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Breast Cancer Clinicopathology based on Neutrophil Levels at Adam Malik Hospital Medan in 2018-2021

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ABSTRACT

Breast cancer is the most frequently diagnosed cancer in the world. Breast cancer occurs due to abnormal cell growth in breast tissue so that it becomes malignant. In Indonesia, breast cancer is the most common cancer in women. That way, many markers are needed as prognostic and predictive of breast cancer. One of the prognostic factors for breast cancer is neutrophil levels combined with clinicopathological factors. Knowing the clinicopathology of breast cancer based on neutrophil levels at the Haji Adam Malik Medan General Hospital in 2018-2021. The research design is observational with a descriptive method and calculated using the Lemeshow formula. Results: Majority aged 40-49 years (39.6%), high school (44.8%), housewives (67.7%), no family history (97.9%), tumor grade II (38.5%) %), Tumor Infiltrating Lymphocytes (TILs) severe (47.9 %), mitotic score 1 (38.5 %), metastatic positive lymph node status (87.5 %), tumor size T1 (36.5 %), The number of positive and negative Estrogen Receptors is the same (50.0%), Progesterone Receptor is negative (56.3%), HER2 is 1+ (60.4%), Ki-67 is positive (84 .4 %), positive angioinvasion (63.5 %), Invasive Ductal Carcinoma (90.6 %), high neutrophil levels (77.1 %). High levels of neutrophils tend to result in severe Tumor Infiltrating Lymphocytes (TILs) which will increase tumor growth, occurrence of metastases, increased positive angioinvasion, negative Estrogen Receptor status, negative Progesterone Receptor status, HER2 1+ status, positive Ki-67 status.

Keyword: Breast Cancer, Clinicopathology, Neutrophil Levels, Prognostic Factors

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1. Introduction

Mangrove Breast cancer in women is the most common cancer diagnosed worldwide with an estimated 2.3 million new cases in 2020.[1] In 2020 it is estimated that the number of new cases of breast cancer will reach 68,858 cases (16.6%) of the total 396,914 new cases of cancer in Indonesia and the number of deaths will reach more than 22 thousand cases.[2] Breast cancer is a very complex and heterogeneous disease. Tumor heterogeneity is observed between different patients (intertumor heterogeneity) and is seen between different primary regions of the tumor, between the primary metastatic tumor and the lesion, or between metastases of different lesions (intratumor heterogeneity).[3]

That way, it takes a lot of markers that can be used as a prognostic or prediction of breast cancer. In determining the best breast cancer prognosis, a combination of clinicopathological prognostic factors, such as age, tumor grade, population, tumor infiltrating lymphocytes (TILs), mitosis, lymph node status, tumor size, immunohistochemistry, angioinvasion, type of cancer. Example, the research by Pramana Putri Gelgel and

Steven Christian which stated that the highest frequency of breast cancer patients was in the age group of 40-49 years. Increasing age as a risk factor may be caused by exposure to the hormone estrogen in the long term.[6]

In addition to clinicopathological prognostic factors, neutrophils can also theoretically be used as a prognostic because growing tumors strongly influence neutrophil development and activity through the large amounts of growth factors and cytokines released.[4]

The role of neutrophils in cancer is multifactorial and not fully understood. Neutrophils reflect the state of inflammation in host cells or hosts, which is a hallmark of cancer. Neutrophils can participate in various stages of the oncogenic process including tumor initiation, growth, proliferation or metastatic spread.[5]

In this study we were interested in seeing neutrophil levels as a prognostic factor for breast cancer.

2. Method

This study was an observational descriptive study with cross-sectional methods. We collected secondary data from medical records. Data were collected at Haji Adam Malik General Hospital Medan. The population in this study were all female patients with breast cancer who underwent clinical and histological examinations as well as complete blood counts at the Surgical Oncology Laboratory Unit from 2018-2021. Samples included in this study had complete data on neutrophil levels and clinicopathology such as age, tumor grade, population, tumor infiltrating lymphocytes (TILs), mitosis, lymph node status, tumor size, immunohistochemistry, angioinvasion, type of cancer. The data taken is data from histopathologically proven breast cancer patients. The data obtained in this research was processed and analyzed using the SPSS (Statistical Package for Social Science). The neutrophil value itself is grouped into "low" and "high", where it is said to be low if <4.6 $10^3/\mu L$ and high if >4.6 $10^3/\mu L$. All collected data were presented in distributive frequency tables.

3. Result

Observations and measurements of *A. marina* seedlings over twelve weeks showed variances in height, leaf diameter and width, and total dry weight gains. The observation data of *A. marina* seedlings subjected to various species of fungi in Pulau Sembilan and Belawan are displayed in Table 1 and 2.

This descriptive study was conducted on 96 patients who met the inclusion and exclusion criteria in the study method.

Table 1. Distribution of Characteristics of patients with Breast Cancer

Individual Characteristics	Frequency	Percentage
Age		
< 40	27	28,1 %
40-49	38	39,6 %
50-59	21	21,9 %
≥ 60	10	10,4 %
Education		
No education	1	1,0 %
Primary school	15	15,6 %
Junior high school	8	8,3 %
Senior high school	43	44,8 %
University	29	30,2 %
Occupation		
Housewife	65	67,7 %
Farmer	2	2,1 %
Self-employed	13	13,5 %

Civil servant	16	16,7 %
Family History		
Yes	2	2,1 %
No	94	97,9 %

From the table above, we found that the majority are in the age group of 40-49 years, senior high school education, work as a housewife, and lacked a family history.

Table 2. Distribution of Clinicopathology of Breast Cancer Patients Based on Neutrophil Levels

Clinicopathology	**Frequency Distribution of Neutrophil Levels**			
	Low	**%**	**High**	**%**
Total Case	22	22,9 %	74	77,1 %
Tumor *Grade*				
I	2	9,1 %	23	31,1 %
II	13	59,1 %	24	32,4 %
III	7	31,8 %	27	36,5 %
TILs				
Mild	5	22,7 %	7	9,5 %
Moderate	16	72,7 %	22	29,7 %
Severe	1	4,5 %	45	60,8 %
Mitosis				
Score 1	6	27,3 %	31	41,9 %
Score 2	10	45,5 %	17	23,0 %
Score 3	6	27,3 %	26	35,1 %
Lymph Node				
Positive	18	81,8 %	66	89,2 %
Negative	4	18,2 %	8	10,8 %
Tumor Size				
T1	4	18,2 %	31	41,9 %
T2	11	50,0 %	18	24,3 %
T3	4	18,2 %	19	25,7 %
T4	3	13,6 %	6	8,1 %
Estrogen Receptor				
Positive	12	54,5 %	36	48,6 %
Negative	10	45,5 %	38	51,4 %
Progesterone Receptor				
Positive	12	54,5 %	30	40,5 %
Negative	10	45,5 %	44	59,5 %
HER2				
1 Positive	15	68,2 %	43	58,1 %
2 Positive	3	13,6 %	2	2,7 %

3 Positive	4	18,2 %	29	39,2 %
Ki-67				
Positive	18	81,8 %	63	85,1 %
Negative	4	18,2 %	11	14,9 %
Angioinvasion				
Positive	11	50,0 %	50	67,6 %
Negative	11	50,0 %	24	32,4 %
Types of Breast Cancer				
Ductal Carcinoma In Situ (DCIS)	2	9,1 %	2	2,7 %
Lobular Carcinoma In Situ (LCIS)	0	0 %	0	0 %
Invasive Ductal Carcinoma (IDC)	19	86,4 %	68	91,9 %
Invasive Lobular Carcinoma (ILC)	1	4,5 %	4	5,4 %

From the data above, we found that breast cancer mostly happened in high neutrophil levels, with the most common type of breast cancer is Invasive Ductal Carcinoma.

4. Discussion

In this study, the breast cancer patients in Haji Adam Malik General Hospital are in the age group of 40-49 years. These results are in accordance with the research by Pramana Putri Gelgel and Steven Christian which stated that the highest frequency of breast cancer patients was in the age group of 40-49 years.[6] Increasing age as a risk factor may be caused by exposure to the hormone estrogen in the long term.[6] The risk of developing breast cancer cells with increasing age is also influenced by the role of the BRCA1 and BRCA2 genes.[7] The majority of the educational level of breast cancer patients in this study was senior high school.

The results of this study are in accordance with the research of Pramana Putri Gelgel and Steven Christian which states that the distribution is based on the highest level of education at the senior high school level.[6] Based on data from the Indonesian Journal of Cancer at the Surabaya Oncology Hospital in 2014, it was found that the majority were at the university level.[8] Education is a basic requirement in building awareness of breast cancer and in conducting screening. BSE (Breast Self Examination) is an efficient form of mass education. By increasing education about BSE, breast cancer can be detected earlier.[8]

The majority of breast cancer patients at Haji Adam Malik General Hospital Medan are housewives. The results of this study are in accordance with study data from the Indonesian Journal of Cancer at the Surabaya Oncology Hospital in 2014 with the highest data, namely working as a housewife.[8] Breast cancer patients who have no family history at Haji Adam Malik General Hospital Medan in 2018-2021 are the highest. Based on data from the Indonesian Journal of Cancer at the Surabaya Oncology Hospital in 2014, it also stated that the majority of breast cancer patients had no family history.[8] The risk of breast cancer in women who have a family history of breast cancer is higher. Women who have a family history of breast cancer in the first generation (mother, sister or daughter) have twice the risk. If a history of cancer is owned by 2 successive generations, the risk increases to three times. However, the exact causal relationship between them is still unknown.[8]

From table 2, It can be seen that breast cancer patients with low neutrophil levels were 22 patients (22.9%), and with high neutrophil levels were 74 patients (77.1%). The majority of breast cancer patients have high neutrophil levels. Neutrophil association with breast cancer plays an important role in tumor development, metastasis, and overall survival.[9] In theory, neutrophil levels in the breast tumor microenvironment would correlate with more aggressive histological subtypes, especially in triple-negative breast cancer, in which high circulating neutrophil counts confer a poor prognosis.[10] As in other tumors, the development of breast

cancer is associated with systemic inflammation. Inflammatory state can accelerate tumor growth, invasion, angiogenesis, etc. Increased inflammatory markers (neutrophils) are associated with reduced survival in breast cancer patients. The neutrophil count can contribute to the diagnosis and prognosis in breast cancer associated with inflammation.[11] Low neutrophil counts can occur due to the effects of chemotherapy or antineoplastic which can cause serial suppression of granulocytes.[12]

The most common tumor grade was II with a total of 37 patients. The results of this study are in accordance with the research of Pramana Putri Gelgel and Steven Christian which stated that grade II breast cancer was the most common case with a total of 43 patients.[6] However, different results were obtained in the Hutahaean study which stated that the highest proportion of research subjects included in the grade III category was 69 cases.[13] This study stated that MMP-8 (Matrix Metalloproteinase 8), a protease enzyme of the neutrophil collagenase type, was overexpressed in grade III but had begun to increase from grade II. The increased expression of MMP-8 strongly influences the role in invasive and metastatic breast cancer.[14]

The majority of Tumor Infiltrating Lymphocytes (TILs) were severe with a total of 46 patients. The results of this study differ from those of Widiana, Suryawisesa and Widiana which stated that the majority of TILs were mild with a total of 45 cases.[15] TILs, namely the migration of lymphocyte cells around the tumor, has become an important issue as a biological marker in breast cancer, especially at an early stage (early breast cancer) and the presence or expression of TILs in breast cancer is associated with the prognosis in HER2 subtype and triple-negative breast cancer, then become important in the development of immunotherapy in breast cancer.[15]

The highest number of mitoses was score 1 with a total of 37 patients. The results of this study are the same as those of Pratiwi and Siregar which stated that breast cancer mitosis score 1 was the most numerous with a total of 36 cases.[16] Bonert and Tate's study also stated that mitosis score 1 was the highest with a total of 96 cases.[17] Mitosis is used in a large number of neoplasms/tumors to predict prognosis, and neoplasms that are highly proliferative (many mitoses) usually have a poorer prognosis.[17]

The most lymph node status was metastatic positive with a total of 84 patients. The results of this study are different from the study of Riyadhi Akbar, Heriady and Adhia G in 2020 which stated that metastatic negative lymph node status was the most common with a total of 41 patients.[18] Lymph node status can be used in assessing the presence or absence of lymph node metastases in breast cancer. Breast cancer metastases via the lymphovascular system to regional lymph nodes in the axilla and to visceral and non-visceral sites.[19]

The tumor size with the highest number was T1 with a total of 35 patients. The results of this study different from those of Baswedan, Purwanto and Rahniayu which stated that the size of T2 tumors was the largest with a total of 227 cases.[20] In tumor nuclei patients at relatively late stages (stages T2, T3, T4) had significantly higher neutrophil infiltration into the tumor site compared to patients at early stages (T1).[9]

In immunochemistry, overall, the status of the estrogen receptor hormone in breast cancer patients at Haji Adam Malik General Hospital Medan was 48 cases each (50.0%) ER+/-. Subiyanto's study results obtained different results where ER+ was the most numerous with a total of 161 cases.[21] Based on table 2, in all groups of neutrophil levels the number of PR+ totaling 42 cases (43.8%), and PR- totaling 54 cases (56.3%). The results of this study differ from Tanggo's 2016 study which stated that PR+ was the most common with 110 cases [22]. The highest total HER2 was HER2 1+ with a total of 58 patients. The results of this study are in accordance with Subiyanto's study which states that the most common HER2 status is HER2 1+ with a total of 139 cases.[21] In each group of neutrophil levels, the most Ki-67 was positive with 81 patients. Study by Pasaribu, Issakh and Maritska also stated that positive Ki-67 was the most numerous with a total of 40 cases.[23] Ki-67 is a tumor marker that provides a static picture of tumor proliferation, and a surrogate marker for evaluating the effectiveness of treatment. High Ki 67 levels can describe poor disease free survival. It can be concluded that Ki67 is only a prognostic factor, not a predictive factor.[23]

The number of positive angioinvasion was the highest with a total of 61 cases. Angioinvasion can assess the prognosis of the presence or absence of blood vessels that stimulate tumor growth and metastasis of breast cancer.[22] The results of this study are different from Tanggo's 2016 study which stated that negative angioinvasion was the most common with a total of 146 cases.[22]

The most common type of breast cancer in each neutrophil level group was Invasive Ductal Carcinoma with a total of 87 cases. The results of this study are in accordance with the Hutahaean study where the type of breast cancer Invasive Ductal Carcinoma has the most cases, namely there are 85 cases.[13] The opposite result

was obtained in the study of Tanriono, Rotty and Haroen which stated that this type of fibroadenoma cancer was the most common with a total of 62 cases.[24] It can be stated that high neutrophil levels in Invasive Ductal Carcinoma breast cancer indicate that there are aggressive invasive neutrophils in the breast duct tissue.

5. Conclusion

Most breast cancer sufferers with high neutrophil levels have a poor prognosis with grade III tumors, severe Tumor Infiltrating Lymphocytes (TILs), mitosis score 1, positive lymph node metastasis status, T1 tumor size, negative Estrogen Receptor (ER) status, Progesterone Receptor (PR) has negative status, Human Epidermal Growth Factor Receptor 2 (HER2) has negative status, Ki-67 has positive status, angioinvasion has positive status, and the cancer type is Invasive Ductal Carcinoma (IDC). High neutrophil levels in the breast tumor microenvironment will correlate with more aggressive histologic subtypes, especially in triple-negative breast cancer. Therefore, every breast cancer patient is advised to check neutrophil levels because neutrophil levels serve as a prognostic and predictive of breast cancer metastasis.

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