Medicina Biomedica Journal
Vol. 1, No. 1, January 2024, pp. 8 ~ 16
ISSN: 2827- 8275, DOI: 10.30596/mbj.v1i1

THE RELATIONSHIP OF GRADING AND HISTOPATHOLOGY WITH RESULTS OF HER-2 PATIENTS' IMMUNOHISTOCHEMICAL EXAMINATION BREAST CANCER AT DR PIRNGADI MEDAN REGIONAL GENERAL HOSPITAL IN 2018-2019

Suryani Eka Mustika [1], Dewi Pangestuti [2]
[1]*Department of Anatomical Pathology, Faculty of Medicine, Universitas Islam Sumatera Utara*
[2]*Department of Pharmacology, Faculty of Medicine, Universitas Islam Sumatera Utara*
suryaniekamustika79@gmail.com

ABSTRACT

Basic Health Research Data 2019 explains that breast cancer prevalence that occurs in Indonesia is the second malignancy phenomenon that often afflicts women with a percentage of 0.5%, and ranked first cervical cancer as much as 0.8%. To choose and predict the prognosis, immunohistochemical examination becomes part of the mandatory examination effort. The general purpose of this study is to test the relationship of grading histopathology and histopathology types with the results of the HER-2 immunohistochemical examination of breast cancer patients at Dr. Pirngadi Medan Hospital in 2018-2019. This type of research is observational analytics conducted using the Cross-Sectional method. Secondary research data in the form of breast cancer patients in the Anatomical Pathology section of Dr. Pirngadi Medan Hospital year 2018-2019. How to take a sample by total sampling method. The statistical test used in the study is the Chi-square test. The study found 66 cases. Breast cancer cases are most common in the age range between 40 to 49 years (43.9%). The most common stages are in stage III (53.0%). This type of histopathology is found in invasive ductal carcinoma (84.8%). The most histopathological grading was grade II (63.6%). HER-2 test results found that the majority of patients had HER-2 +3 (positive 3) (59.1%). As for the Chi-Square test, if $p \leq 0.05$ found a significant association and if $p \geq 0.05$ did not have a significant association. There is no significant association between the type of histopathology and the results of HER-2 immunohistochemical examination ($p = 0.208$) and there is no significant association between grading histopathology results of HER-2 immunohistochemical examination ($p = 0.492$).

Keyword : Breast cancer, grading histopathology, type of histopathology, immunohistochemical examination results, HER-2

Corresponding Author:
Suryani Eka Mustika
Department of Anatomical Pathology
Universitas Islam Sumatera Utara
Jalan Kapten Muktar Basri No 3 Medan 20238, Indonesia.
suryaniekamustika79@gmail.com

1. INTRODUCTION

The graph of breast cancer patients rose with an estimated more than two million new cases detected in 2018 with a percentage of 23% of all cancers.[1] The American Cancer Society estimates about 231,840 new cases of invasive breast cancer in the United States this year. The disease is diagnosed in women. A total of 60,290 new cases of carcinoma in situ (CIS) were diagnosed as noninvasive breast cancer. About 40,290 women have died from breast cancer.[2] Data Basic Health Research in 2018 said the prevalence of breast cancer that occurred in Indonesia has reached 0.5 per 1000 women.[3]

Examination to detect Human Epidermal growth factor Receptor (HER-2)/neu/c-ErbB-2. HER- 2 is the epidermal growth factor receptor (EGFR) category that is at the 17q21 chromosome level. HER-2 expression is easy to find in normal cells and proteins that can function during the

process of growth and differentiation as normal epithelial. In breast cancer cells, for example, which express HER-2 in excess, the activity of growing and differentiation of cancer cells can increase. HER-2 positive is estimated to account for 18-20% of breast cancers.[4]

Discussion of breast cancer differentiation found three parts; The degree of differentiation is well, moderate, then severe. Many factors can influence the assessment of the degree of differentiation, namely the formation of the nucleus, tubules, and mitosis. Then the discussion of breast cancer differentiation can affect the effect on prognosis. Data from grade II and III research is the most data. Grade II and grade III are numerous in HER-2 positive, poor degrees of differentiation can worsen a patient's prognosis. Breast cancer can be affected by metastasis, tumor size, histopathological type, and degree of differentiation.

Overexpression of HER-2/neu is found in almost all cases. The discovery is with a high degree of differentiation of DCIS. Estimates of 20-30% Invasive IDC, with a lower percentage on ILC. A positive HER-2 expression will provide a different follow-up therapy.[5]

Based on this background, it is necessary to examine whether there is a link between HER-2 expression with the type of histopathology and grade of breast cancer. Dr. Pirngadi Medan Hospital has conducted an HER-2 examination service. The research regarding this examination has never been done on cancer data in the city of Medan so researchers are interested in proving how the relationship grading histopathology and the type of histopathology with the results of the HER-2 immunohistochemical examination in breast cancer patients at Dr. Pirngadi Medan Hospital in 2018-2019.

2. METHOD

In this discussion, the research used is observational analytic by using a cross sectional approach, namely by reviewing the results of medical records of patients diagnosed with breast cancer in the Laboratory of Anatomical Pathology. This effort was obtained by HER-2 immunohistochemical examination data Dr. Pirngadi Medan hospital in 2018-2019. This research uses a total sampling of samples. Samples were taken from all medical records of patients with a diagnosis of breast cancer at the Anatomical Pathology Laboratory that conducted HER-2 immunohistochemical examination. A study analysis to see whether there is a relationship between grading histopathology and histopathological types with HER-2 immunohistochemistry profiles in breast cancer patients.

Then the statistical test used the chi-square test. If the value on p-value ≤ value (0.05), the decision is otherwise H_0 rejected. In a sense, there is a significant relationship between groups of one and the other. If the value p ≥ value (0.05), then the decision failed to be H0 rejected, meaning that there was no correlation between group one and another.[6]

3. RESULTS

Redistribution breast cancer based on age

Here is data on breast cancer patients who perform HER-2 immunohistochemical examination based on age. Data is divided by description per year, as in the following table.

Medicina Biomedica Journal
Vol. 1, No. 1, January 2024, pp. 8 ~ 16
ISSN: 2827- 8275, DOI: 10.30596/mbj.v1i1

Table 1: Age of breast cancer patient who have an HER-2 immunohistochemical examination

Age	201		2019		The total year 2018-2019	
	n	%	n	%	Frequency (n)	Percentages (%)
25-39 years	7	20.0	1	3.2	8	12,1%
40-49 years	17	48.6	12	38.7	29	43,9%
50-59 years	9	25.7	16	51.6	25	37,9%
60-65 years	2	5.7	2	6.5	4	6,1%
Total	35	10	31	100	66	100%

Most breast cancer patients are in the age range of 40 to 49 years with a total of 29 patients (43.9%). In 2018 the most incidence at the age of 40- 49 years with a total of 17 patients (48.6%). Then in 2019, the age group of 50-59 years was the most incidence with the number of 16 patients (51.6%).

Redistribution stage breast cancer patients who have done HER-2 immunohistochemical examination. As for the explanation.

Here is the stage of breast cancer patients who have done HER-2 immunohistochemical examination. As for the explanation. As for the explanation as follows.

Table 2: Breast cancer stadium in patients with the HER-2 immunohistochemical examination

Stadium	2018		2019		Total 2018-2019	
	n	%	n	%	n	%
Stadium 0	0	0	0	0	0	0
Stadium I	0	0	7	22.6	7	10.6
Stadium II	3	8.6	8	25.8	11	16.7
Stadium III	23	65.7	12	38.7	35	53.0
Stadium IV	9	25.7	4	12.9	13	19.7
Total	35	100	31	100	66	100

Medicina Biomedica Journal
Vol. 1, No. 1, January 2024, pp. 8 ~ 16
ISSN: 2827- 8275, DOI: 10.30596/mbj.v1i1

Stadium III increased with the largest number reaching 35 cases or 53%. While stage IV the case of stages I and II. Then there was also an increase in the percentage of cases, namely stages III and IV.

Redistribution type of histopathology of breast cancer patients who have done HER-2 immunohistochemical examination

The data explained above is displayed as follows.

Table 3: Types of histopathology of breast cancer patients with HER-2 immunohistochemistry examination

Histopathology types	2018		2019		Total 2018-2019	
	n	%	n	%	n	%
Invasive ductal carcinoma	31	88.6	25	80.6	56	84.8
Invasive lobular carcinoma	0	0	2	6.5	2	3.1
Other carcinomas	4	11.4	4	12.9	8	12.1
Total	35	100	31	100	66	100

Most breast cancer patients with the type of histopathology of invasive ductal carcinoma with the number of 56 cases (84.8%), in 2018 the most incidence with the type of histopathology of invasive ductal carcinoma with the number of 31 cases (88.6%). In 2019 with the type of histopathology of invasive ductal carcinoma is still the most common occurrence with the number of 25 cases (80.6%).

Grading distribution of histopathological breast cancer patients who have done HER-2 immunohistochemical examination.

Data on histopathological *grading* are also featured in the results of this study. The distribution is displayed as follows.

Table 4: Grading histopathology of breast cancer patients with HER-2 immunohistochemical examination

Grade	2018		2019		Total 2018-2019	
	n	%	n	%	n	%

Medicina Biomedica Journal
Vol. 1, No. 1, January 2024, pp. 8 ~ 16
ISSN: 2827- 8275, DOI: 10.30596/mbj.v1i1

X	0	0	0	0	0	0
I	5	14.3	6	19.4	11	16.7
II	22	62.8	20	64.5	42	63.6
III	8	22.9	5	16.1	13	19.7
Total	35	100	31	100	66	100

The results than the grading assessment of histopathology of patients affected by breast cancer 2018-2019 grade II allegedly with the largest number of cases (63.6%). Then in 2018 histopathological grading was rated a lot in grade II with 22 cases (62.8%). Lastly, in 2019 grade II which is the largest number of cases is 20 cases (64.5%).

Distribution of the results of HER-2 breast cancer immunohistochemical examination results.

Patients with breast cancer who do HER-2 immunohistochemical examination will get the following results.

Table 5 Distribution examination results from HER-2 breast cancer patients

HER-2/ Cerb-B2	2018		2019		Total 2018-2019	
	n	%	n	%	n	%
0	9	25.7	9	29.0	18	27.3
+1	1	2.9	0	0	1	1.5
+2	5	14.3	3	9.7	8	12.1
+3	20	57.1	19	61.3	39	59.1
Total	35	100	31	100	66	100

In table 5, we can see based on the results of HER-2

breast cancer patients 2018-2019 +3 (positive 3) is the most 39 cases (59.1%). In 2018 HER-2 was at +3 (positive 3) with 20 cases (57.1%). In 2019 +3 (positive 3) is still the most with 19 cases (61.3%).

The relationship of histopathological grading with the results of the HER-2 immunohistochemical examination.

The relationship of the two variables has gone through the statistical variable significance test stage, the Chi-Square test. It found a significance value of p = 0.492 in the test to provide a conclusion of independent variable grading histopathology had no significant association to HER-2 immunohistochemical examination in breast cancer patients.

Medicina Biomedica Journal
Vol. 1, No. 1, January 2024, pp. 8 ~ 16
ISSN: 2827- 8275, DOI: 10.30596/mbj.v1i1

Table 6: Grading histopathology with the results of HER-2 immunohistochemical examination

Histopathology gradings	HER-2				Total	Significance
	0	+1	+2	+3		
Grade 1	3	0	3	5	11	
Grade 2	12	1	5	24	42	
Grade 3	3	0	0	10	13	p = 0,492
Total	18	1	0	39	66	

Relationship of histopathology with the results of the HER-2 immunohistochemical examination.

The relationship of these two variables is through a significant statistical test, the Chi-Square test and we found a significance value of p= 0.208 in the test so that it can be conclusive, variable independent with the type of histopathology has no significant relationship toHER-2 immunohistochemical examination in patients with breast cancer.

Table 7: Types of histopathology with the results of HER-2 immunohistochemical examination

Histopathological types	HER-2				Total	Significances
	0	+1	+2	+3		
Invasive ductal carcinoma	15	1	8	32	56	
Invasive lobulus carcinoma	2	0	0	0	2	p = 0,208
Other carcinomas	1	0	0	7	8	
Total	18	1	8	39	66	

4. Discussions

Breast cancer cases are based on age range according to data from Muhammad Anggo at Arifin Ahmad Hospital (2013) that breast cancer patients are dominated by the age range of 40-49 years (41.38%). This is in accordance with the theory that the age of over 40 years has a greater tendency to get the risk of breast cancer. The risk of breast cancer increases with age. This is thought to be related to exposure to other risk factors that take a long time to induce the occurrence of cancer. Like studies comparing the incidence of breast cancer by age category by age, the incidence of breast cancer in the Asian region tends to be more frequent at the age of 40 and 50 years, while the incidence in western countries is more frequent at the age of 60 and 70 years.

Based on existing data, it is known that the proportion of HER-2 immunohistochemical examinations in 2018 and 2019 compared to breast cancer cases is still very small. The difference

in the proportion of HER-2 immunohistochemical examinations with breast cancer cases can occur because the cost of this examination is also quite expensive so not all patients are able to do so.

HER-2 expression can be found in normal cells and this protein functions in the process of growth and differentiation of various normal epithelial. In breast cancer cells that express excessive HER-2, the growth activity and differentiation of cancer cells will increase so that the histopathological grade is higher. Grading histopathology and immunohistochemical examination are prognosis factors for breast cancer.

The same results were obtained in the study of Rahman and Sampepanjung (2010). The results of the study said HER-2 / Neu negative in as many as 12 people or 37.50%. Then HER-2/Neu "+1" found 2 people or 6.30%. Her2/Neu "+2" numbered 5 people or 15.60%, and HER-2/Neu "+3" numbered 13 people or 40.6%. The appraisers "-" and "+1" can be categorized negatively. While the assessment of "+2" and "+3" tested positive, so it was found that HER-2/Neu expression was found to be 18 patients or 56.20%.

Based on the results of the study found a relationship between the two variables were tested significantly statistics, namely the Chi-Square test. From the results of the test, there is a significant value of p = 0.492 so that it can be conclusively independent variable grading histopathology does not have a significant relationship to the examination of HER-2 immunohistochemical in breast cancer patients, so this study cannot prove the above theory because many factors affect the body. The examination of HER-2 breast cancer immunohistochemistry.

Various factors that can affect the immune- staining process include tissue handling. Tissue handling is served as the most important factor to produce staining of quality immunohistochemical. That is with a network fixation that uses Neutral Buffer Formalin (NBF) of 10%. The next step is immersed with a volume equivalent to 20-30x, then the tissue can produce good morphological details. Antibodies that can be used are monoclonal antibodies and polyclonal antibodies. As well as protocols include blocking reagents selection, epitope retrieval, incubation duration, antibody dilution, temperature, as well as detection methods.

Rilke et al research found HER-2 positive at 3.9% in grade I, 20.4% in Grade II, and 38.9% in grade III. In a case study conducted by Hoff et al, 388 cases found that HER-2 was positive ≤1% grade I, 17% for grade II, and 23% for grade III.

Ali Akbar Firasi's 2016 research found the comparative value between HER-2 with the degree of differentiation obtained from both variable relationships through significant statistical tests, namely the Chi-Square test. The value of significance obtained is p= 0.218 in the sense that the independent variable HER-2 has no significant relation to the degree of differentiation of women with breast cancer. The results are in line with Rahman et al research in the Oncology Surgery section of Dr. Wahidin Sudirohusodo Hospital and networking hospitals in Makassar in 2010. The results of the study found no significant relationship between PR, ER, and HER-2.

The factors that cause a large number of breast cancer patients at Dr. Pirngadi Hospital to come with locally advanced stages are unclear, but it is suspected that screening against breast cancer in Indonesia is still individualized so early detection programs are still not effective and efficient. Lack of information, geographical location, education, many advertisements explaining alternative medicine, lack of diagnostic tools, such as mammography, ultrasound, and lack of medical skills in diagnosing breast malignancies allow cancer patients already at the stage.

HER-2 overexpression expression increases at higher grades, causing cancer to become more invasive and more likely to occur. Invasive ductal carcinoma has a greater risk of lymph node involvement compared to other types.

The relationship between the two variables thus falls into the realm of a statistical significancetest, namely the Chi-Square test. Found a significance value of p=0.208 in the test so that it can be conclusive, independent variables of histopathological type do not have a significant relationship to HER-2 immunohistochemical examination in breast cancer patients. so this study cannot prove the theory above because of many factors that affect the examination HER-2 immunohistochemical breast cancer patients.

Similar results were obtained by Shokouh Taghipour Zahir from Shahid Sadoughi General Hospital, Yazd, Iran in the range of 2008-2014. HER- 2 overexpression was examined in 514 patients, with 182 breast cancers showing HER-2 overexpression. Invasive ductal carcinoma and in situ have the highest frequencies of HER-2 overexpression (34.5% and 34.9%). However, there was no significant association between the two types of breast cancer and HER-2 overexpression with fisher p = 0.63.

REFERENCES

Zoubida Zaidi and Hussain Adlane Dib, The worldwide female breast cancer incidence and survival, 2018.https://cancerres.aacrjournals.org/content/79/13_Supplement/4191.short.

American Cancer Society. 2018. Breast Cancer Facts and Figures 2018. Atlanta: American Cancer Society.

Kesehatan Republik Indonesia. 2018. Situasi Penyakit Kanker. Jakarta. Available from: http://www.depkes.go.id/resources/download/pu sdatin/infodatin/infodatin-kanker.pdf).

Anggo Muhammad. 2013. Profil imunohistokimia pasien kanker payudara di bagian Patologi Anatomi Rumah Sakit Umum Daerah Arifin Achmad Pekanbaru Periode Januari 2010–Desember 2011. Fakultas Kedokteran Universitas Riau.

Firasi Ali Akbar. 2016. Hubungan Usia Terhadap Derajat Diferensiasi Kanker Payudara Pada Wanita. Fakultas Kedokteran Universitas Diponegoro.

Notoatmodjo S. 2012. Usulan Penelitian, Metode Pengambilan Sampel, Pengolahan dan Analisa Data. Metodologi Penelitian Kesehatan. Jakarta: Rineka Cipta. Hal: 75-176.

Rahman A, Sampepanjung D. 2010. Hubungan ekspresi HER-2/neu dan hormonal reseptor dengan grading histopatologi pada penderita kanker payudara wanita usia muda. Fakultas KedokteranUniversitas Hasanuddin, Makassar.

Dabbs DJ. 2013. Diagnostic Immunohistochemistry: Theranostic and Genomic Applications: Techniques of Immunohistochemistry: Principles. Pitfalls, and Standarization 4th Edition. United States of America: Elsevier Saunders p.1-19.

Laella Kinghua Liana. 2015. Karakteristik Pasien Kanker Payudara Dan Penanganannya Di Rsud Arifin Achmad Pekanbaru Periode Januari 2010–Desember 2012. Fakultas Kedokteran Universitas Kristen Maranatha. Bandung.

Alam Nasir Bayhaqi Ahmad, Rahayu M, Islani Sukma. 2016. Pengaruh Pemberian Radiasi Sinar Gamma Terhadap Ekspresi Caspase-3 Pada Sel Otak Rattus Norvegicus Varian Wistar Jantan Dengan Metode

Pengecatan Imunohistokimia. Fakultas Kedokteran Universitas Brawijaya. Malang. MNJ.2015;1(2):72-79.

Alamanda Putri T. 2017. Ana;isa Faktor-Faktor Yang Berhubungan Dengan Karakteristik Pasien Kanker Payudara Di RSUD Dr. H.Abdul Moeloek Bandar Lampung Year 2016. Fakultas Kedokteran Universitas Lampung. Bandar Lampung.

Prichard J, Hicks DG, Hammond MEH. 2015. Predictive Biomarkers in Breast Cancer: ER, PR and HER-2/neu. Researchgate. Available from: https://www.researchgate.net/figure/278680888_fig5_Figure-3-43-HER2-IHC-assay-scoring-a- HER2-IHC-Negative-0-result-with

Priti Lal, MD, Lee K. Tan, MD, and Beiyun Chen, MD, PhD. 2005. Correlation of HER-2 Status With Estrogen and Progesterone Receptors and Histologic Features in 3,655 Invasive Breast Carcinomas. American Society for Clinical Pathology.

Suyatno, Pasaribu ET. 2014. Kanker Payudara. Bedah onkologi diagnostic dan terapi. Jakarta: Sagung seto. Hal : 39-82.

Taghipour Zahir Shokouh, MD, Aalipour Ezatollah, MSc, and Poorya Barand, GP. 2015. Interrelationships Between Ki67, HER2/neu, p53, ER, and PR Status and Their Associations With Tumor Grade and Lymph Node Involvement in Breast Carcinoma Subtypes. Iran.

Masruro AY. 2016. Pengecatan imunohistokimia HER 2 menggunakan susu skim dan normal serum. Fakultas Ilmu Keperawatan dan Kesehatan Universitas Muhammadiyah Semarang.

Vinay K, Cotran RS, Robbins SL, editor. 2013. Sistem Genitalia Perempuan dan Payudara. Buku ajar Patologi Robbins. Edisi ke-7. Jakarta: EGC. Hal : 794-800.

Wolff AC, Hemmond ME et al. 2013. Recommendation human epidermal growth factor receptor 2 testing in breast cancer. American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update.