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CLINICOPATHOLOGICAL PROFILE OF HER2 POSITIVE (NON-LUMINAL) BREAST CANCER SUBTYPE AT HAJI ADAM MALIK GENERAL HOSPITAL FROM 2020-2021

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ABSTRACT

Background: Breast cancer is one of the cancers with the highest prevalence in Indonesia. According to 2020 GLOBOCAN data, the number of new breast cancer cases reached 68,858 (16.6%) cases out of a total of 396,914 new cancer cases in Indonesia. There are numerous factors that can trigger the occurence cancer with different clinical manifestations and subtypes, therefore we are interested in researching the profile of breast cancer patients with the HER2 subtype at H. Adam Malik General Hospital in 2020-2021. **Objective:** In the present study, we aim to determine the clinicopathological profile of HER2 positive (non-luminal) breast cancer subtype patients at Haji Adam Malik General Hospital from 2020-2021. **Methods:** The method used in this study is descriptive quantitative with total sampling technique. The data samples was obtained from medical records of breast cancer patient with HER2 positive (non-luminal) subtype which was then sorted according to the availability of characteristic needed for this study. **Results:** All breast cancer patients with HER2 positive (non-luminal) subtype at H. Adam Malik General Hospital in 2020-2021 (with majority aged >50) are married. More than half (68,7%) subjects has normal BMI weight while no previous history of family cancer diagnosis has been found. Most (52,9%) of the tumour size found in this study is >5cm with 54,9% of the tumour having metastasized to 1-3 lymph nodes and 39,2% having distant metastases. Majority (35,3%) of histopathological degree is in grade 1 and grade 3 , the histopathological classification of the majority (86,3%) was IDC type. **Conclusion:** Overall, diversity of frequencies within the observed clinicopathological characteristics is found.

Keywords: Breast Cancer, HER2 Positive, Non-Luminal, pathological profile

INTRODUCTION

Breast cancer is one of the most common types of cancer in Indonesia. It ranks first amongst other cancer with relative frequency of 16.7%. It is estimated that the incidence rate in Indonesia is 42.1 out of 100,000 women, with a fairly high mortality of 17 out of 100,000 in individuals. The highest prevalence of cancer occurence is found in the province of DI Yogyakarta which counts for 4.86 per 1000 individuals, followed by West Sumatra 2.4779 per 1000 Individuals and Gorontalo 2.44 per 1000 individual. This disease can also affect men with prevalence of 1%. In Indonesia, more than 80% of the cases are found to be at advanced stage, where treatment choices are limited.[1] Breast cancer is the malignancy of breast tissue which originated from the ductal or lobule epithelium. In general, there are several risk factors believed to promote the occurence of breast cancer, including: age, breast cancer gene 1 and 2 (BRCA1 and BRCA2), gene mutation, family history, exposure to radiation, nulliparity, endogenous disregulation of oestrogen, hormonal therapy, obesity and alcohol consumption, etc.[2] Although cases of breast cancer in Indonesia are rising day by day, and are amongst the highest cancer cases, many examinations and inspection are not always followed by a complete set of clinical and histopathological staging due to issues regarding highly-priced examination bills and strict requirements imposed by finance companies such as private insurance companies or government-owned health insurance organizations. Other reasons include patient's apprehensiveness to avoid health screening and low level of education. Clinical and histopathological staging are required by health providers to determine the diagnosis along with further enhancing accuracy of patient's treatment management. Information about the staging of the cancer suffered by patient as well as description of cancer histopathological type is also an important indicator in predicting the prognosis and progression of breast cancer. To this date, while there are several methods used to diagnose breast cancer, the gold standard is through histopathological examination which can determine the type of breast cancer with a biopsy procedure. Biopsy results can be used for the

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diagnosis of breast cancer and determining the success of the given therapies.[3] Apart from histopathological examination, there is another classification system based on immunohistochemistry test in which the examination procedure uses antibodies as probes to detect antigens in tissue sections or other forms of cell preparations. Through immunohistochemistry examination, the subtype of breast cancer can be identified. IHC plays a role in helping to predict systemic therapy response and prognosis. Common immunohistochemistry tests for breast cancer are: hormonal receptors count, namely estrogen receptor (ER) and progesterone receptor (PR), Human Epidermal Growth Factor 2 (HER2) count, and Ki-67 expression.[4] Breast cancer management and prognosis are influenced by several variables, such as: grading, staging, estrogen receptor (ER) status, progesterone receptor (PR) & over-expression of HER2/neu. Cancers with over-expression of hormone receptors tend to have a better prognosis. HER2+ breast cancer cells are generally believed to act more aggressively than HER2- breast cancer cells, and consequently, have poorer prognosis and greater tendency to metastasize or reoccurence after treatment.[5]

To this day, there have been a lot of researches done to uncover more possibilities to increase the accuracy of diagnosis, prognosis and treatment. However, there are still limited number of researches exploring HER2 non-luminal subtype due to the rarity of the cases which is believed only account for 10-15% of total breast cancer cases. [5] For the reason mentioned above, the objective of this study was to determine the clinicohistopathological profile of HER2 positive (non-luminal) breast cancer subtype in Haji Adam Malik General Hospital from year 2020-2021, in hope that this study could provide a general understanding of the aforementioned breast cancer subtype.

METHODS

This study uses a descriptive-quantitative research method. Sampling technique used in this study is the 'total sampling technique'. Sample data was acquired from the medical records of respondents. The number of respondents in this study are 51 respondents which is the entirety of patients with HER2 positive (non-luminal) breast cancer subtype at Haji Adam Malik General Hospital Medan in 2020-2021. All respondents are sorted based on the inclusion and exclusion criteria. The inclusion criteria for this study are: breast cancer patients with HER2 positive (non-luminal) subtype at Haji Adam Malik General Hospital in Medan in 2020-2021 who are willing to become research subjects, having evidence of immunohistochemistry test done, and having evidence of required characteristics (age, marital status, body mass index, family cancer history, primary tumor size, regional lymph nodes metastasis, distant metastasis, histopathological grading, and histopathological classification) available on the medical record. The exclusion criteria included patients with incomplete personal data, incomplete information of required characteristics (age, marital status, body mass index, family cancer history, primary tumor size, regional lymph nodes metastasis, distant metastasis, histopathological grading, and histopathological classification), illegible or ambiguous test results presented in medical records. Variables used in this study include age, marital status, body mass index, family cancer history, primary tumor size, regional lymph nodes metastasis, distant metastasis, histopathological grading, and histopathological classification. This research is conducted by calculating the distribution of frequency with statistical software applications to avoid human error in the data processing.

RESULTS

Characteristics were obtained from 51 respondents, who fulfill the inclusion criteria. From the sum of 51 respondents, 31 respondents data is taken from 2020 and the other 20 respondents data is taken from 2021.

Table 1. HER2 Positive (Non-Luminal) 2020-2021 Characteristics

Characteristics		Frequency n(%)
Year	2020	31(60,8)
	2021	20(39,2)
Age	<30 Years Old	1(2)
	30-40 Years Old	8(15,7)
	40-50 Years Old	19(37,3)
	>50 Years Old	23(45,1)
Marital Status	Married	51(100)
	Not Married	0(0)
Body Mass Index	Underweight	1(2)
	Normal	35(68,6)
	Overweight	5(9,8)
	Obese	10(19,6)

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Family History	No Family History	51(100)
	Evidence Of Family History	0(0)
Tumor Size	<2 CM	6(11,8)
	2-5 CM	18(35,3)
	>5 CM	27(52,9)
Regional Lymph Node Metastasis	No Lymph Node Metastasis	6(11,8)
	1-3 Nodes Metastasis	28(54,9)
	4-9 Nodes Metastasis	14(27,5)
	>10 Nodes Metastasis	3(5,9)
Distant Metastasis	Metastasis	20(39,2)
	No Metastasis	31(60,8)
Histopathological Grading	Grade 1	18(35,3)
	Grade 2	15(29,3)
	Grade 3	18(35,3)
Histopathological Grading	Invasive Ductal Carcinoma	44(86,3)
	Invasive Lobular Carcinoma	7(13,7)
Total		51(100)

Based on table 1, it can be seen that the majority of patients with HER2 breast cancer subtype at H. Adam Malik General Hospital in Medan are over 40 years old which accounts for 81,4% of the total respondents. Whereas only one patient (2%) is found under the age of 30 years. The frequency distribution between the age group 40-50 years and the group >50 years has a difference of 7.8 percent which may seem inconsequential but is quite significant if this pattern is applied to a larger population scale. All of the samples that fulfil the inclusion criteria are married and have families. Regarding the body mass index of breast cancer patients, it was found that the majority of patients have a normal body mass index which accounts for 68.6% of respondents and obesity in 19.6% respondents, followed by overweight BMI which accounts for 19,6% respondents. Only one respondents with underweight BMI. all of the samples in breast cancer cases with the HER2+/ER-,PR- subtype claimed to have no previous family history of ever diagnosed with cancer. most tumors were found in the size range greater than 5 cm which accounts for 52.9% of respondents, followed by tumors measuring 2-5 cm which accounts for 35,3% respondents (11,8%) measuring around <2 cm. Most of the patients has 1-3 nodes metastases which accounts for 54.9% of the respondents, follow by metastasis to 4-9 nodes around 27,5% of respondents, and 5,9% respondents with >10 nodes metastasis. Only six respondents (11,8%), has no regional lymph nodes metastasis. Distant metastatic HER2 breast cancer was found in 39.2% of the total sample. majority of patients have histopathological grades of grade 1 and 3, as much as 35.3% each, follow by grade 2 which accounts for 29,3% of the remaining respondents.

classified as Invasive Ductal Carcinoma, the remaining 13,7 got classified as Invasive Ductal Carcinoma.

Metastasis, Primary Tumor Size, Histopathological Grading,

Characteristics	Frequency n(%), n=51 Lymph Nodes Metastasis (Nodes)			
	0	1-3	4-10	>10
Primary Tumor Size (cm)				
<2	3(5,8)	2 (3,9)	1 (1,9)	0(0)
2-5	0 (0)	14 (27,4)	3(5,8)	1 (1,9)
>5	3(5,8)	12(23,5)	10(19,8)	2 (3,9)
Histopathological Grading (Grade)				
1	5 (9,8)	11 (21,5)	2 (3,9)	0 (0)
2	1 (1,9)	7 (13,7)	7 (13,7)	0 (0)
3	0 (0)	10 (19,6)	5 (9,8)	3 (5,8)
Distant Metastasis				
Metastasis	1 (1,9)	6 (11,7)	10 (19,6)	3 (5,8)
No Metastasis	5 (9,8)	22 (43,1)	4 (7,8)	0 (0)

Based on table 2, tumor size less than 2 cm had not metastasized more than 10 nodes. In tumor sizes of more than 2 cm, only 3 samples did not metastasize to any nodes. Most tumor with the size of 2-5 cm metastasize to 1-3 nodes. tumors >5 cm in size are the most likely to metastasize to more than 3 nodes. It can be observed that the majority of respondents with no lymph node metastases mostly have grade 1 histopathological grade and only one respondent with no lymph nodes metastasis show the appearance of grade 2 histological grade. In patients with metastases to 1-3 regional lymph nodes, 39% are shown to be grade 1, the others 35% are shown to be grade 2 and 35% others are found in grade 3. In patients with 3-9 nodes metastases 14% were found in grade 1, 50% were found in grade 2 and 35% were found in grade 3. In patients with metastases > 10 nodes, 100% showed grade 3 appearance. Only 1 sample had distant metastases in the sample group that did not have nodes metastases, 21% of sample group with 1-3 nodes metastases found distant metastases in the examination. In the sample group with metastases to

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4-9 nodes, 71% had aquired distant metastases and distant metastasis appeared in all samples with >10 lymph nodes metastasis.

Table 3. HER2 Breast Cancer Cross Tabulation Of Distant Metastasis, Tumor size and Histopathological grading.

Characteristics	Frequency n(%), n=51	
	Distant Metastasis	
	Metastasis	No Metastasis
Primary Tumor Size (Cm)		
<2	0 (0)	6 (11,7)
2-5	5 (9,8)	13 (25,4)
>5	15 (29,4)	12 (45)
Histopathological Grading (Grade)		
1	4 (7,8)	14 (27,4)
2	7 (13,7)	8 (15,6)
3	9 (17,6)	9 (17,6)

Based on table 3, it can be observed that there are no metastases in tumors with a size of <2 cm, the majority of respondents with tumor sizes of 2-5 cm do not experience metastases, only 27% of the total patients with a size of 2-5 cm have metastases. Meanwhile, of the total respondents with tumor size > 5 cm, 55.6% had distant metastases. respondents with grade 1 cancer have the smallest percentage of distant metastases where only 22.2% have distant metastases. In grade 2 hitological grade, the percentages increases to 46% and in grade 3 the percentages of distant metastases rise to 50% of the respondents.

Table 4. HER2 Breast Cancer Cross Tabulation Of Tumor size and Hostopathological grading

Characteristics	Frequency n(%), n=51		
	Histopathological Grading (grade)		
	1	2	3
primary tumor size (cm)			
<2	3 (5,8)	2 (3,9)	1 (1,9)
2-5	7 (13,7)	4 (7,8)	7 (13,7)
>5	8 (15,6)	9 (17,6)	10 (19,8)

Based on table 4, it was found that tumors with a size < 2cm were most commonly identified with grade 1, tumors with a size of 2-5 cm were equally dominated by grades 1 and 3, while tumors with size > 5 cm were most commonly found with grade 3.

DISCUSSION

Majority of patients with HER2 breast cancer subtype at H. Adam Malik General Hospital in Medan are over 40 years old which accounts for 81,4% of the total respondents. According to research conducted at RSUP dr. Kariadi in Semarang in 2016 found that the incidence of breast cancer was found 5 times more in women aged over 40 years than women under 40 years.[6] This is in accordance with the results obtained. This conclusion was also corroborated by a survey conducted in America where the samples taken were women from various ethnicities and different races, also showing an almost identical pattern where 78% of cancer cases occurred over the age of 40.[5]

The older you get, the more individuals are exposed to cancer-triggering factors and carcinogenic substances directly that trigger the cancer itself.[7]

Marital status indirectly affects the risk factors for breast cancer. Nulliparity is believed to increase the risk of cancer because after marriage and during the pregnancy phase, women will not experience menstruation which reduces hormone exposure. Likewise, breastfeeding helps the final differentiation of breast cells so they are more resistant to stress.[8] Through research conducted by Meng *et al*, marital status is also doubtful to be a risk factor because through several studies, no significant correlation was found.[9] Because in this study, the conclusions were strongly influenced by the suboptimal quality of research controls, the lack of exploratory data collection in marriage samples, and also the lack of clear evidence due to the difficulty of monitoring over a long period of time which led to less optimal quality of research results.

Regarding the body mass index of breast cancer patients, it was found that the majority of patients had a normal body mass index. This study is in line with the results obtained from Dr. Moewardi Jakarta General Hospital from the 2018 period, where patients with normal BMI accounted for 60% of the total sample.[10] However, the results of this study are contradictory with a study conducted by Kang *et al* which showed that women with overweight or obese BMI status tend to have greater risk factors for developing breast cancer.[11] This is because in normal women, the ovaries are the main place that produces the hormone estrogen, but in postmenopausal women, fat tissue is a source of estrogen which is biosynthesized by the aromatase enzyme so that excess fat tissue will produce more hormones. In addition, overweight and obesity conditions increase the risk of changes in cytokines that cause inflammation and changes in growth factor properties

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such as insulin resistance properties.[10] This difference may be due to the fact that patients tend to be late in detecting cancer, so height and weight checks are carried out when patients come to the hospital after weight loss due to cancer.

All of the samples in breast cancer cases with the HER2+/ER-,PR- subtype claimed to have no previous family history. This data is in line with data obtained through research by Lei *et al* at the Tianjin Hospital which found that out of 10,549 breast cancer patients, more than 70% of sufferers claimed to have no family history of breast cancer or other cancers.[12] However, this is different from a study conducted at the Abdoel Moeloek General Hospital for the 2020 period which found that out of 77 breast cancer patients, more than 60% had a family history. Genetics play a role in the incidence of cancer, where people with genetic mutations in certain genes, especially mutations in the proto-oncogenes and BRCA genes, have a high risk of developing breast cancer, but many other risk factors also have great potential for cancer, such as history of radiation exposure and others.[13] This difference is very likely caused by the lack of cancer detection where the incidence of cancer is not detected in the patient's family, the lack of adequate medical facility services in remote areas, patient subjectivity and lifestyle as well as other factors that influence the incidence of breast cancer.

Most tumors were found in the size range greater than 5 cm at 52.9%,The results are in line with research conducted at Hasan Sadikin General Hospital, where it was found that the most common tumor size is a tumor with a size of > 5 cm.[14] HER2 expression is usually associated with more aggressive immunophenotypes and manifestations with more gland involvement and faster growth than other types of breast cancer.[15] Breast cancer with the HER2+/HR- subtype also shows clinical manifestations and symptoms of faster metastases even though the primary tumor size is not large.[16]

It is found through the research that most patients experience metastases in 1-3 nodes as much as 54.9% of patients. This data is supported by the research of Anaid *et al* in which the study found that the most of cancer metastasizes to 1-3 lymph nodes.[17] The result is also in accordance with a study conducted by Ivan *et al* which found of 49 breast cancer patients, 61.2% were found to have metastasized to 1-3 regional lymph nodes.[18] Characteristics of HER2 breast cancer has a prevalence of more aggressive spread than the luminal subtype and one of the main initial sites of spread is regional lymph nodes. This difference can occur due to differences in study locations and differences in the status of other indicators such as Ki-67 where Ki-67 itself is associated with positivity from the lymph nodes.[19]

The number of patients with distant metastatic breast cancer was 39.2% of the total sample. These data are not much different from a study conducted by Melya *et al* where they found that a third of breast cancer patients who came had distant metastases.[20] Similar data was also obtained from a study conducted by Jinliang *et al* where they found that out of a total of 127 positive HER2 breast cancer patients, 27% had distant metastases.[21] The most common locations for metastases to occur are bone, brain, lung and liver and based on the pattern of metastases, breast cancer of the HER2+/HR- subtype tends to metastasize to the liver and brain while breast cancer of the HER2+/HR+ subtype tends to metastasize to the bone.[22]

The majority of patients had histopathological grades 3 and 1 as much as 35.3% of the total sample. In a study conducted by Wang *et al* using samples of breast cancer patients who experienced metastases, it was found that 48% had grade 3 histopathological degrees due to a positive correlation between histopathological grading and cancer cell aggressiveness.[23] High histopathological grading is usually associated with active dividing properties, a worse prognosis and is associated with over-activation of the HER2/neu receptor.[18]

The histopathological classification of majority breast cancer respondents are IDC types with a percentages reaching 86.3% of the total samples. This data is supported by research conducted by Suhyun *et al*.[24] where it was found that of the 323 breast cancer patients who were sampled, 88% had an Invasive ductal carcinoma classification, not otherwise specified. This is also in line with research conducted at Mt. Sinai Medical Center in New York which confirmed IDC as the most common (59,8%) type suffered by breast cancer patients worldwide.[18]

CONCLUSION

Breast cancer patients with the subtype HER2+/ER-PR- are most commonly found in the age

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group >50 years. Based on marital status, breast cancer patients with subtype HER2+/ER-PR- were all found to be married. Most of breast cancer patients with subtype HER2+/ER-PR- are found with a normal body mass index during physical examination. according on family history, none of the HER2+/ER-PR- subtype breast cancer patients in this study had a family history of cancer. Based on tumor size, breast cancer patients with subtype HER2+/ER-PR- in this study had the majority of tumor sizes >5 cm. Metastases to 1-3 lymph nodes is happening to majority of the subtype HER2+/ER-PR- breast cancer patients. Only 39.3% of the total respondents with subtype HER2+/ER-PR- were found to have distant metastases. Based on histopathological grade, the majority of breast cancer patients with subtype HER2+/ER-PR- have tumors with histopathological grades of grade 1 and 3. Based on histopathological classification, the majority of HER2+/ER-PR- subtype breast cancer patients have tumors classified as Invasive Ductal Carcinoma.

ETHICAL APPROVAL

This study has obeyed procedures and ethics from The Health Research Ethics Committee of Sumatera Utara University. The ethical clearance certificate issued by the committee is No. 827/KEPK/USU/2022.

CONFLICT OF INTEREST

The authors declare no conflict of interests whatsoever related to this study.

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