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Immunohistochemical Profiles of Breast Cancer Patients at MRCCC Siloam Semanggi Hospital in 2018

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ABSTRACT

Immunohistochemistry examination (IHC) is one of the additional tests to diagnose and determine breast cancer subtype. IHC examination is a method to check intracellular protein using a monoclonal and polyclonal antibody to detect the antigen in tissue. IHC examination determined by hormone receptor markers (ER and PR), HER-2/Neu expression, and apoptotic and proliferation markers (Ki-67 and p53) can be used to determine therapy and prognosis. This study aims to determine the hormonal status of breast cancer patient at Siloam Semanggi Hospital in 2018, in the form of age, gender, pathology diagnose, and the result of IHC (ER, PR, HER2, and Ki-67). This study is a retrospective descriptive study using pathological anatomy laboratory results of breast cancer in MRCCC Siloam Semanggi Hospital and 208 patients following inclusion and exclusion criteria. The result obtained is that the age group with the highest frequency is 50-59 years, with 34.1%. The highest frequency by gender is a woman with 99.5%. Carcinoma mammae NST with grade II and III was found in 38.0% of patients. The hormonal receptor with ER and PR positive was found in 51.0% of patients. HER2 expression negative was found in 56.7% of patients. High proliferation Ki-67 was found in 82.7% of patients. Luminal B with HER2 negative subtype was found in 32.2% of patients. Patients in 50-59 years with Luminal B with HER2 negative subtype was found in 26 patients. Patients in carcinoma mammae NST with grade II with Luminal B with HER2 negative subtype was found in 27 patients.

Keywords: *Breast cancer, pathologic anatomy, immunohistochemistry, breast cancer subtype*

INTRODUCTION

Breast cancer is a malignancy in the breast tissue with various biological subtypes, origins, and pathological features grouped into various groups that produce response patterns and clinical features to given therapy [1; 2; 3]. Globocan, through the International Agency for Research on Cancer (IARC) in 2018, the incidence of new cancer cases reached 18,078,957 cases with breast cancer occupying second place as the newest cases with a total of 2,088,849 cases (11.6%) after lung cancer. Asia is the most significant contributor to the incidence of breast cancer in the world, with 911,014 (43.6%). In Southeast Asia, the incidence of breast cancer is the highest (270,401 (13.5%)) when compared to the incidence of other types of cancer [4; 5; 6].

Breast cancer can be diagnosed through a history taking, physical examination, and histopathological examinations. Anamnesis can find the main complaints that patients complain of in the form of lumps in the breasts, breast growth speed with or without pain, nipple discharge, skin disorders around the breasts, or lumps around the armpits and oedema of the arms. Physical examination was carried out locally, regionally, and systemically.

Additional investigations that can be performed include imaging studies (mamogafi, breast ultrasound, or MRI) and anatomical pathology examination [7].

One of the anatomical pathology examinations carried out in Indonesia is the immunohistochemical examination. The immunohistochemical examination is used because of the many differential diagnoses of abnormalities in the breast glands. Molecularly, immunohistochemistry can be used to identify subtypes or molecular phenotypes with markers of intracellular proteins present in tissues. The results of the identification of subtypes can be used as a patient prognosis and predict the response to a given therapy [8]. Based on the consensus of St. Gallen in 2017, immunohistochemistry can be used to determine estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2), and Ki-67. Clinically St. Gallen classified breast cancer broadly into triple-negative tumours, HER2 positive tumour regardless of ER status, and two types of ER-positive. Meanwhile, what we usually use is divided into Luminal A, Luminal B with HER2 negative, Luminal B with HER2 positive, HER2 positive, and basal-like (triple-negative) [9; 10].

Research related to hormonal status was carried out previously by Wiguna at Sanglah General Hospital in 2013 and Amiria at Fatmawati General Hospital in 2017. Many patients were undergoing IHC examinations, respectively 147 (14.49%) examinations and 108 patients from all cases [11]. The research conducted by writing is similar to research that has been done before, but the data that the author uses are medical records from MRCCC Siloam Semanggi Hospital in 2018. Previously no one has conducted research related to breast cancer at Siloam Semanggi Hospital, so the authors are interested in conducting research. The problem answered in this study is "What is the picture of the immunohistochemical profile at Siloam Semanggi Hospital in 2018? To determine the immunohistochemical profile in breast cancer patients.

LITERATURE REVIEW

Breast Cancer - Breast cancer has several definitions, according to various studies. According to the European Society for Medical Oncology (ESMO), breast cancer originates from breast cells that develop abnormally and multiply to form a lump or tumour [12]. According to the American Cancer Society, a group of diseases form a lump or mass in the gland through changes and the irregular spread of cells [13]. According to the Indonesian Ministry of Health, breast cancer can originate from the epithelial tissue of the ducts and lobules, which is malignant and is one of the most common types of cancer in Indonesia [7].

Epidemiology - Based on data from Globocan in 2018, the average incidence of breast cancer in the world occurred at the age of 46 years with an incidence rate of 2,088,849 (5.03%) cases. The incidence rate in Asia is the highest and reaches 911,014 (43.6%) cases. Southeast Asia is one of the regions with the third-highest incidence of breast cancer compared to other parts of Asia.4,5 Focusing on Indonesia, one of the regions in Southeast Asia, with the incidence of breast cancer in 2018 reaching 58,256 (16.7%) cases and is the highest incidence rate in Indonesia with an average age of 42 years [14]. The death rate due to breast cancer in 2018 reached 626,679 (1.41%) cases with an average age of 13 years and being the fourth cause of death caused by cancer. Due to breast cancer in Asia itself, the death rate is still the highest compared to other countries, namely 310,577 (49.6%) cases. However, in Southeast Asia, the mortality rate is higher when compared to other parts of Asia [4; 5]. The death rate due to breast cancer in Indonesia in 2018 reached 22,692 (11.0%) cases with an average age of 17 years and is the second leading cause of death after lung cancer [14].

Immunohistochemistry or IHC is a method of examining intracellular proteins using monoclonal and polyclonal antibodies to detect antigens on the surface of the tissue. [7,8,15]. The principle of using the IHC has existed since 1930, but only the first study of IHC was published in 1941. Next, Coons used the antibody marker Fluorescein isothiocyanate (FITC) in determining the Streptococcus pneumonia antigen that infects tissues with fluorescein staining and the help of ultraviolet light. The enzymes obtained are peroxidase and alkaline phosphatase [15; 16].

IHC examination in breast cancer is used to characterize intracellular proteins and cells in the surface of a tissue and is widely used to classify subtypes that are biologically and pathophysiologically different in breast cancer. IHC examination is more advantageous when compared to staining using a particular enzyme because it only involves a specific antigen-antibody reaction. Therefore, IHC examination is critical and is widely used in laboratory studies and as a diagnostic tool for clinicians [8; 15; 18]. Classification of breast cancer into several subtypes is significant in determining therapy and patient prognosis. Examination of IHCin breast cancer in terms of determining therapy and prognosis is generally determined by hormone receptor markers (ER and PR), HER-2 / Neu expression, and markers of apoptosis and cell proliferation (Ki-67, p53) [8].

Hormone receptors - In routine breast cancer IHC checks, hormone receptor assessments are detected via Estrogen Receptor (ER) and Progesterone Receptor (PR). The presence of ER indicates a need for tamoxifen therapy [8]. ER plays a significant role in mediating the effects of endogenous hormones and therapeutic agents to be used as a marker of therapeutic response or resistance to therapy. The greater the ER and PR values of breast cancer, the greater the likelihood of response to therapy [19; 20].

HER-2 / Neu - HER-2 influences the course of cancer in the form of cell growth, cell survival, and cell differentiation. Determination of HER-2 / Neu was detected by two methods, namely, IHC and fluorescence in situ hybridization (FISH). HER-2 IHC reactions were assessed by Hercep Test, where 0 and 1+ were negative, 2+ was weakly positive, and 3+ were positive. Weakly positive or 2+ a further FISH should be tested to detect gene amplification. HER-2 gene amplification can predict disease recurrence time and cure rate of breast cancer patients [8; 21; 22]. HER-2 / Neu examination can be used as a marker of the sensitivity of Trastuzumab (Herceptin) therapy and tamoxifen resistance [8].

Ki-67 is a non-histone protein, affects the initial steps of the synthesis of ribosomal RNA polymerase I-dependent and acts as a prognostic marker of cancer. In all proliferating cells, Ki-67 will appear as a marker of proliferation. Based on the consensus of St. Gallen in 2011, "low proliferation" Ki-67 with an index <14%. However, in 2013, the threshold for Ki-67 “high” status was ≥20% [8; 22; 23]. In breast cancer proliferation, Ki-67 expression was used to determine the effect of tamoxifen administration at different doses [8].

Breast cancer subtype - The current subtype of breast cancer can be determined by several parameters. Patients who undergo further surgery will undergo routine examinations with macroscopic and microscopic histological analysis, TNM staging, IHC grouping based on ER, PR, HER-2/Neu, and Ki-67. The latest classification of breast cancer subtypes based on the St's consensus. Gallen divides into five subtypes, Luminal A, Luminal B with HER2 negative, Luminal B with HER2 positive, HER2 enriched, basal-like (triple-negative). It is hoped that the determination of breast cancer subtypes can help determine the prognosis and administration of therapy [10; 25].

The author attaches the division of breast cancer subtypes to make it easier for readers to understand the results of the IHC examination.

Table 2. Molecular Subtypes according to St. Gallen [10; 25]

Breast cancer subtypes	ER and PR	HER-2	Ki-67
Luminal A.	ER + and/or PR +	HER-2 -	Ki-67 <20%
Luminal B with HER-2 negative	ER + and/or PR +	HER-2 -	Ki-67 ≥20%
Luminal B with HER-2 positive	ER + and/or PR +	HER-2 +	*Any* Ki-67
HER-2 *enriched*	ER -, PR -	HER-2 +	*Any* Ki-67
Basal-like (triple-negative)	ER -, PR -	HER-2 -	Ck5/6 + and/or egfr +

Histopathological grading - Determination of breast cancer grading is critical, and the clinician is used as information to help provide therapy. Grading represents the degree of aggression of a tumour as well as a prognostic factor [26]. Pathological grading is determined based on three factors according to the Nottingham Histologic Score system, namely: a) The number of glands formed (differentiation); b) Characteristics of the cell nucleus (pleomorphic); and c) activity of splitting (proliferation) [26]. Each factor is assigned a value of 1-3, then added up so that the total score ranges from 3-9. The total score determines the grading, where: a) Grade I: has a value of 3-5; b) Grade II: has a score of 6-7, and c) Grade III: has a value of 8-9 [26].

Breast cancer with a malignant degree of ductal proliferation and invasive stromal invasion features invasive ductal carcinoma (IDC). The IDC classification is classified into several histological subtypes, which are assessed according to several criteria: a) Cell type (apocrine carcinoma); b) The number, type, and location of secretions (carcinoma mucinous); c) Architectural form (Papillary, tubular and micropapillary carcinoma); and d) IHC profile (neuroendocrine carcinoma). The term currently widely used in IDC is "No Special Type" (NST), and its use has been accepted internationally [27].

RESEARCH METHOD

This type of research uses descriptive research methods with retrospective studies, and the samples were the laboratory patient carried out at MRCCC Siloam Semanggi Hospital from 11 September 2019 - 25 September 2019. This research is a retrospective descriptive study by looking at laboratory data from patients diagnosed with breast cancer to obtain the patient's IHC examination results in 2018. The method used in selecting samples was the total sampling method. That is, all subjects who meet the selection criteria are included in the study. The author determined that the population in this study were breast cancer sufferers in Indonesia, while the study sample was breast cancer patients at MRCCC Siloam Semanggi Hospital with IHC examination. The total number of IHC examinations for breast cancer patients at Siloam Hospital in 2018 was 245 reports. Of the total, 208 samples were taken based on inclusion and exclusion criteria. The research instrument used was the anatomic pathology laboratory report of the IHC examination in breast cancer patients in 2018 at Siloam Semanggi Hospital. This research was conducted after obtaining approval from the Faculty of Medicine, Christian University of Indonesia and MRCCC Siloam Semanggi Hospital. Approval was obtained by submitting a cover letter to the Director of Siloam Semanggi Hospital.

RESULT AND DISCUSSION

In this study, data on breast cancer patients who underwent IHC examinations in 2018 at MRCCC Siloam Semanggi Hospital were 208 patients based on inclusion criteria. From 208 patients, data were obtained in the form of age, sex, and IHC examination results (including pathology diagnosis, ER, PR, HER2, and Ki-67).

Table 1. Age distribution of breast cancer patients who underwent IHC

Age	Frequency	%
20-29	6	2.9%
30-39	19	9.1%
40-49	58	27.9%
50-59	71	34.1%
60-69	40	19.2%
≥70	14	6.7%
Total	208	100.0%

The table above shows that the highest age group of breast cancer patients who underwent IHC examinations at MRCCC Siloam Semanggi Hospital for 2018 was 50-59 years, as many as 71 patients (34.1%). These results are similar to research conducted by Amiria (2017) at Fatmawati General Hospital that breast cancer patients are dominated by the age range of 50-59 years (37.9%). According to the theory, breast cancer is found in female with menopause at the age of 40-59 years and peaks at the age of 70. In Asia alone, the highest incidence of breast cancer occurs at 40-50 years, 60-70 years in western countries, and America occurs at the age above 40 and 60 years [28; 29; 30].

Table 2. Sex distribution of breast cancer patients who underwent IHC

Gender	Frequency	%
Female	207	99.5%
Male	1	0.5%
Total	208	100.0%

In the table above, it was found that from a total of 208 data on the sex of patients who have breast cancer and doing IHC, one data was obtained from men (0.5%). From a study, it is said that the incidence of breast cancer in men is infrequent. Worldwide the incidence is less than 1% [31]. Family history with BRCA gene mutations is the most significant factor in the incidence of breast cancer in men. Men who carry the BRCA mutated gene have a higher risk. When BRCA2 mutated, the risk was 6% higher than BRCA1 in the incidence of breast cancer in men [32].

Table 3. Distribution of pathological diagnoses on IHC examination

Pathology Diagnosis	Frequency	%
NST I breast carcinoma	4	1.9%
NST II breast carcinoma	**79**	**38.0%**
NST III breast carcinoma	**79**	**38.0%**
Non-NST breast carcinoma	27	13.0%
Mixed breast carcinoma	7	3.4%
Breast carcinoma not available	12	5.8%
Total	208	100.0%

NST, *No Special Type*.

The table above shows that the most dominant frequency of pathological diagnoses at MRCCC Siloam Semanggi Hospital is breast carcinoma NST II and breast carcinoma NST III with the same number of each, namely 79 patients (38.0%). The histopathological grade in European countries is often low, while in Indonesia, grade II and III are the most dominant [33].

Table 4. Distribution of IHC examination results

No	Diagnosis	Frequency	%
1	Receptor Hormone		
	ER and PR are positive	106	51.0%
	ER-positive PR negative	27	13.0%
	ER-negative PR positive	9	4.3%
	ER and PR are negative	66	31.7%
	Total	208	100.0%
2	HER2		
	Negative	118	56.7%
	+2	27	13.0%
	+3	63	30.3%
	Total	208	100.0%
3.	Ki-67		
	<20%	36	17.3%
	≥20%	172	82.7%
	Total	208	100.0%

The table above found that the most dominant hormone receptors in patients were double-positive (ER and PR positive) with 106 patients (50.96%). Cases with double negative (ER and PR negative) also showed the second-highest frequency with 66 patients (31.73%), whereas others did not reach 20%, the highest incidence was found. For HER2 examination, the highest incidence of negative HER2 was 118 patients (56.7%). The second highest frequency was HER2 with +3 with 63 patients (30.3%), and the lowest was HER2 with +2 as many as 27 patients (13%). Many patients who underwent FISH examination were 17 patients, with 15 patients being amplified and 2 patients not amplified. The highest Ki-67 value in patients was ≥20%, with frequency of 172 patients (82.7%) and Ki-67 with a value of <20% as many as 36 patients (17.3%).

The study results related to hormone receptors, the highest incidence of multiple positive hormonal receptors with 106 patients (50.96%). These results are almost consistent with research conducted by Reiner et a (2017), double-positive (ER and PR positive) with the highest frequency (41%) [34]. This result is different from the research conducted by Wiguna at Sanglah

General Hospital (2013), where the highest frequency in the study with a sample of 147 patients was multiple negative hormonal receptors (54.4%). Several factors cause differences in the appearance of ER and PR. Differences in racial and ethnic factors can cause this. The American and European regions tend to have dominant hormone receptors when compared to Asian regions. The limited number of samples also influences these differences [11].

The dominance of negative HER2 results in this study is following other studies such as Wiguna (2013) research at Sanglah General Hospital, where negative HER2 was more dominant, amounting to 74.8% [11]. Likewise, in a study conducted by Siregar et al. at RSUP H. Adam Malik Medan, HER2 negative predominates with a frequency of 62.5% [35]. HER2 plays a significant role in the course of cancer and is often associated with poor differentiation. HER2 can be used as a predictive factor in prognosis and therapeutic targets [11; 21; 22]. Determination of Ki-67 in this study, which later can be used to differentiate breast cancer subtypes between Luminal A or Luminal B [25].

Table 5. Distribution of molecular subtypes

Subtype	Frequency	%
Luminal A	26	12.5%
Luminal B HER2 -	67	32.2%
Luminal B HER2 +	49	23.6%
HER2 *enriched*	41	19.7%
Basal-like	25	12.0%
Total	208	100.0%

The table above shows the number of breast cancer patients with the most dominant subtype at MRCCC Siloam Semanggi Hospital who performed IHC was Luminal B with negative HER2 with a frequency of 67 patients (32.2%). The second highest frequency was Luminal B with positive HER2 (19.7%) with a slight difference with HER2 enriched (19.7%) and the least frequency subtypes were Luminal A and Basal-like with a slight difference of 12.5% and 12%, respectively. These results are following Amiria (2017) research. The most dominant frequency obtained is Luminal B (30.55%), but it is not explained whether HER2 is positive or negative. Wiguna obtained different results at Sanglah General Hospital. The highest frequency was Luminal A and basal-like with 37.4%, respectively [11]. Different results were also obtained by Setyawati et al. (2018). The dominant frequency was found in Luminal A (41.3%) [36].

Table 6. Distribution of subtype characteristics of breast cancer patients by age and subtype

Age	Luminal A	Luminal B HER2 -	Luminal B HER2 +	HER2 *enriched*	*Basal-like*
20-29 years	0	0	1	1	4
30-39 years	1	6	6	1	5
40-49 years	10	17	17	9	5
50-59 years	3	**26**	18	19	5
60-69 years	6	15	5	10	4
≥70 years	6	3	2	1	2
Total	26	67	49	41	25

As described in the table above, the patient age distribution is dominated by patients aged 50-59. And in table IV.4. The distribution of subtypes of breast cancer patients who are predominantly Luminal B with HER2 -. When connected, it turns out that the highest frequency was found at the age of 50-59 years with Luminal B HER2 - as many as 26 patients. This result is different from Wiguna's research at Sanglah General Hospital, where the dominant results obtained were at the age of 40-49 years with a basal-like subtype of 26 patients [11]. Age as a risk factor in breast cancer can be associated with two processes that occur in the elderly: progressive DNA damage and decreased immunity to tumour growth. Deactivation of tumour suppressor genes can occur due to damage to DNA due to cellular ageing of cells and apoptosis of specific genes [37]. Overgrowth of hormone receptors is associated with mutations in PIK3CA. PIK3CA, which is part of

BRCA2, gives rise to positive ER hormone receptors [38].

Table 7. Distribution of the characteristics of the subtypes of breast cancer patients based on pathological diagnosis

Pathology Diagnosis	Luminal A	Luminal B HER2 -	Luminal B HER2 +	HER2 *enriched*	*Basal-like*
NST I breast carcinoma	2	2	0	0	0
NST II breast carcinoma	13	**27**	23	11	5
NST III breast carcinoma	1	20	18	21	19
Non-NST breast carcinoma	8	11	5	3	0
Mixed breast carcinoma	1	2	2	1	1
Breast carcinoma not available	1	5	1	5	0
Total	26	67	49	41	25

NST, *No Special Type*.

The table above shows that the most dominant pathology grade at MRCCC Siloam Semanggi Hospital is in grade NST II and NST III. The most common subtypes in NST II were Luminal B with HER2 negative and Luminal B with HER2 positive. Meanwhile, in NST III, the most common subtype is Luminal HER2 enriched. Different results were obtained by Wiguna (2013) at Sanglah General Hospital, where the most dominant results were seen in grade II breast cancer patients with subtype Luminal A [11]. In theory, grade I cells where the cells are less aggressive have a better prognosis and hormone receptors found to be ER-positive. Grade II has a prognosis between grade I and III. With highly active and more aggressive cell mitosis, Grade III has a worse prognosis and usually presents with the triple-negative subtype (ER-, PR-, HER2-) [26].

CONCLUSION

Based on the objectives and results of the study, conclusions can be drawn: a) The largest age group diagnosed with breast carcinoma underwent an IHC examination was 50-59 years old; b) The gender of breast cancer patients is dominated by female; c) The most common pathological diagnoses are breast carcinoma NST II and III, and d) Subtype dominated by Luminal B with negative HER2 at age 50-59 years. Thus, it can be suggested that the examination data by practitioners of anatomic pathology should be uniformed from all over Indonesia so that the next researcher can research with more complete data.

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