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Research Article

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

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ABSTRACT

Background: 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. **Objective:** Knowing the clinicopathology of breast cancer based on neutrophil levels at the Adam Malik Medan General Hospital in 2018-2021. **Methods:** 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 %). **Conclusion:** 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.

Keywords: breast cancer, clinicopathology, neutrophil levels, prognostic factors

1. Introduction

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 was estimated that the number of new cases of breast cancer would reach 68,858 cases (16.6%) of the total 396,914 new cancer cases in Indonesia, with deaths reaching more than 22,000 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].

Thus, it requires many markers that can be used for the prognosis or prediction of breast cancer. In determining the best breast cancer prognosis, a combination of clinicopathological prognostic factors is needed, such as age, tumor grade, population, tumor-infiltrating lymphocytes (TILs), mitosis, lymph node status, tumor size, immunohistochemistry, angioinvasion, and type of cancer. For example, research by Pramana Putri Gelgel and Steven Christian 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 long-term exposure to the hormone estrogen [6].

In addition to clinicopathological prognostic factors, neutrophils can also theoretically be used as a prognostic marker 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, which is a hallmark of cancer. They can participate in various stages of the oncogenic process, including tumor initiation, growth, proliferation, and metastatic spread [5]. In this study, we were interested in observing neutrophil levels as a prognostic factor for breast cancer.

2. Methods

This study was an observational descriptive study with cross-sectional methods. We collected secondary data from medical records. Data were collected at 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/µL and high if >4.6 10^3/µL. All collected data were presented in distributive frequency tables.

3. Results

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

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

Most breast cancer patients at Haji Adam Malik General Hospital Medan were housewives. This finding is consistent with data from the Indonesian Journal of Cancer at the Surabaya Oncology Hospital in 2014, which also reported the majority of patients were housewives [8].

Additionally, breast cancer patients without a family history represented the highest proportion at Haji Adam Malik General Hospital Medan from 2018 to 2021. This is consistent with data from the Indonesian Journal of Cancer at the Surabaya Oncology Hospital in 2014, which also stated that most breast cancer patients had no family history [8]. However, the risk of breast cancer in women who have a family history is significantly higher. Women with a first-degree relative (mother, sister, or daughter) with breast cancer have twice the risk, and if cancer is present in two successive generations, the risk increases threefold. Nevertheless, the exact causal relationship remains unclear [8].

From Table 2, it can be seen that among the breast cancer patients, 22 patients (22.9%) had low neutrophil levels, while 74 patients (77.1%) had high neutrophil levels. Thus, the majority of breast cancer patients had high neutrophil levels. Neutrophils play an important role in tumor development, metastasis, and overall survival [9]. In theory, neutrophil levels in the breast tumor microenvironment correlate with more aggressive histological subtypes, particularly in triple-negative breast cancer, where high circulating neutrophil counts are associated with a poorer prognosis [10]. As with other tumors, the development of breast cancer is associated with systemic inflammation. This inflammatory state can accelerate tumor growth, invasion, and angiogenesis. Elevated inflammatory markers (such as neutrophils) are associated with reduced survival in breast cancer patients [11]. Neutrophil counts can contribute to both the diagnosis and prognosis of breast cancer related to inflammation [11]. Low neutrophil counts, on the other hand, can occur as a result of chemotherapy or antineoplastic therapy, which can cause serial suppression of granulocytes [12].

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

The majority of Tumor Infiltrating Lymphocytes (TILs) were classified as severe, with a total of 46 patients. This finding differs from the study by Widiana, Suryawisesa, and Widiana, who reported that the majority of TILs were mild, totaling 45 cases [15]. TILs, which involve the migration of lymphocyte cells around the tumor, have become an important biological marker in breast cancer, particularly in early-stage disease. The presence or expression of TILs is associated with prognosis in HER2 subtype and triple-negative breast cancer and is significant in the development of immunotherapy [15].

The highest mitotic score observed was score 1, with 37 patients. This result is consistent with the findings of Pratiwi and Siregar, who also reported that mitosis score 1 was the most common, with a total of 36 cases [16]. Similarly, Bonert and Tate's study indicated that mitosis score 1 was the most frequent, with a total of 96 cases [17]. Mitosis is widely used in neoplasms/tumors to predict prognosis, where highly proliferative tumors (many mitoses) usually have a poorer outcome [17].

The majority of lymph node statuses were metastatic positive, with a total of 84 patients. This result differs from the study by Riyadhi Akbar, Heriady, and Adhia G in 2020, which reported that metastatic-negative lymph node status was the most common, with a total of 41 patients [18]. Lymph node status is critical in

assessing the presence of lymphatic metastasis in breast cancer. Breast cancer typically metastasizes 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 frequency was T1, involving 35 patients. This finding contrasts with the study by Baswedan, Purwanto, and Rahniayu, which reported T2 as the most common tumor size, with 227 cases [20]. In patients with relatively late-stage tumors (T2, T3, T4), neutrophil infiltration into the tumor site was significantly higher compared to those at an early stage (T1) [9].

Regarding immunohistochemistry, the status of the estrogen receptor (ER) hormone among breast cancer patients at Haji Adam Malik General Hospital Medan was balanced, with 48 cases each for ER+ and ER- (50.0%). This finding differs from Subiyanto's study, which reported that ER+ was the most common, with 161 cases [21]. Based on Table 2, in all neutrophil level groups, the number of PR+ cases was 42 (43.8%), and PR- cases totaled 54 (56.3%). This result also differs from the study by Tanggo in 2016, which found PR+ to be the most frequent with 110 cases [22].

The highest HER2 status observed was HER2 1+, with 58 patients. This finding is consistent with Subiyanto's study, which also reported HER2 1+ as the most common, with 139 cases [21]. In all neutrophil level groups, Ki-67 positivity was predominant, with 81 patients. The study by Pasaribu, Issakh, and Maritska similarly reported Ki-67 positivity as the most frequent, with 40 cases [23]. Ki-67 is a tumor marker that provides a static picture of tumor proliferation and serves as a surrogate marker for evaluating treatment effectiveness. High Ki-67 levels are associated with poorer disease-free survival. It can be concluded that Ki-67 acts as a prognostic factor, but not a predictive factor [23].

The number of positive angioinvasion cases was the highest, with 61 patients. Angioinvasion is important for assessing prognosis as it indicates the presence of blood vessels that stimulate tumor growth and metastasis in breast cancer [22]. However, these findings differ from the study by Tanggo in 2016, which reported that negative angioinvasion was more common, with 146 cases [22].

The most common type of breast cancer observed across all neutrophil level groups was Invasive Ductal Carcinoma, with a total of 87 cases. This finding is in line with the study by Hutahaean, which also reported Invasive Ductal Carcinoma as the most prevalent type, with 85 cases [13]. In contrast, the study by Tanriono, Rotty, and Haroen stated that fibroadenoma was the most common type, with a total of 62 cases [24]. It can thus be suggested that high neutrophil levels in Invasive Ductal Carcinoma indicate aggressive invasive neutrophil activity within 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.

6. Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author upon reasonable request.

7. Ethical Statement

Sumatera Medical Journal (SUMEJ) is a peer-reviewed electronic internationaljournal. This statement clarifies ethical behavior of all parties involved in the act of publishing an article in Sumatera Medical Journal (SUMEJ), including the authors, the chief editor, the Editorial Board, the peer-reviewer and the publisher (TALENTA Publisher UniversitasSumatera Utara). This statement is based on COPE's Best Practice Guidelines for Journal Editors.

8. Author Contributions

All authors contributed to the design and implementation of this research, data analysis, and finalizing the manuscript.

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11. Conflict of Interest
Authors declares no conflict of interest.

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