survival time observation was 51 months (range 9.0 to 128.0 months). During the period of observation, 66 (29.6%) recurrences and 21 (9.4%) deaths were documented.

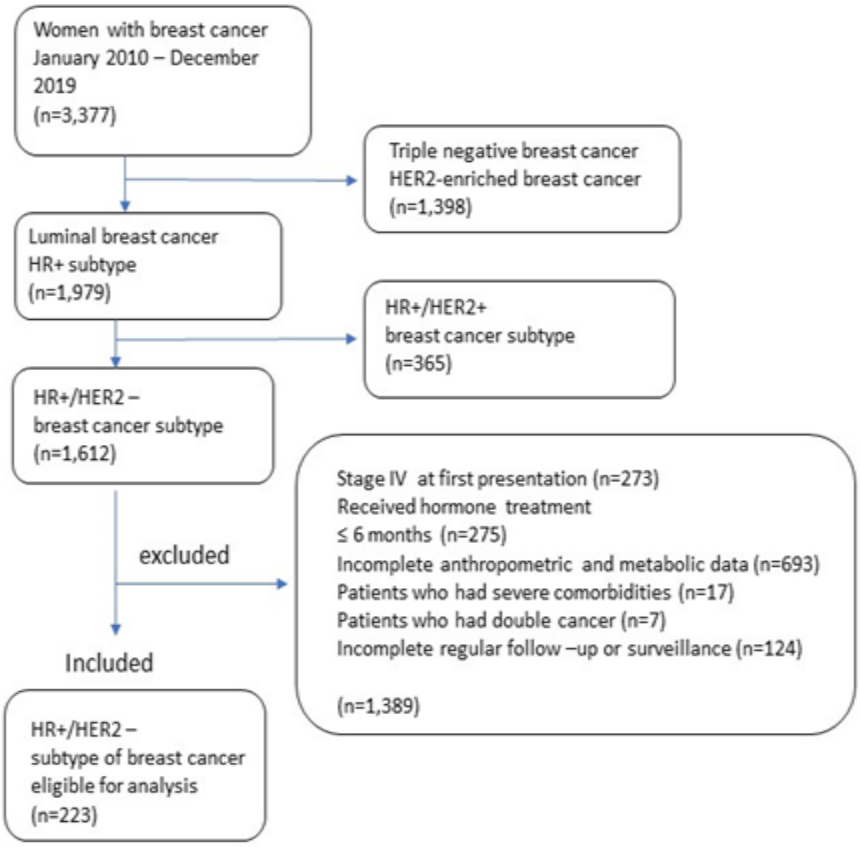

Figure 1. Flow Chart for Patient Selection. HR+, hormone receptor positive; HER2 +, human epidermal receptor 2 positive; HER2 -, human epidermal receptor 2 negative.

Table 1. Baseline Characteristics of Patients with HR+/HER2- Breast Cancer

Characteristics		N= 223; n (%)
Age, median (range)	49 years (32.0-74.0)	
Tumor size:	T1	27 (12.1)
	T2	81 (36.3)
	T3	75 (33.6)
	T4	39 (17.5)
Node involvement:	N0	126 (56.5)
	N1	57 (25.6)
	N2	33 (14.8)
	N3	4 (1.8)
Grade	G1	21 (9.4)
	G2	72(32.3)
	G3	97(43.5)
Hormone receptor positivity	ER+/PR-/HER2-	47 (21.1)
	ER-/PR+/HER2-	2 (0.9)
	ER+/PR+/HER2	174 (78.8)
Menstrual status:	premenopause	142 (63.7)
	menopause/postmenopause	81 (36.3)
First line treatment	Chemotherapy followed by hormone	207 (92.8)
	Hormone alone	16 (7.2)
Hormone treatment:	tamoxifen	142 (63.7)
	aromatase inhibitor	81 (36.3)
BMI (WHO/IASO/IOTF for Asian)	underweight <18.5	20 (9.0)
	normo-weight 18.5-22.9	72(32.3)
	overweight 23.0-24.9	46(20.6)
	obese ≥25.0	85(38.1)
WHR	<0.85	114 (51.1)
	≥0.85	109 (48.9)
Metabolic syndrome (MetS)	absent	98 (43.9)
	present	125(56.1)

Note: HR+/HER2-, positive hormone receptor and negative human epidermal growth factor receptor; T1-T4 tumor size criteria by breast cancer staging system; N0-N3 node involvement by breast cancer staging system; G1-G3 grading of differentiation; ER, estrogen receptor; PR, progesterone receptor; BMI, body mass index; WHO/IASO/IOTF, World Health Organization/International Association for the Study of Obesity/International Obesity Task Force; WHR, waist-to-hip ratio; MetS, metabolic syndrome

Obesity at breast cancer diagnosis was not associated with recurrence/metastasis or mortality (HR = 0.678, 95% CI 0.403-1.142, p = 0.144 for DFS and HR = 1.15, 95% CI 0.468-2,641, p = 0.811 for OS). Among premenopausal women, obesity was associated with longer DFS than BMI < 25 (97.7 months ± SD 6.6 vs. 73.9 months ± SD 5.3, log rank p = 0.026), but it was not associated with longer OS (114.8 months ± SD 3.9 vs. 112.2 months ± SD 5.0; p = 0.386). There was a 5.5% lower proportion of patients who were disease-free in postmenopausal women with obesity compared to the same group with BMI < 25 (64.5% vs. 70.0%; p = 0.727). Postmenopausal women with obesity had similar DFS compared to those with BMI <25 (DFS 77.4 months ± SD 8.6 vs 69.8 months ± SD 5.3; p = 0.727). In postmenopausal women, there was a trend that obesity was associated with shorter survival compared to BMI < 25 (91.3 months ± SD 7.3 vs 119.4 months ± SD 4.2; p = 0.134).

Abdominal obesity, which is represented by WHR ≥ 0.85, tended to be associated with short DFS (HR = 1.539, 95% CI 0.945-2.506, p = 0.083) and OS (HR = 3.117, 95% CI: 1.206-8.053, p = 0.019), as shown in Tables 2 and 3.

Metabolic syndrome did not worsen the survival of breast cancer patients (HR = 1.033, 95% CI 0.633-1.685, p = 0.896 for DFS and HR = 1.441, 95% CI 0.582-3.572, p = 0.430 for OS). Subgroup analysis for subjects who had survived more than 60 months (n = 151 patients) showed an increased risk for worse survival for those with MetS, but still it did not reach a significant value (HR = 3.99, p = 0.200).

Kaplan–Meier estimation survival curves for DFS and OS by MetS and WHR are shown in Figure 2.

Multivariate analysis of factors associated with DFS and OS

Multivariate analysis showed that WHR ≥ 0.85 was independently associated with recurrence (HR = 1.907, 95% CI 1.077- 3.375, p = 0.027), as well as a larger tumor

Table 2. Association of Clinical Characteristics, Obesity Markers and Metabolic Syndrome with Disease-Free Survival of Patients with HR+/HER2- Breast Cancer

Variable	Median (months)	Number of subjects	Censored (%)	Disease-free survival (DFS)	
				HR (95% CI)	p*
Age					
< 50-year-old	93	129	74.4	1 (reference)	
≥ 50-year-old	NA	94	64.9	1.468 (0.904-2.384)	0.12
Tumor stage					
T1-T2	NA	108	80.6	1 (reference)	
T3-T4	97	114	60.5	2.040 (1.223-3.449)	0.006
Nodal Stage					
N0-N1	NA	183	73.8	1 (reference)	
N2-N3	65	37	56.8	1.659 (0.940 – 2.927)	0.081
Grade					
G1-2	NA	93	81.7	1 (reference)	
G3	95	97	62.9	2.252(1.263 – 4.013)	0.006
Hormone treatment					
Tam	95	134	71.8	1 (reference)	
Tam followed by AI	NA	8	97.5	0.413 (0.057-3.010)	0.383
AI	93	81	67.9	1.333 (0.810-2.193)	0.258
1st line chemotherapy					
Anthracycline or taxane	95	66	75.8	1 (reference)	
Anthracycline + taxane	93	141	65.2	0.759 (0.431 – 1.337)	0.34
BMI					
< 25	91	138	68.1	1 (reference)	
≥ 25	NA	85	74.1	0.678 (0.403-1.142)	0.144
WHR					
< 0,85	95	114	74.6	1 (reference)	
≥ 0,85	NA	109	66.1	1.539 (0.945-2.506)	0.083
Metabolic syndrome (MetS):					
no-MetS present	93	98	71.4	1 (reference)	
MetS present	NA	125	69.6	1.033 (0.633-1.685)	0.896

Statistical analysis performed by Cox proportional hazard model with p*< 0.05; median survival time estimated by Kaplan–Meier; HR+/HER2-, positive hormone receptor and negative human epidermal growth factor receptor; T1-T4 tumor size criteria by breast cancer staging system; N0-N3 node involvement by breast cancer staging system; G1-G3 grading of differentiation; tam, tamoxifen; AI, aromatase inhibitor; BMI, body mass index; WHR, waist-to-hip ratio; MetS, metabolic syndrome; HR, hazard risk; 95% CI; confidence interval; NA, not achieved

size group (HR = 2,119, 95% CI 1.157-3.881, p = 0.015) and a higher grade of differentiation (HR = 2.273, 95% CI 1.256-4.114, p = 0.007), as shown in Table 4. The waist-hip ratio was not an independent factor for worse survival after adjusting for tumor, node, and grade of differentiation.

Discussion

MetS is a common disorder affecting approximately 25% of adults (Grundy, 2008). MetS as a risk factor for breast cancer has been elucidated previously (Agnoli et al., 2010; Espocito et al., 2012). Previous studies showed that MetS was present in 29.8%-50.5% of women with breast cancer (Agnoli et al., 2010; Wu et al., 2018; Shahril et al., 2021), similar to our results. The ORDET cohort showed that after menopause, MetS increased the risk for breast cancer with a rate ratio 1.58 times higher compared to the group without any component of MetS (Agnoli et al., 2010). MetS in women with breast cancer was also induced by the treatment they had received. After neoadjuvant or adjuvant chemotherapy, MetS presented in 72.5% of patients, as well as worsening of anthropometric scales and glucose metabolism (Dieli-Conwright et al., 2016). Our study subjects presented with Mets as much as 56.1% at the time of cancer diagnosis. Unfortunately, a lack of serial metabolic and anthropometric data prevented us from observing any associations between MetS and cancer treatment.

The effects of MetS on breast cancer prognosis and mortality have been widely reported; however, the conclusions have been inconsistent. Obesity, the main component in MetS, was modestly associated with poorer prognosis (Protani et al., 2010; Sun et al., 2018). Dibaba et al., (2018) reported that MetS was associated with a 73% increase in the breast cancer mortality rate, as well

Table 3. The Association between Clinical Characteristics, Obesity Markers, and Metabolic Syndrome and the Overall Survival of Patients with HR+/HER2- Breast Cancer

Variable	Mean (months)	Number of subjects	Censored (%)	Overall survival (OS)	
				HR (95% CI)	p*
Age					
< 50-year-old	114.3	129	91.5	1 (reference)	
≥ 50-year-old	113.9	94	89.4	1.228 (0.521 -2.893)	0.639
Tumor stage					
T1-T2	117.3	108	96.3	1 (reference)	
T3-T4	108.9	114	86.1	3.824 (1.287-11.368)	0.016
Nodal Stage					
N0-N1	117.2	183	92.3	1 (reference)	
N2-N3	92	37	81.1	2.593 (1.041– 6.459)	0.041
Grade					
G1-2	116.8	93	95.7	1 (reference)	
G3	105.6	97	87.6	3.029 (0.974-9.416)	0.055
Hormone treatment					
Tam	115.7	134	91	1 (reference)	
Tam followed by AI	62.4	8	87.5	0.748(0.305-1.834)	0.525
AI	113.3	81	90.1	1. 475(0.183-11.875)	0.715
1st line chemotherapy					
Anthracycline or taxane-based	101.4	66	86.4	1 (reference)	
Anthracylin + taxane	117	141	91.5	0.440 (0.185 -1.047)	0.064
BMI					
< 25	114.9	138	91.3	1 (reference)	
≥ 25	110.5	85	89.4	1.11(0.468-2.641)	0.811
WHR					
< 0,85	120.6	114	94.7	1 (reference)	
≥ 0,85	95	109	86.2	3.117 (1.206-8.053)	0.019
Metabolic states:					
no-MetS present	118.3	98	92.9	1 (reference)	
MetS present	112	125	88.8	1.441 (0.582-3.572)	0.43

Statistical analysis performed by Cox proportional hazard model with p*< 0.05; median survival time estimated by Kaplan–Meier; HR+/HER2-, positive hormone receptor and negative human epidermal growth factor receptor; T1-T4 tumor size criteria by breast cancer staging system; N0-N3 node involvement by breast cancer staging system; G1-G3 grading of differentiation; tam, tamoxifen; AI, aromatase inhibitor; BMI, body mass index; WHR, waist-to-hip ratio; MetS, metabolic syndrome; HR, hazard risk; 95% CI; confidence interval; NA, not achieved

as with postmenopausal status, obesity, and ER+/PR+ breast cancer subtype. Calip et al., (2014) also reported in their cohort of 4,216 women with breast cancer that 26% of them developed MetS, and those with MetS had an increased risk for a second breast cancer event and breast cancer-specific mortality. A meta-analysis of 9 cohort studies by Li et al., (2020) concluded that MetS may predict the risk for relapse and mortality for Caucasians but not for Asians. In contrast, the Women's Health Initiative cohort reported that cardiometabolic factors were more associated with cardiovascular-related mortality but not associated with breast cancer-specific mortality in postmenopausal early breast cancer (Simon et al., 2018). The Danish Breast Cancer cohort study reported that survival of breast cancer in Denmark since 2000-2011 improved regardless of the number of comorbidities (Ording et al., 2013). To our knowledge, advances in cancer care along with the availability of effective treatment for metabolic disease have made the presence of metabolic abnormalities not significantly associated with cancer patient survival.

Obesity, which is represented by BMI ≥ 25 for the Asian population, did not increase the recurrence rate or impair the survival rate of patients with breast cancer. Our results showed concordance with Saleh et al. (2021) and contrasted with a meta-analysis of 82 follow-up studies (Chan et al., 2014). Most studies showed a negative effect of overweight and obesity on the survival of breast cancer in a U or J shape, with underweight and obesity associated with all-cause mortality, which could not be shown from our data.

Although BMI is the standard to measure body adiposity, it cannot represent abdominal obesity, especially for all Asians, due to higher abdominal fat and adipose tissue. Asians have more metabolic risks at lower WC and WHR (WHO, 2008). Our study showed that

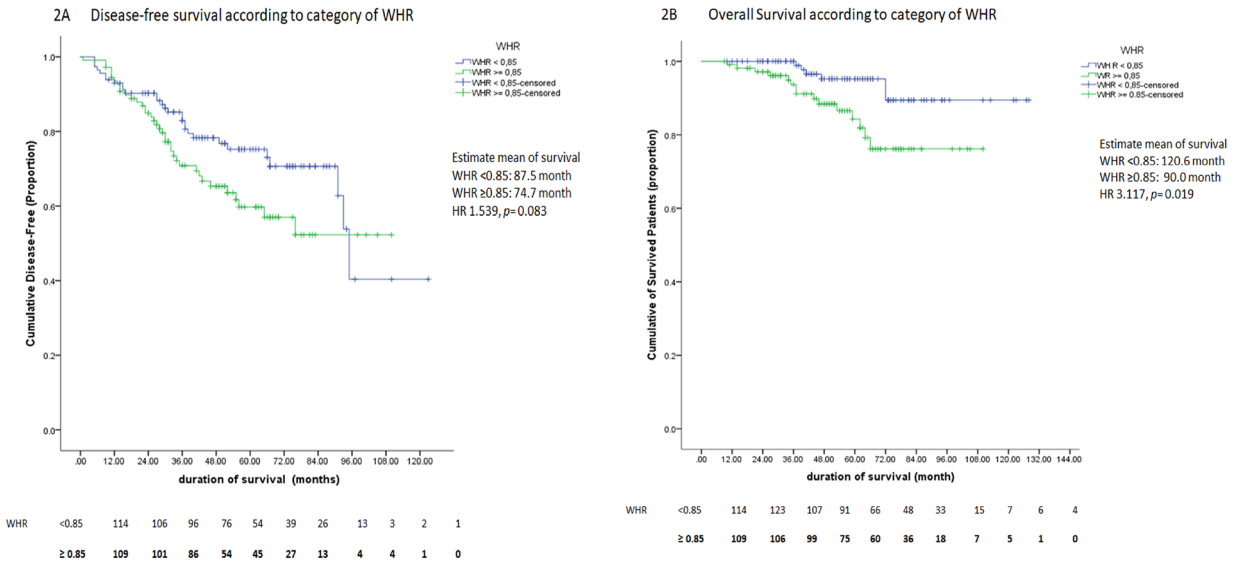

Figure 2. A. Disease-free survival according to category of WHR; B. Overall survival according to category of WHR Patients with HR+/HER2- breast cancer and WHR ≥0.85 had shorter mean DFS (74.7 months vs. 87.5 months, HR 1.539, p=0.083) and shorter mean OS (90 months vs. 120.6 months; p=0,019). HR+/HER2-, hormone receptor positive, HER2 negative breast cancer subtype

Table 4. Multivariate Analysis of Factors Associated with Disease-Free Survival and Overall Survival

Variable	DFS			OS		
	HR	95% CI	p	HR	95% CI	p
Tumor	2.119	1.157 – 3.881	0.015	3.165	1.028 – 12.713	0.045
Node	0.946	0.487 – 1.835	0.868	1.373	0.458 - 4.117	0.571
Grade	2.273	1.256 - 4.114	0.007	2.834	0.911- 8.820	0.072
WHR	1.907	1.077- 3.375	0.027	2.178	0.754 – 6.298	0.151

Note DFS, disease-free survival; OS, overall survival; HR, hazard risk; 95% CI, confidence interval; WHR, waist-to-hip ratio

premenopausal women with BMI ≥ 25 were associated with better DFS, and postmenopausal women with BMI ≥ 25 tended to have shorter OS and DFS. The disadvantage of higher BMI on DFS or OS was more pronounced in postmenopausal women. One of the possible reasons is that in premenopausal and younger women, BMI does not accurately reflect fat mass. Body weight in premenopausal women consists of more muscle mass, while higher BMI in postmenopausal women reflects a large fat component. In postmenopausal women with excess fat, adipose tissue was the primary source of estrogen. Increased estrogen production leads to growth stimulation and proliferation of HR+ breast cancer cells. Therefore, the effect of BMI on DFS and OS was influenced by menopausal status.

The WHR, a visceral obesity marker, was the only obesity index associated with an increased recurrence rate and decreased survival rate in our study. The power of our result was 0.997 calculated with the PS Power calculation program version 3.1.2

Similar results were published by Borugian et al., (2003). Tryggvadottir et al., (2018) showed that changes in WHR were associated with a decreased survival rate of women with breast cancers and increased recurrence, especially in estrogen receptor-positive subtypes. Zhang et al., (2017) reported that WHR beyond the range 0.81-0.86 increases late all-cause mortality without being modified by stage, estrogen receptor, or menopausal status.

There were several weaknesses of this study. First, we collected retrospective data after diagnosis (presystemic treatment). Metabolic abnormalities caused by cancer treatment were sorted out. Second, our study had a short follow-up observation (median follow-up of 72 months) for luminal-type breast cancer, which might prevent us from seeing the long-term effects of metabolic abnormalities on survival. Third, we did not distinguish between the causes of mortality (all-cause or breast cancer-specific mortality) and existing comorbidities. Treatments for comorbidities and their efficacy were not analyzed. Fourth, the number of subjects who developed MetS and obesity during cancer treatment was not analyzed in this study. Fifth, the cancer treatment given upon breast cancer progression might influence overall survival, which was not analyzed in this study. All mentioned factors might have some contributions as sources of biases in our study, in addition to unavoidable selection bias due to small eligible subjects compared to the target population. A prospective study including larger subjects with longer follow-up periods (more than 120 months) is warranted. Despite several weaknesses, the potential role of WHR as a predictor for recurrence in women with HR+/HER2- breast cancer cannot be neglected. Added to evidence that increased WHR was a risk factor for certain cancers, the

present study showed an independent association between increased WHR and recurrence.

The main implication from this study is that either MetS or BMI after breast cancer diagnosis does not appear to compromise OS and DFS. There is an increased tendency for MetS to worsen the long-term survival (> 60 months after diagnosis) of patients with breast cancer. Abdominal obesity, especially WHR, is more accurate in predicting recurrence and is modestly associated with poor survival outcomes. Survivors of breast cancer should practice regular exercises to keep their bodies lean, keep their metabolic parameters within the normal range, and reduce abdominal obesity.

Author Contribution Statement

KWT conceived the idea and designed the study, collected data, performed the analysis and wrote the paper. YRP performed the analysis and collected anthropometric data. NFA collected study data and performed follow-up survival. IW validated the pathological data. HS, MSH, and TA read the final draft and approved the submitted manuscript. All authors discussed the results and contributed equally to the final manuscript.

Acknowledgments

We acknowledge all the study participants, clinicians, study nurses and research assistants. We thank Cancer Registry Dr. Sardjito Hospital, Yogyakarta and Faculty of Medicine, Public Health, and Nursing for providing patient data and Raras Sekti for managing data collection.

Ethical Statement

The Medical and Health Research Ethics Committee of the Faculty of Medicine, Universitas Gadjah Mada, granted approval for this study (Ref. no: KE/FK/0676/EC/2018; continuing approval no: KE/FK/0793/EC/2019). Patients signed consent forms approving the use of their medical data in this study.

Availability of Data

Data are available upon request to the first author and The Medical Record Installation of Dr Sardjito Hospital.

Disclosure

The authors had nothing to be declared. There is no potential conflict of interest relevant to this article, which was declared by the authors.

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