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Relationship of Histopathological Grading and Age of HER2-type Breast Cancer Patients at Adam Malik Hospital in January 2022 – June 2024

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ABSTRACT

Background: Breast cancer is one of the most common cancers that can cause death in Indonesia. Histopathological examination are required to assess tumor activity and prognosis. Other examination includes immunohistochemistry of biomarkers such as estrogen (ER), progesterone (PR), and HER2 receptors. HER2-type breast cancer tends to be more invasive with a poor prognosis and susceptible to recurrence and metastasis. **Objectives:** This study aims to determine the relationship between histopathological grading and age of patients with HER2-type breast cancer. **Methods:** This is an analytical research with cross-sectional approach using the total sampling technique. Secondary data were taken from medical records of breast cancer inpatients at Adam Malik Hospital (January 2022 - June 2024) and analysed using Fisher's exact test. The study sample included 54 patients with fulfilled inclusion criteria. **Results:** HER2-type breast cancer identified was 31,3%. The most frequent characteristics included female, age ≥45 years, obese nutritional status, and no family history. Poorly differentiated tumors were the most common (38,9%). Result of Fisher's exact test showed p=0,044 (p<0,05) and OR=0,134. **Conclusion:** There is a relationship between histopathological grading and age of patients with HER2-type breast cancer.
Keyword: breast cancer, HER2, histopathological grading, immunochemistry, molecular subtypes

ABSTRAK

Pendahuluan: Kanker payudara merupakan salah satu jenis kanker yang dapat menyebabkan kematian dan paling sering terjadi di Indonesia. Pemeriksaan histopatologi perlu dilakukan untuk menilai aktivitas tumor dan prognosis. Pemeriksaan lainnya meliputi pemeriksaan imunohistokimia terhadap biomarker seperti reseptor estrogen (ER), progesteron (PR), dan HER2. Kanker payudara tipe HER2 cenderung lebih invasif dengan prognosis yang buruk dan rentan terhadap kekambuhan serta metastasis. **Tujuan:** Penelitian ini bertujuan untuk mengetahui hubungan antara *grading* histopatologi dengan usia penderita kanker payudara tipe HER2. **Metode:** Penelitian ini berjenis analitik non-eksperimental dengan pendekatan cross-sectional yang menggunakan teknik total sampling. Data sekunder diambil dari rekam medis pasien rawat inap kanker payudara di RS. Adam Malik (Januari 2022 – Juni 2024) dan dianalisis menggunakan uji Fisher's exact. Sampel penelitian ini mencakup 54 pasien yang telah memenuhi kriteria inklusi. **Hasil:** Kasus kanker payudara yang teridentifikasi tipe HER2 didapati sebesar 31,3%. Karakteristik yang lebih banyak dijumpai meliputi perempuan, usia ≥45 tahun, status gizi mengalami obesitas, dan tanpa riwayat keluarga. Tumor dengan diferensiasi buruk menjadi derajat yang paling banyak ditemukan (38,9%). Hasil uji *Fisher's exact* menunjukkan nilai p=0,044 (p<0,05) dan OR=0,134.

Kesimpulan: Terdapat hubungan antara *grading* histopatologi dengan usia penderita kanker payudara tipe HER2.
Kata Kunci: *grading* histopatologi, HER2, imunohistokimia, kanker payudara, subtipe molekuler

1. Introduction

Breast cancer is a malignancy that occurs when abnormal breast cells grow uncontrollably and form tumors. In 2022, the number of breast cancer cases reached 2.3 million and it was recorded that breast cancer is the most common cancer in women, occurring in 157 (out of 185) countries in the world with 670,000 deaths [1]. Meanwhile, in Indonesia, new cases of breast cancer reached 66,271 (30.1%) out of a total of 220,266 new cases of cancer in women with a death rate of 22,598 cases in 2022[2]. This counts breast cancer as the most common cancer with 3rd most mortality in Indonesia.

Histopathological examination is a gold-standard procedure to help confirm the diagnosis of cancer. Breast cancer cells, based on their similarity to normal cells, are be classified into three different grades. According to the Nottingham Histological Grade (NHG) criteria, based on its histopathological features, breast cancer is divided into grade 1, grade 2, and grade 3. This division is based on glandular formation, nucleus pleomorphism, and mitotic activity of the growing abnormal cells. Histopathological grading of breast cancer can be used to assess tumor activity and prognosis of invasive breast cancer[4]. Based on immunohistochemistry examination of the expression of certain biomarkers, such as estrogen (ER) and progesterone hormone receptor (PR), HER2, and Ki-67, breast cancer is molecularly divided into three subtypes: luminal-like, human epidermal growth factor receptor 2 (HER2) positive, and basal-like (triple negative)[5]. HER2-type breast cancer is a molecular subtype that is invasive, and prone to recurrence and metastasis with a poor prognosis[6]. Excessive activation of HER2 can cause cancer cell proliferation to increase and lead to a higher degree of cancer cell malignancy[7]. HER2-positive breast cancer has a higher rate of cell proliferation, tends to have lymph node metastasis, and is resistant to chemotherapy hence its characteristics are more aggressive compared to HER2-negative. HER2-positive breast cancers with metastasis tend to show worse outcomes. Depending on the grade, tumor biology, and initial treatment given to the patient, up to 25% of early-stage breast cancer patients with overexpression of the HER2 biomarker will experience recurrence within the next ten years[8].

At older ages, breast cancer shows a more severe stage. Age is related to hormone receptor and HER2 status, where positive hormone receptor expression is found to decrease while HER2 expression will increase in old age[9]. The age factor in HER2-type breast cancer is associated with increased breast cancer-specific mortality (BCSM), where the risk of death will increase gradually with age and is found to be lower at the age of <40 years[10]. Therefore, this study aims to determine the relationship between histopathological grading and the age of HER2-type breast cancer patients at Adam Malik Hospital from January 2022 - June 2024.

2. Method

This study is an observational analytical research design with a cross-sectional approach where both variables were collected simultaneously through medical record data. The research started from March to November 2024 and was conducted at Adam Malik Hospital in Medan, North Sumatra, Indonesia.

The study sample included hospitalized patients diagnosed with breast cancer with HER2-type at Adam Malik Hospital from January 2022 - June 2024. Sampling was done using a total sampling technique where all patients who fulfilled certain criteria would be taken as research samples. Inclusion criteria included patients with a complete data of both immunohistochemistry examination (against estrogen receptors (ER), progesterone (PR), and HER2) and histopathological grading. Of the 492 inpatients with a diagnosis of breast cancer in January 2022 - June 2024 at Adam Malik Hospital, 195 patients had an immunohistochemistry examination. A total of 61 patients were identified as HER2-type, but only 54 patients were taken as research samples as the histopathological grading data of the remaining patients were unidentified.

Both variables are categorical data, where the histopathological grading variable is classified into grade 1 (well differentiated tumor) and grade 2 and 3 (moderately to poorly differentiated tumor). The age of HER2-type breast cancer patients variable is classified based on the reproductive age limit for female, namely <45 years and ≥45 years. Descriptive analysis to determine the occurrence rate, patient characteristics, and

histopathological grading in HER2-type breast cancer was performed using univariate analysis through frequency distribution tables. To determine the relationship between histopathological grading and age of HER2-type breast cancer patients, statistical test was performed using Fisher's exact test as a non-parametric analysis with the help of SPSS software. This method was selected because the chi-square test, which was initially intended as the primary analysis, was identified to be unsuitable as the expected count value of <5 was found to be >20%.

This study has received approval from the ethics committee of health research at Universitas Sumatera Utara by ethical clearance No. 741/KEPK/USU/2024. During the process of conducting the study, patients' data written in medical records remained confidential and data processing was only carried out on those related to this study.

3. Results

Table 1. Molecular Subtype and Characteristics of HER2-Type Breast Cancer Patients

	Amount (n)	%
Molecular Subtype		
Luminal A	33	16.9
Luminal B	87	44.6
HER2	61	31.3
TNBC	14	7.2
Characteristics of HER2-Type Breast Cancer Patients		
Sex		
Female	54	100
Male	0	0
Age		
<45 years	12	22.2
≥45 years	42	77.8
Nutritional Status (BMI; kg/m²)		
Underweight (<18,5)	0	0
Normal (18,5 – 22,9)	7	13.0
Overweight (23 – 24,9)	5	9.3
Obesity (≥25)	14	25.9
Unidentified	28	51.9
Family History		
No family history	40	74.1
Unclear	4	7.4
Unidentified	10	18.5
Histopathological Grading		
Well-differentiated tumor (grade 1)	18	33.3
Moderately differentiated tumor (grade 2)	15	27.8
Poorly differentiated tumor (grade 3)	21	38.9

Out of 195 breast cancer cases that underwent immunohistochemistry examination at Adam Malik Hospital in the period January 2022 - June 2024, 61 patients were found to have HER2-type breast cancer (31.3%). In addition, the most common molecular subtype of breast cancer found was luminal B with 87 patients (44.6%) and the least was triple negative (TNBC) with 14 patients (7.2%).

Patient characteristics identified in this study include gender, age, nutritional status based on body mass index, and family history. Out of 54 HER2-type breast cancer samples, all of them were found to be female (100%). In terms of age, 42 patients were ≥45 years old (77.8%) and the remaining 12 patients were <45 years old (22.2%). Based on the nutritional status of the patients, patients with obesity were found to be more than others, namely 14 patients (25.9%). Meanwhile, the nutritional status that was not found in the sample was underweight (0%). Unfortunately, there were 28 patients with unidentified nutritional status data in the medical record (51.9%). In terms of family history, 40 patients were identified with no family history (74.1%) and 4 patients with unclear family history (7.4%). It was also found that out of the 54 HER2-type breast cancer

samples taken, the most common histopathological grading was grade 3 (38.9%). Meanwhile, the least histopathological grading found was grade 2 (27.8%).

Table 4. Cross-tabulation of Histopathological Grading with Age of HER2-type Breast Cancer Patients

		Age of HER2-type Breast Cancer Patients				Total		P*	OR
		<45 years		≥45 years					
		n	%	n	%	n	%		
Histopathological Grading	1	1	1.9	17	31.5	18	33.3	0.044	0.134
	2 & 3	11	20.4	25	46.3	36	66.7		
	Total	**12**	**22.2**	**42**	**77.8**	**54**	**100**		

***Fisher's exact test**

In terms of histopathological grading, of the 54 patients, there were 18 patients with grade 1 (well differentiated tumor) (33.3%) and 36 patients with grade 2 and 3 (moderately to poorly differentiated tumor) (66.7%). Meanwhile, when viewed by the patient's age group, of the 12 patients aged <45 years, there was 1 patient with grade 1 (1.9%) and 11 patients with grade 2 and 3 (20.4%). Of the 42 patients aged ≥45 years, 17 patients had grade 1 (31.5%) and the remaining 25 patients had grade 2 and 3 (46.3%).

Fisher's exact test showed a p-value of 0.044 (2-sided) which interprets that there is a significant relationship between histopathological grading and age of HER2-type breast cancer patients ($p<0.05$). The odds ratio (OR) value of 0.134 in the table showed that HER2-type breast cancer patients aged <45 years old are less likely to show a higher histopathological grading (OR<1).

4. Discussion

In this study, it was found that the total number of breast cancer cases that underwent immunohistochemistry examination at Adam Malik Hospital from January 2022 - June 2024 reached 195 cases. The occurrence rate for HER2-type breast cancer itself reached 61 cases (31.3%). The results of this study have increased from the previous study, where the total cases of breast cancer with performed immunohistochemistry examination at Adam Malik Hospital in 2016 - 2018 were found to be 131 cases, with 31 of them (23.7%) being HER2-type breast cancer[11].

Based on gender as a patient's characteristics, this study found that all HER2-type breast cancer patients were female (100%). This result is not significantly different from previous research at Ibnu Sina Hospital Makassar in 2018 - 2019 where breast cancer with female gender was found more (98%) than male (2%)[12]. This happens because women have higher estrogen hormone stimulation compared to men[13].

In terms of age, the number of patients with ≥45 years of age was found the most (77.8%). The results of this study are in accordance with previous research in the Netherlands which explained that breast cancer patients with negative hormone receptors and HER2-positive were dominated by the age range of 50 - 59 years (36%)[14]. These results are also similar with previous research in China that found more percentage of HER2-type breast cancer with >45 years of age (59.26%)[15].

According to body mass index (BMI) and interpretation of nutritional status, the nutritional status that was found to be more was obesity with BMI ≥25 kg/m2 (25.9%). This is in accordance with previous research in Louisiana which explained that of 115 patients with HER2-type breast cancer, 31 patients were found to be overweight (27%) and 57 patients were obese (49.5%)[16]. This event is associated with higher estrogen levels in obese women, caused by peripheral aromatization of adipose tissue and increased conversion rate of androgenic precursors to estrogen[17].

Based on family history, patients without family history were found to be more common (74.1%). Previous research in the United Kingdom explained that HER2-positive breast cancer patients who did not have a family history showed a low possibility of finding hereditary gene mutations such as BRCA1, BRCA2, or TP53[18]. In addition, another study in Makassar also stated that there was no association between family history and the expression of ER, PR, and HER2[19].

In this study, HER2-type breast cancer patients with histopathological grade 3 were found to be the most (38.9%), which indicates that the tumor has poor differentiation. Meanwhile, HER2-type breast cancer patients with grade 1 were found to be 33.3% and grade 2 were found to be 27.8%. The results of this study are slightly different from previous research at Adam Malik Hospital regarding breast cancer cases in 2016 - 2018, where HER2 molecular subtypes were found to be more frequent with grade 2[11]. However, another study at Cipto Mangunkusumo Hospital stated that breast cancer with HER2 was more common in grade 3[20]. The results of this study are in accordance with the theory of HER2 which generally has a high proliferation with a high histopathological grade. Nevertheless, the finding of grade 1 (well differentiated tumor) in this study is thought to be related to the possibility of a response to therapy. This is supported by the theory that HER2-positive tumors will respond to trastuzumab targeted therapy and anthracycline-based chemotherapy, resulting in improved prognosis[21].

Statistical analysis test revealed that there was a significant relationship between histopathological grading and age of HER2-type breast cancer patients, with a p-value of 0.044 ($p<0.05$). This is in accordance with previous research at Adam Malik Hospital which explained that there was a relationship between histopathological grading and molecular subtypes of breast cancer[22].

This study found that women who were still in reproductive age (<45 years) is less likely to have moderately to poorly differentiated tumor. This contrasts with a previous study at Dr Kariadi Hospital which explained that histopathological grade with moderately differentiated tumors (grade 2) was more common in patients aged <40 years[22]. A poorer prognosis at a young age may be due to multifactorial factors, one of which is the uniqueness of tumor biology and genomic mutation profile[23].

However, the results of this study are supported by research at Bethesda Hospital Yogyakarta which stated that there was an association between molecular subtypes and age, where breast cancer patients with negative hormonal receptors were associated with patients aged >50 years[24]. In addition, a previous study in Makassar found that there was a correlation between age and the expression of ER, PR, and HER2[19]. Other than that, a study in Sarawak General Hospital Malaysia also explained that patients with HER2-type breast cancer were predominantly in the age range of 45 - 55 years (35.1%) with moderately (46.5%) and poorly (49.6%) differentiated tumor[25]. Previous research in Yogyakarta also found that tumor differentiation in patients aged ≥40 years was worse than in patients aged <40 years[26].

In relation, the results of this study found that HER2-type breast cancer patients who were older and had entered menopausal age (≥45 years old) tend to have more severe histopathological grade with poorly to moderately differentiated tumors (grade 2 and 3). This is thought to happen due to the aging process that carries a high risk of cancer development, such as long-term estrogen exposure, decreased ability of cells to repair DNA because of higher p53 mutation rates, and decreased immunity to carcinogenesis[27]. Another possible cause that poorly differentiated tumors were found to be more prevalent in older age groups is delayed diagnosis. This is related to the lack of self-awareness and screening of older people[28].

This study is supported by the theory that the rate of cell proliferation in HER2-type breast cancer is higher when compared to HER2-negative, resulting in more aggressive characteristics[8]. HER2-type breast cancer is associated with HER2 overexpression and higher biomarkers of c-Met, EGFR, and survivin. These biomarkers play a role in the cell survival process, such as cell proliferation by c-Met and EGFR or inhibition of apoptosis by survivin[29]. HER2 is also a prognostic marker of breast cancer, where overexpression and amplification of the HER2 gene cause abnormal activation of signaling pathways, leading to uncontrolled and disordered cell growth with poor characteristics as the outcome[30].

The weakness of this study is the limitation of data exposure on several patient characteristics such as body mass index and family history due to some unidentified data. Incomplete medical record data regarding the patient's age of menarche and menopause also resulted in less information regarding duration of estrogen exposure which could have been studied.

A key strength of this study is that it provides new insights regarding the relationship between histopathological grading and age of HER2-type breast cancer patients, particularly in North Sumatera. This study also provides updated information on the occurrence rate, patient characteristics, and histopathological grading of HER2-type breast cancer patients.

5. Conclusion

In this study, it was found that the histopathological grading that was more commonly found in HER2-type breast cancer included grade 3 (poorly differentiated tumor). Meanwhile, the age of HER2-type breast cancer patients was mostly ≥45 years old. This study proves that there is a significant relationship between histopathological grading and the age of HER2-type breast cancer patients, where patients aged <45 years are less likely to have moderately to poorly differentiated tumor. The results of this study might have an impact on determining the prognosis of HER2-type breast cancer patients.

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