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Relationship of Obesity Recurrence Events in Triple Negative Breast Cancer Patients in Dr. Soetomo General Hospital Surabaya

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Abstract

Breast cancer is one of most major cause of death in women. One of the forms of breast cancer that has poor prognosis is triple negative breast cancer (TNBC). TNBC occurs in 10-20% of breast cancer, with high number of relapse/recurrence and metastasis. In some earlier research, it was found that the number of TNBC was higher in patients with obesity. Therefore, obesity is associated with poor prognosis in patients with breast cancer. This research wants to study the relationship of obesity with recurrence in TNBC patients. This research is a prospective cohort research in patients with triple negative breast cancer. Research was carried out by recording patients with TNBC and measurement of the degree of obesity by calculating the body mass index (BMI). Patients was followed-up for 6 months after surgery to monitor if there is any recurrence. In this research, it was obtained a total of patients of 58, 33 people (56.9%) with normal BMI and 25 people (43.1%) with obesity. From the terms of recurrence, it was obtained 30 people (51.7%) did not experience recurrence and 28 people (48.3%) experienced a recurrence. Statistical tests proved that there is significant relationship between obesity with the incidence of recurrence (p = 0.002) with an odds ratio (OR) of 6.29. Increased BMI increase the incidence of recurrence cases in patients with Triple Negative Breast Cancer

Keywords: Triple Negative Breast Cancer, Recurrence, Obesity, Cancer Breast

1.0 INTRODUCTION

In the past 25 years, the prevalence of obesity increased by two times as much in 70 countries, including the United States, and nearly a third of the adults in the entire world are now excess weight or obese (Afshin et al., 2017). Obesity is concerned because obesity is a risk factor in a variety of chronic diseases, diseases that weaken the immune system, as well as diseases that threaten life (WHO, 2000), for example, in diseases like rheumatoid arthritis, diabetes mellitus type 2, cardiovascular disease, and cancer (WHO, 2000). Cancer Breast is a case of cancer causes of death most in women. The incidence of breast cancer in developing countries in Asia is increasing. Studies in the year 1970 show a woman obese has a risk of cancer of the breast is high (Sun et al, 2017).

In the treatment of breast cancer, there are currently developments in the form of estrogen receptor blockers, progesterone receptors, and human epidermal growth factor receptor 2 (HER2 / neu). Therapy that is a component of therapeutic cancer is breast when this in patients with the receptor of estrogen and progesterone, and HER2- positive (Aysola, 2013). Triple-Negative Breast Cancer (TNBC) is a subtype of cancer breast that is based on immunohistochemistry (IHC) with receptors estrogen (ER) negative, receptor progesterone (PR) negative and human epidermal growth factor receptor 2 (HER2) negative. TNBC is associated with special characteristics, including aggressiveness, poor prognosis, and poor response to treatment (Aysola, 2013).

2.0 BACKGROUND

TNBC occurs in 10-20% of the entire cancerous breast, which has several recurrences, and metastasis is high. The relationship between obesity and TNBC is still not fully explained. The theory of insulin resistance, an increase in hormones such as leptin and adiponectin, is a suspected cause of the increased incidence of TNBC and other malignancies in obese patients (Mowad, 2013). Patients obesity with a receptor of estrogen-positive has the result that bad if it had a high BMI. This has been seen from several studies, especially in postmenopausal patients. The relationship between obesity and poor prognosis in breast cancer is caused due to an increase in the production of estrogen from tissue adipose,

thus increasing the stimulation of cells cancerous breast with a receptor of estrogen positive. But the case is not to be applied to the cancerous breast with receptors estrogen negative (Mowad, 2013).

Figures incidence of patients TNBC with obesity is high in comparison with patients with non-obese. A study retrospective mentions the 620 patients of Caucasian with cancer of breast invasive in West Virginia, in whom obesity is 49.6% of patients with TNBC, but only 35.8% of patients with non-TNBC (P = 0.0098). In another study, it was obtained 112 patients with TNBC at Ege University Medical Oncology Clinic at the period of more than five years reported that 82 patients (73.2%) have excess weight/obesity and 30 patients (26.8%) had severe normal weight and underweight when the diagnosis is made (Claw et al, 2015). Similarly, also a researcher from Louisiana reviewing the database of a total of 183 patients with TNBC, in whom 24 patients (13.1%) had a weight of normal weight (BMI <25 kg / m2), 42 (23.1%), overweight (BMI = 25 -30 kg / m2), and 117 (63.7%) were obese (BMI> 30 kg / m2). Ademuyiwa et al reported the data of patients were classified by BMI in the study retrospective and reported that of the total 418 patients, 124 patients (29.7%) has normal weight or underweight, 130 (31.1%) overweight and 164 (39, 2%) are obese (Sun et al, 2017).

In patients with TNBC, several recurrence events tend to occur early, and survival after diagnosis of disease metastasis is only about one year although it was managed early, 19% of patients reported with TNBC who had a recurrence, the reported mortality risk occurred within 2 years of the first after the diagnosis (Lin et al, 2012). Also, according to the results of basic health research or Riskesdas, the level of obesity in adults in Indonesia increased to 21.8 percent. This prevalence increased from the results of Riskesdas 2013 which states that the obesity rate in Indonesia only reached 14.8 percent. Obesity itself refers to the condition in which the index of the mass of the body above 27. The prevalence of obesity with BMI between 25 to 27 also increased from 11.5 percent in 2013 to 13.6 percent in 2018. In the position of the highest that is North Sulawesi, then located in DKI Jakarta, East Kalimantan, and West Papua. (Riskesdas, 2018).

3.0 METHODOLOGY

This study was an observational analytic study with a prospective cohort design. Patients women with cancer breast stage III which meet the criteria for inclusion and exclusion of studies that the criteria of inclusion in the form of breast cancer patients which examined the results in the pathology department of Dr. Soetomo Hospital, the examination result of immunohistochemistry staining are TNBC, aged 18-65 years, the patient was first diagnosed with breast cancer between December 2017 - December 2019, agreed to be followed up in oncology outpatient clinic of Dr. Soetomo hospital and agreed to be research subject by signing informed consent. Criteria for exclusion in the form of breast cancer patients with liver disease, kidney failure, histopathology examination is Luminal A, B, and HER (+), incomplete medical records, patients cannot be contacted, and patients cannot control regularly at the RSUD Dr. Soetomo.

The research subjects have then explained the aims and benefits of the study and were asked to participate in the study by signing informed consent. Furthermore, the data common subjects such as name, age, type of sex, address, and a number of the phone are recorded. Other data is recorded according to the data collection form. The study subjects then underwent a BMI examination. Data verification is done by recording data from the medical record to the research sheet that has been made. Furthermore, the research subjects were examined for the completeness and suitability of the data with the operational limitations set. After all, data has been collected, data entry is made to the SPSS 23.0 for Windows program. Data are grouped according to type, between nominal, scale, or ordinal.

4.0 RESULTS

The subjects of the study consisted of 58 women (100%), with the age of majority is the age > 50 years ie 30 patients (51.7%). In research it got kind of pathological anatomy most is infiltrating ductal carcinoma as many as 46 patients (79.3%). The characteristics of research subjects can be seen in Table 1.

Table 1: Characteristics of Research Subjects

Subject Characteristics		Frequency	Percentage (%)
Sex	Female	58	100
Age	Premenopause	28	48.3
	Postmenopouse	30	51.7
Anatomical Pathology	Infiltrating Ductal Carcinoma	46	79.3
	Mixed Carcinoma	7	12.1
	Infiltrating Lobular Carcinoma	1	1.7
	Mucinous Carcinoma	2	3.4
	Phyllodes Tumor	2	3.4

From the study, it in terms of age and rate of recurrence found that in the group aged > 50 years obtained the recurrence of the number is high compared with the group of age <50 years of which as many as 16 patients. From these results, a regression test was performed to determine the relationship of age with the recurrence rate of TNBC patients, and the *p*-value = 0.389 was obtained, meaning that age was not statistically related to the level of recurrence, but old age increased the risk of recurrence by 1.68 x than younger age (OR = 1.68). The description of the age group with the recurrence of TNBC patients is seen in Table 2.

		Recurrence				
		No Recurrence	Recurrence	Total	*P-value*	OR
Age group	Premenopouse	16	12	28	0.389	1.68
	Postmenopouse	14	16	30		
Total		30	30	28		

Table 2 Overview of the age group with the recurrence of TNBC patients

From the research, it reviewed the results of pathological anatomy found that *I infiltrate ng ductal carcinoma* have a level recurrence much higher compared with the type of pathological anatomy else that is as much as 24 patients. From the results of these then do the test regression to determine the relationship pathological anatomy at the level of recurrence of patients with TNBC, and obtained the value *p*-value = 0736, which means that the pathological anatomy is statistically not associated with the level of recurrence but increases the risk of recurrence by 0.9 x (OR = 0.09). An overview of anatomic pathology with the recurrence of TNBC patients is seen in Table 3.

Table 3: An overview of anatomic pathology with recurrence of TNBC patients

		Recurrence				
		No Recurrence	Recurrence	Total	*P-value*	OR
Anatomical Pathology	Infiltrating Ductal Carcinoma	22	24	46	0.736	0.90
	Mixed Carcinoma	6	1	7		
	Infiltrating Lobular Carcinoma	1	0	1		
	Mucinous Carcinoma	1	1	2		
	Phyllodes Tumor	0	2	2		
Total		30	28	58		

In this study, there were 58 subjects. Characteristics anthropometric from the subject of the study are as follows: high body obtained value of the minimum of 147cm, the value of a maximum of 165cm, and a mean of 156.88 5.03 cm. The minimum weight value is 45kg, the maximum value is 83kg, and the average 60 is 9.74kg. The BMI obtained the results of a minimum value of 18, a maximum value of 31, and a mean of 24.3 3.31 (Table 5.1). From the category of BMI obtained patients with normal BMI as many as 33 people

(56.9%) and 25 (43.1%) with BMI *Obesity*. At recurrence obtained in 30 (51.7%) and 28 (48.3%) without recurrence.

Table 4 - Anthropometric Characteristics of Research Subjects

Characteristics	Minimum Value	Maximum Value	Average	Standard Deviation
Height	147	165	156.88	5.03
Body weight	45	83	60	9.74
BMI	18	31	24.3	3.31

Table 5 - Characteristics of BMI and Recurrence

		Amount (n)	Percentage
BMI group	Normal	33	56.9%
	Obesity	25	43.1%
Recurrence Group	No Recurrence	30	51.7%
	Recurrence	28	48.3

From the data then performed a statistical test with the *chi-square* test. The results of the *chi-square test* found that there is a difference in meaning between the two groups (p = 0.00 2, p <0.05). It is demonstrated that with an increase in BMI is obtained an increase in the incidence of recurrence in cases of Triple-Negative Breast Cancer with an increase in the recurrence of 6:29 times in the group obese compared to a group of nonobese (OR = 6.29)

Table 6 - Relationship between BMI and TNBC Recurrence

		Recurrence		*P-value*	OR
		No Recurrence	Recurrence		
BMI category	Normal	22 (37.9%)	11 (18.9%)	0.002	6.29
	Obesity	8 (13.7%)	17 (29.3%)		

5.0 DISCUSSION

Triple-Negative Breast Cancer (TNBC) is a breast cancer subtype based on immunohistochemistry (IHC) with estrogen receptor (ER) negative, progesterone receptor (PR) negative and human epidermal growth factor receptor 2 (HER2) negative. TNBC is associated with special characteristics, including aggressiveness, poor prognosis, and poor response to treatment (Aysola, 2013). In this study, it was found that the most age of patients suffering from Triple Negative Breast Cancer (TNBC) was> 50 years old, namely 30 patients (51.7%).

The results of this study are in line with a report from the National Institutes of Health which states that age over 30 years are more likely to suffer from triple-negative breast cancer and this risk will increase until the age of 50 years and after menopause. From the recurrence level research, it was found that in the age group> 50 years the recurrence rate was higher compared to the <50 years age group, but from the chi-square test results found that there were no significant differences between the two groups (p = 0.425) this was in line with a study from Radosa et al., (2018) which stated that age was not significantly related to local and distant recurrence in triple-negative breast cancer patients (Radosa et al., 2018).

In this study, the most common type of anatomic pathology was infiltrating ductal carcinoma by 46 patients (79.3%) with a higher recurrence rate compared to other types of anatomic pathology which were 24 patients but from the chi-square test results found that there were no significant differences between the types of anatomic pathology with the level of recurrence (p = 0.159) this is not in line with research from Urru et al., (2018) which states that sufferers of Triple-Negative Breast Cancer (TNBC) who have histopathological types of invasive ductal carcinoma have recurrence rates rather than type others (Urru et al., 2018).

Biglia et al. reported that obese patients who were pre-menopausal showed a worse histopathological picture than the normal/underweight group. Pre-menopausal obese patients more often have axillary metastatic lymph nodes and tumors that invade blood vessels more often

In this study, it was found that patients suffering from Triple Negative Breast Cancer (TNBC) 43.1% were obese. This is in line with the clinicopathological study obtained from 112 TNBC patients at Ege University Medical Oncology Clinic over 5 years reporting that 82 patients (73.2%) were overweight/obese and 30 patients (26.8%) had normal weight and underweight at diagnosis (Cakar et al, 2015). Similarly, researchers from Louisiana reviewed a database of a total of 183 TNBC patients, including 24 patients (13.1%) having normal weight (BMI <25 kg / m2), 42 (23.1%), overweight (BMI = 25- 30 kg / m2), and 117 (63.7%) are obese (BMI> 30 kg / m2). Ademuyiwa et al reported patient data classified by BMI in a retrospective study and reported that out of a total of 418 patients, 124 patients (29.7%) had normal or underweight, 130 (31.1%) overweight and 164 (39, 2%) are obese (Sun et al, 2017).

In this study, patients who were obese experienced more recurrence, as many as 17 patients (29.3%) than those who were not obese and from the results of the chi-square test found that there were significant differences between the two groups (p = 0.009, p <0, 05). This shows that with an increase in BMI, there is an increase in the incidence of recurrence in Triple-Negative Breast Cancer cases. The results of this study are in line with research from Berclaz et al. reported that in their study of 6,792 women who participated in the International Breast Cancer Study Group Therapeutic Trials, patients who were overweight (BMI: 25.0 -29.9) or obese had significantly shorter survival and more recurrence rates high compared with patients with a BMI of 24.9 or less (p <0.01)

Obesity is an independent prognostic factor for the development of metastases away from breast cancer. The risk of developing breast cancer to distant metastasis after 10 years increased significantly by 46% in obese patients. In the long run, adjuvant therapy appears to be less effective in obese breast cancer patients. A retrospective study conducted by Osman et al. in 118 patients with metastatic breast cancer found a significant relationship between chemotherapy response and first-line metastatic chemotherapy in non-obese patients compared with obese patients. Likewise, survival rates and recurrence in non-obese patients are much better than non-obese ones (Eric C. Dietze, Tanya A. Chavez, 2018)

Recent studies have identified several potential mechanical relationships between obesity and TNBC initiation, TNBC development, and recurrence in TNBC. The mechanism is there are several namely

1. Insulin in Akt / mammalian rapamycin (mTOR) and glycolysis signals;
2. Obesity-mediated inflammatory cytokine, such as leptin, and the activation of signaling pathways that encourage invasion and metastasis;
3. Microenvironment breast cancer tissue in an obese patient

Usually, when eating, insulin is released in response to an increase in blood glucose. Increased insulin levels stimulate the synthesis and secretion of leptin. The circulating leptin then sends a full signal through the hypothalamus and acts on the pancreas to inhibit insulin release. In obesity, circulating levels of both insulin and leptin increase. Leptin levels increase even in the absence of hyperinsulinemia in obesity. A feedback loop that limits food consumption and reduces insulin circulation does not work. High-level leptin acts to directly stimulate mitogenesis and reduce apoptosis in breast cancer cells.

Furthermore, insulin stimulates the excess of leptin and its receptors in breast cancer cells, which form an autocrine loop that stimulates the growth of breast cancer cells. Leptin also stimulates proinflammatory cytokine secretion from macrophages IL-6 and tumor necrosis factor (TNF) -α, as well as T cells and mononuclear cells (IL-2 and interferon-γ). Obesity increases the inflammatory state which is characterized by an increase in serum and tissue inflammatory cytokines. Inflammatory cytokines are increased in obese individuals including IL-6, IL-8, TNF-α, and leptin. Together these inflammatory cytokines increase tissue inflammation and activate signaling pathways that promote aggressive TNBC biology. IL-6, IL-8, and leptin are increased in obese individuals and activate STAT3, NF-κB, and Wnt / EZH2 signaling. Activation of STAT3, NF-κB, and Wnt / EZH2 increases invasion and metastasis and predicts a poor prognosis in women with TNBC (Eric C. Dietze, Tanya A. Chavez, 2018).

6.0 CONCLUSION

In the study, it was found that patients who suffer from Triple Negative Breast Cancer (TNBC) 43.1% experiencing obesity. At the study 's patients who undergo obesity is much to experience recurrences that as many as 17 patients (29.3%) than that is not experiencing obesity and of the results of chi-square test found that there is a difference in meaning between the two groups (p = 0.009, p <0, 05). It is demonstrated that an increase in BMI is obtained an increase in the incidence of recurrence in cases of Triple-Negative Breast Cancer.

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