IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

DIFFERENCES IN EXPRESSION OF INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR (IGF1R) ACCORDING TO SUBTYPES OF BREAST CANCER IN VERY YOUNG WOMEN IN RSUP H. ADAM MALIK MEDAN

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ABSTRACT

Background: Breast cancer is the most common cancer in women (24.2%) and the second most common cancer in the world (11.6%). Approximately 2.089 million new cases of breast cancer were identified in 2018. Expression of IGF-1R correlates with ER expression and predicts a favorable phenotype. Several studies have confirmed further cross-talk between ER and IGF-1R in breast cancer.

Objective: The purpose of this study was to determine differences in IGF1R expression according to breast cancer subtypes in very young women at H. Adam Malik General Hospital Medan.

Methods: This study was an observational analytic study using a cross-sectional design. The sample in this study was a woman with a diagnosis of breast cancer at a very young age at RSUP H. Adam Malik Medan from January 2015 to December 2019 who met the inclusion and exclusion criteria of 52 samples.

Results: In this study, the median age of patients in luminal A breast cancer subtype was 33 years, where the age of the youngest patient was 23 years and the age of the oldest patient was 35 years. It was found that 33 patients (63.5%) had low IGF1R expression and 19 patients (36.5%) and 20 patients (38.5%) with an advanced

local stage and only 1 patient (1.9%) with an early stage. In the test of significant differences in IGF1R expression according to breast cancer subtypes in very young women at H. Adam Malik General Hospital Medan with a p-value of 0.031 (p <0.05).

Conclusion: There is a significant difference in IGF1R expression according to breast cancer subtype in very young women at RSUP H. Adam Malik Medan where higher expression was found in luminal A compared to luminal B and TNBC.

Keywords: IGF1R, subtype, breast cancer

INTRODUCTION

Breast cancer is the most common cancer in women (24.2%) and the second most common cancer in the world (11.6%). Approximately 2.089 million new cases of breast cancer were found in 2018 (WHO, 2018). Breast cancer is divided into four subtypes identified based on excessive or no Estrogen Receptor (ER) and Progesterone Receptor (PR) and the presence of excessive amplification of the oncogene Human Epidermal Growth Factor Receptor-2 (HER-2). Four subtypes are known, namely luminal A, luminal B, HER-2 positive, and triple-negative breast cancer (TNBC) (Zaha, 2014). Signaling via insulin-like growth factor type 1 receptor (IGF-1R) is complex, and its role in breast cancer tumorigenesis remains controversial. Early studies reported that IGF-1R expression correlated with ER expression and predicted a favorable phenotype. Several studies have confirmed further cross-talk between ER and IGF-1R in breast cancer. Consistent with these data, loss of IGF-1R has been associated with breast tumor development, suggesting that IGF-1R is involved in tumor suppression. However, other findings suggest that IGF signaling is a positive mediator of breast cancer growth and survival. Because IGF signaling promotes tumor cell proliferation and survival, various inhibitors have been developed to attenuate IGF signaling. Collectively, these mixed outcomes support the possibility that IGF-1R has a dual function as a tumor suppressor as well as an oncogene. (Alison, 2018)

Research on the expression and role of IGF1R in various subtypes of breast cancer, and in particular its role in inducing resistance to targeted therapies has been carried out by identifying the subtypes of IGF1R that actively promote tumor initiation and progression to benefit from anti-IGF1R therapy. Most of the IGF pathways, including IGF1R, tended to be overexpressed in luminal A and luminal B subtypes and relatively unexpressed in the basal tumor (TNBC) and HER2 + types. (Farabaugh, 2015). In other studies, IGF1R is present in all subtypes of breast cancer, regardless of hormone receptor or HER2 status. However, data regarding its prognostic role in early breast cancer are controversial, with several studies reporting the negative impact of IGF1R overexpression on clinical outcomes and clinical outcomes. others suggest a favorable prognostic role. (Giannis, 2014) From the description above, IGF1R levels can be used as a new prognostic marker in patients with breast cancer. However, so far, there are still few studies that discuss differences in IGF1R expression with

breast cancer subtypes, especially in North Sumatra. Apart from that, several studies also show some controversial results. From this phenomenon, the researchers were interested in examining the differences in IGF1R expression with breast cancer subtypes.

METHODS

This study was an observational analytic study using a cross-sectional design which was carried out in the Surgical Oncology Division of the Department of Surgery and the Anatomical Pathology Laboratory of H. Adam Malik Hospital Medan. The research was started after obtaining approval from the ethics committee. The sample in this study was a woman with a diagnosis of breast cancer at a very young age at RSUP H. Adam Malik Medan from January 2015 to December 2019 who met the inclusion and exclusion criteria of 52 samples. The inclusion criteria of this study were breast cancer patients aged ≤ 35 years, had complete data including age, cancer stage, cancer subtype, cancer histopathology grading, and still stored paraffin block of cancer tissue to assess IGF1R. Meanwhile, the exclusion criteria for this study were patients with other malignancies, patients with other chronic diseases, and patients with immune system disorders. The data obtained were then presented descriptively in the form of narrative, proportion distribution tables, and statistical analysis to look for differences in IGF1R expression according to breast cancer subtypes in very young women using the Chi-square test in the SPSS ver.24.

RESULTS

The demographic descriptions of the patients included in this study are presented in table 1. 52 patients were consisting of 13 patients in each subtype of breast cancer. The median age of patients in luminal A breast cancer subtype was 33 years, where the age of the youngest patient was 23 years and the age of the oldest patient in luminal A was 35 years. The median age of patients in the luminal B breast cancer subtype was 33 years, where the age of the youngest patient was 19 years and the age of the oldest patient in luminal B was 35 years. The median age of patients with HER 2 overexpression of breast cancer subtype was 29 years, where the age of the youngest patient was 22 years and the age of the oldest patient in HER 2 overexpression was 34 years. It was found that the median age of patients in the triple-negative breast cancer subtype was 33 years, where the age of the youngest patient was 22 years and the age of the oldest patient in the triple-negative was 35 years.

Table 1. Demographic Characteristics of Breast Cancer Patients in Very Young Women at H. Adam Malik General Hospital Medan

		Luminal A	**Luminal B**	**Overexpression HER 2**	**TNBC**
Age	Median (Min-Max)	33 (23-35) years old	33 (19-35) years old	29 (22-34) years old	32 (22-35) years old
Marital status	Married	12 (92.3%)	10 (77%)	12 (92.3%)	9 (69%)
	Not married	1 (7.7%)	3 (23%)	1 (7.7%)	4 (31%)
Birth history	Has given birth	9 (69%)	10 (77%)	7 (53.8%)	7 (53.8%)
	Has not given birth	4 (31%)	3 (23%)	6 (46.2%)	6 (46.2%)
Family History of Breast Cancer/Ovarian Cancer	Present	1 (7.7%)	2 (15.3%)	2 (15.3%)	5 (38.5%)
	Absent	12 (92.3%)	11 (84.6%)	11 (84.6%)	8 (61.5%)

Of the 52 patients, the mean tumor size was 28.1 ± 3.98 mm. No one had a tumor size ≤of 20 mm. It was found that 42 patients in this study had a tumor size of> 50mm (80.8%), while 10 patients had a tumor size of 20-50mm (19.2%). Of the 10 patients with a tumor size of 20-50mm, 9 patients did not experience infiltration while 1 patient experienced infiltration to the chest wall. In the other 42 patients with tumor size> 50mm, 8 patients had no infiltration, 17 patients had infiltration to the chest wall, 13 patients had infiltration into the skin/satellite lesions, and 4 patients had infiltration to the chest wall and skin/satellite lesions. So the larger the tumor size, the more obvious the infiltration that occurs.

In table 2, it was found that from 52 patients included in this study, 33 patients (63.5%) had enlargement of the axillary lymph nodes and 19 patients (26.5%) had no enlargement of the axillary lymph nodes who were examined clinically.

Table 2. Characteristics of axillary lymph node enlargement in breast cancer patients in very young women at H. Adam Malik General Hospital, Medan

Axillary lymph node enlargement	Total (%)
Absent	19 patients (36,5%)
Present	33 patients (63,5%)
Total	52 patients (100%)

There were 31 patients (59.6%) who had distant metastases and 21 patients (40.4%) who had no distant metastases at the time of diagnosis who underwent a bone scan, ultrasound, and chest X-ray. This can be seen in table 3.

Table 3 Characteristics of Distant Metastatic Breast Cancer Patients in Very Young Women at H. Adam Malik General Hospital Medan

Distant Metastasic	Total (%)
Absent	21 patients (40,4%)
Present	31 patients (59,6%)
Total	52 patients (100%)

It can be seen in table 4.4. that the patients in this study were mostly patients with a metastatic stage with a total of 31 patients (59.6%). There were also 20 patients (38.5%) with an advanced local stage and only 1 patient (1.9%) with an early stage

Table 4 Characteristics of Stage in Breast Cancer Patients in Very Young Women at H. Adam Malik General Hospital Medan

Breast Cancer Stage	Total (%)
Early	1 patients (1,9%)
Locally advanced	20 patients (38,5%)
Metastatic	31 patients (59,6%)
Total	52 patients (100%)

**The American Joint Committee on Cancer 8th edition (AJCC 8)*

In this study, the maximum number of about 21 patients (40.4%) had a grade II histopathological grade. This was followed by 18 patients (34.6%) whose histopathological grade was grade I and 13 patients (25%) were grade III. This can be seen in table 5.

Table 5 Characteristics of Histopathological Grading of Breast Cancer Patients in Very Young Women at H. Adam Malik General Hospital Medan

Histopathological Grading	Total (%)
Grade I	18 patients (34,6%)
Grade II	21 patients (40,4%)
Grade III	13 patients (25,0%)
Total	52 patients (100%)

**Nottingham (Modified Scarff Bloom Richardson)*

In table 6, it can be seen that the most histopathological type in this study was invasive ductal carcinoma. This type of histopathology was found in 39 of 52 patients (75%) who were included in this study. There were also about 8 patients (15.4%) with histopathological types in the form of invasive lobular carcinoma and 5 patients (9.6%) with other types of histopathology.

Table 6 Characteristics of Histopathological Types of Breast Cancer Patients in Very Young Women at H. Adam Malik General Hospital Medan

Histopathological Types	Total (%)
Invasive Ductal Carcinoma	39 patients (75,0%)
Invasive Lobular Carcinoma	8 patients (15,4%)
Other histopathological types	5 patients (9,6%)
Total	52 patients (100%)

* *WHO Breast classification 2019*

In Table 7, it was found that 33 patients (63.5%) had low IGF1R expression and 19 patients (36.5%) had high IGF1R expression. 4 (7.7%) of 13 patients with luminal breast cancer subtype A had low IGF1R expression while the other 9 patients (17.3%) had high IGF1R expression. From the luminal B breast cancer

subtype group, 9 patients (17.3%) had low IGF1R expression and 4 patients (7.7%) had high IGF1R expression. Of the 13 patients with subtype HER2 breast cancer, 11 patients (21.2%) had low IGF1R expression and 2 patients (3.8%) had high IGF1R expression. In the TNBC breast cancer subtype group, 9 patients (17.3%) had low IGF1R expression and 4 patients (7.7%) had high IGF1R expression.

Table 7. Expressions of Insulin-Like Growth Factor 1 Receptor (IGF1R) according to subtypes of breast cancer patients in very young women at H. Adam Malik General Hospital Medan

		Breast Cancer Subtypes				Total	p-value*
		Luminal A	Luminal B	Overexpression HER 2	TNBC		
IGF1R Expression	**Low**	4/13 (7,7%)	9/13 (17,3%)	11/13 (21,2%)	9/13 (17,3%)	33 patients (63,5%)	0,031
	High	9/13 (17,3%)	4/13 (7,7%)	2/13 (3,8%)	4/13 (7,7%)	19 patients (36,5%)	
Total		13 patients (25,0%)	13 patients (25,0%)	13 patients (25,0%)	13 patients (25,0%)	52 patientc (100,0%)	

* The p-value <0.05 was statistically significant, using the Chi-square test

In table 8, it is found that 33 patients (63.46%) with low IGF-1R expression, 8 patients (24%) had grade I, 14 patients (42%) had grade II, and 11 patients (34%) had grade III. In 19 patients (36.54%) who had high IGF-1R expression, 10 patients (52.6%) had grade I, 7 patients (36.8%) had to grade II and 2 patients (10.6%) had grade III. The p-value is 0.067 (p> 0.05) which is not statistically significant.

Table 8 Expression of IGF-1R Based on Histopathological Grading

		IGF-1R		Total	p-value*
		Low	High		
Grading	1	8 (24%)	10 (52.6%)	18 (34.6%)	0,067
	2	14 (42%)	7 (36.8%)	21 (40.4%)	
	3	11 (34%)	2 (10.6%)	13 (25%)	
Total		33 (100%)	19 (100%)	52 (100%)	

* The p-value <0.05 was statistically significant, using the Chi-square test

DISCUSSIONS

In this study, the benchmark for very young age in breast cancer was under 35 years. This is in line with research conducted by Martinez et al. In 2019 which also used the same age benchmark (Martinez et al, 2019). The results of the demographic characteristics of this study indicate that the largest age of patients with breast cancer is 33-35 years at H. Adam Malik General Hospital Medan. This is in line with the study by Yazdani-Charati regarding the comparison of the pathological characteristics of breast cancer in younger and older women who also found that the mean (± SD) age of the patients was 49.7 ± 11.9 years (ranging from 17 to 95 years.). The majority of patients (80.5%) were aged ≥40 years versus 19.5% at age <40 years. The most common age group is 40-49 years (33.0%) (Yazdani-Charati, et al. 2019). Fabiano's 2020 study of breast cancer in emerging young women with more aggressive pathological characteristics also found that young patients comprised 10.40% of patients with invasive breast cancer. The mean age in this group was 35.61 years. Also, tumors were more likely to be detected clinically on physical examination in young women (90.10%) than in patients aged 40 years (76.99%; P = 0.001) (Fabiano et al. 2020).

In a study conducted at RSUP H. Adam Malik Medan, 78% of the respondents were married and 60% of the respondents had a history of childbirth. Ghiasvand et al. Stated that age at first marriage showed a significant association with breast cancer risk, and further age at first marriage was associated with an increased risk of breast cancer. Furthermore, those who have never married compared to those who are married under the age of 20 have a higher risk of developing breast cancer. Age at first pregnancy showed an inverse association with breast cancer risk, and those who first became pregnant over the age of 25 had almost double the risk of developing breast cancer (OR: 2.10; 95% CI: 1.47–3.02). Nulliparous women (this group consists of married and unmarried women) compared to those who first became pregnant under the age of 25 had a higher risk of developing breast cancer.

No significant association was observed between age at first gestation and breast cancer risk. Concerning parity, a significant difference was seen between cases and controls (p <0.001). Parity equal to or more than three compared with parity of 1–2 has a strong protective effect for developing breast cancer. Premenopausal women tend to be at higher risk of developing breast cancer but this relationship is not significant (Ghiasvand, 2011). The early age of menarche appears to be associated with a higher risk of breast cancer. One explanation for this association is that women at an earlier age at menarche were exposed to endogenous estrogens for a longer time, but it is unclear whether this association was causal or due to correlations with other early life exposures. This study found a non-significant association between age at menarche and risk of breast cancer in a multivariate analysis, which is consistent with other studies investigating this association in young or middle-aged women (Mahouri, 2007).

The highest stage of breast cancer in this study was stage IV as much as 59.6%. In a study conducted by Hartaningsih, it was stated that there were 36.7% of young cancer patients with stage IIIB and 31.2% with stage IV (Hartaningsih, 2014). The number of young patients who come with an advanced stage diagnosis (stage III

and IV) is due to the low knowledge of breast cancer (Dyanti, 2016). The current literature supports the hypothesis that breast cancer is generally more aggressive in younger women than in older women. These studies have identified an increased proportion of high-grade estrogen and progesterone receptor-negative tumors that multiply rapidly in younger patients who are also likely to be larger with associated vascular invasion and regional lymph node involvement (Partridge, 2016).

In the 54 case reports of tumors that we found, 57.4% were grade II while the lower proportion (40.7%) were grade III. This study contrasts with previous reports of breast cancer in women in this age group. Fernandopulle et al. (2006) reported 60% grade III rates in young East Asian women while Foxcroft et al. (2004) reported 69.3% grade III rates in the group of women under 40 from Australia compared to 35.2% in women over 40 years.

In this study, it was seen that in the breast cancer subtype Luminal A, there was an increase in IGF-1R expression compared to other groups by 69.2% and low by 30.6%. Whereas in the luminal B, HER2, and TNBC subtypes, there was a decrease in IGF-1R compared to other groups of 69.2%, 84.6%, and 69.2% respectively with a p-value of 0.029 which means that there is a significant difference between IGF-1R expression according to breast cancer subtypes in women of age. very young at H. Adam Malik Hospital, Medan. Noorwati (2008) explained that based on IGF-1R expression there was a weak positive in 4 patients, moderate positive in 7 patients, strong positive in 6 patients, and negative in 25 patients. It was found that a total of 59.5% of the sample was negative for IGF-1R expression at <35 years of age, this may indicate an interaction between ER and IGF-1R (Noorwati, 2008).

In this study, the expression of IGF-1R based on histopathological grading showed a value of $p = 0.067$ ($p > 0.05$) which was not statistically significant. The results of this study are in line with Carlson's 2010 study which stated that among patients younger than age 55, high IGF-1R expression was associated with longer survival but no association between IGF-1R and tumor grading (Carlson, 2010). In another study, it was found that increased IGF-1R expression was associated with the HER2 overexpression subtype and low histological grading (Shin et al. 2014). Reinholz in 2017 also found that the increase in IGF-1R expression was related to the histological grade of well / intermediate differentiation, namely the grade I and III histology (Reinholz, 2017).

The limitation of this study is that the sample in this study did not go through a randomization process so that the bias tendency was greater and the data dissemination was not comprehensive. This study used the determination of subtypes using the immunohistochemistry method whose reading results were subject to subjectivity and this IGF1R examination was the first in breast cancer patients at RSUP. H. Adam Malik Medan.

CONCLUSION

In this study, there was a significant difference in the expression of IGF1R according to breast cancer subtypes in very young women at H. Adam Malik General Hospital Medan with a p-value of 0.031 ($p < 0.05$) where higher expression was found in luminal A compared to luminal B and TNBC.

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