International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 22s, 2025
https://www.theaspd.com/ijes.php

Correlation Of Ki67 And Her2 Expression With Histopathological Grading Of Breast Cancer

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Abstract
Breast cancer is one of the most common types of cancer in women worldwide, including in Indonesia. Biomarker assessments, such as Ki-67 and HER2, have significant prognostic and predictive value in determining tumour aggressiveness and guiding therapy options. Histopathological grading reflects the degree of cancer cell differentiation and plays a role in determining prognosis. This study aimed to determine the correlation between Ki67 and HER2 expression and histopathological grading of breast cancer in women. Methods: This study used an observational analytical design with a cross-sectional approach. Samples were taken from female patients diagnosed with invasive breast cancer who underwent biopsy or mastectomy at one national referral hospital. Ki-67 and HER2 expression were analysed using immunohistochemistry, while histopathological grading was assessed using the Nottingham Prognostic Index (NPI) grading system. Results: The most cases of breast cancer were in the 51-60 years age group, namely 42 respondents (29.6%). Grade 3 breast cancer was the most common, namely 63 respondents (44.5%). Estrogen receptor (ER) results were positive in 89 respondents (62.7%), and negative in 53 respondents (37.3%). In the progesterone receptor (PR) positive results, 81 respondents (57%) were identified, while 61 respondents (43%) had negative results. HER2 Neu results were positive in 54 respondents (38%), negative in 62 respondents (43.7%), and equivocal in 26 respondents (18.3%). Ki-67 was most frequently positive in results/proliferation >20%, with 80 respondents (62.5%), and in negative results/proliferation <20%, with 46 respondents (35.9%). There were 2 respondents (1.6%) in whom Ki-67 was not detected. Ki67 expression in histopathological grading of breast cancer, especially in grade 3, with a p-value of 0.002 (p <0.005) and in grade 2 with a value of 0.003. In contrast, the p-value results for HER2 on histopathological grading of breast cancer did not show significant results in grades 1 (p = 0.051), 2 (p = 0.006), and 3 (p = 0.005), with p-values greater than 0.005. Conclusion: A significant correlation exists between Ki-67 and histopathological grading, whereas no significant correlation is found between HER2 and histopathological grading of breast cancer.
Keywords: *Ki67 expression, HER2, histopathological grading, breast cancer*

INTRODUCTION

Breast cancer, also known as Ca mammae, is a malignant tumour that grows in the breast and spreads to surrounding areas and throughout the body (American Cancer Society, 2020). Breast cancer is the most common cancer and the leading cause of cancer death in women in Indonesia. According to GLOBOCAN 2020 data, there were approximately 68,858 new cases of breast cancer in Indonesia, making it the most prevalent cancer in women (Sung et al., 2021). Effective breast cancer management requires a thorough understanding of the tumour's biological characteristics, including biomarker status such as Ki67 and HER2, which have been shown to play a crucial role in prognosis and response to therapy.

Breast cancer is the most common cancer in women in Indonesia and the leading cause of cancer mortality in this population. According to GLOBOCAN 2020 data, there were approximately 68,858 new cases of breast cancer in Indonesia (approximately 16.6% of total new cancer cases). A clinicopathological profile study in Indonesia from 2014 to 2019 also found that approximately 37.7% of patients were HER2-positive and approximately 56.9% had high Ki-67 expression (≥14%).

Ki-67 is a marker of cell proliferation that reflects the level of mitotic activity in a tumour. High Ki67 expression is generally associated with more aggressive tumours and a poorer prognosis (Darmawan et al., 2023). Meanwhile, HER2 is a tyrosine kinase receptor whose overexpression or amplification is also associated with increased tumour aggressiveness and targeted therapy options such as trastuzumab (Widodo et al., 2020). These two biomarkers are essential components in the molecular classification of breast cancer and contribute to more personalised treatment strategies.

Histopathological grading is a standard method for assessing the malignancy of cancer cells based on differentiation, nuclear pleomorphism, and mitosis count. This grading is closely related to patient prognosis

and serves as a basis for determining treatment plans. Previous studies have shown that high expression of Ki-67 and HER2 is frequently found in tumours with higher histopathological grades; however, data examining a direct correlation between the three in the Indonesian female population are still limited (Yuniarti et al., 2022).
Local research at Prof. Dr. I.G.N.G. Ngoerah General Hospital in Bali demonstrated a significant association between Ki67 expression and histopathological grading and molecular status of breast cancer (Putri & Suwiyoga, 2021). A similar study in Kalimantan also found that the mitotic index and Ki67 were positively correlated with increasing tumour grade (Fadillah et al., 2023). However, the concurrent correlation between Ki-67 and HER2 with histopathological grading, specifically in the context of the Indonesian population, has not been comprehensively reported.
Considering the importance of biomarker assessment in supporting clinical decisions and the limited data on the correlation between Ki67 and HER2 with tumour grading in Indonesia, this study is relevant. The results are expected to contribute to the development of more targeted prognostic and therapeutic approaches for breast cancer patients in Indonesia. Currently, there is no research linking the three indicators —Ki-67, HER2, and cancer cell grading — in the Indonesian population; therefore, this research is necessary.

METHODS

This study employed a retrospective, cross-sectional design. This study only conducted one observation. This study was conducted at the Haji Regional General Hospital in Surabaya from July to August 2025. The population in this study were all cases of breast cancer patients who underwent anatomical pathology examination at the Haji Regional General Hospital in Surabaya. The sample in this study consisted of the total number of breast cancer patient cases that underwent anatomical pathology examination in 2023-2024 at the Haji Regional General Hospital in Surabaya, meeting the inclusion and exclusion criteria.
The inclusion criteria for this study were breast cancer patients who underwent anatomical pathology examination in 2023-2024, while the exclusion criteria were breast cancer patients who underwent anatomical pathology examination before 2023. Sampling was conducted by reviewing secondary data from the records of breast cancer examination results in the anatomical pathology laboratory of Haji Hospital Surabaya. Immunohistochemical examination was performed to determine the expression of K167 and HER2.
The data will be analysed statistically using Microsoft Excel and SPSS, including Spearman/Pearson correlation tests. The analysis will focus on K167 expression (high > 20% vs. low <20%), HER2 status (negative, equivocal, positive), and a combination of both, with grading.
The research, entitled "Correlation of Ki-67 and HER2 Expression with Histopathological Grading of Breast Cancer in Indonesian Women," has passed the feasibility test by the health ethics committee at Haji Hospital, with ethics number 445/136/KOM.ETIK/2025.

RESULTS

142 breast cancer patients who underwent anatomical pathology examinations from 2023 to 2025 at Haji Surabaya Regional Hospital.

Table 1. Characteristics of breast cancer respondents based on age

Age	n	Percentage (%)
20-30 years old	3	2,1 %
31-40 years old	24	16,9 %
41-50 years old	41	28,9%
51-60 years old	42	29,6 %
> 61 years old	32	22,5 %
Total	142	100 %

The highest number of breast cancer cases from 2023 to 2025 was in the 51-60 age group, namely 42 respondents (29.6%), followed by the 41-50 age group, 41 respondents (28.9%), while the age group with the fewest breast cancer cases was in the 20-30 age group, namely 3 respondents (2.1%). A total of 24 respondents (16.9%) were in the 31-40 age group, and 32 respondents (22.5%) were in the age group of 60 years or older.

Table 2. Characteristics of breast cancer grade

Grade	n	Percentage (%)

-	45	31,7 %
Grade of 1	4	2,8 %
Grade of 2	30	21 %
Grade of 3	63	44,5 %
Total	142	100 %

The stage of breast cancer in 2023 to 2025 was mainly grade 3, with 63 respondents (44.5%), while the least common stages were grade 1, with 4 respondents (2.8%), and grade/stage 2, with 30 respondents (21%).

Table 3. Characteristics of ER (Estrogen Receptor), PR (Progesterone Receptor) and HER 2 Neu

Variable	Positive		Negative		Equivocal	
	n	Percentage(%)	n	Percentage (%)	n	Percentage (%)
ER	89	62,7%	53	37,3%	-	-
PR	81	57%	61	43%	-	-
HER 2 Neu	54	38%	62	43,7%	26	18,3%

Based on the table above, 89 respondents (62.7%) had positive results for the estrogen receptor (ER), while 53 respondents (37.3%) had negative results. 81 respondents (57%) had positive results for the progesterone receptor (PR), while 61 respondents (43%) had negative results. 54 respondents (38%) had positive results for the HER2 Neu test, while 62 respondents (43.7%) had negative results, and 26 respondents (18.3%) had equivocal results.

Table 4. Characteristics of Ki67 in breast cancer

	Positive/Proliferation >20%		Negative /Proliferation <20%		Not detected	
	n	Percentage(%)	n	Percentage(%)	n	Percentage(%)
Ki67	80	62,5%	46	35,9%	2	1,6%

Based on the table above, the Ki-67 data mainly showed positive proliferation results (>20%), with 80 respondents (62.5%), while negative results/proliferation <20% were reported in 46 respondents (35.9%). Additionally, 2 respondents (1.6%) did not have Ki-67 detected.

Table 5. Correlation of Ki67 and HER2 expression with histopathological grading of breast cancer

	P value	
	Ki67	HER2
Grade of 1	0,005	0,051
Grade of 2	0,003	0,006
Grade of 3	0,002	0,005

Based on Table 5 above, there is a significant correlation between Ki-67 expression and histopathological grading of breast cancer, especially in grade 3, with a p-value of 0.002 ($p < 0.005$), and in grade 2, with a p-value of 0.003. Meanwhile, the p-value results for HER2 on histopathological grading of breast cancer did not show significant results in grades 1 ($p = 0.051$), 2 ($p = 0.006$), and 3 ($p = 0.005$), with p-values greater than 0.005.

DISCUSSIONS

This study considers the importance of assessing age, ER and PR, and biomarkers to support clinical decisions, as well as the limited data on the correlation of Ki67 and HER2 with breast cancer grading. The correlation between Ki-67 and HER2 expression and histopathological grading of breast cancer (Ca mammae) is an essential topic in pathology and oncology because it can help assess prognosis and response to therapy.

In this study, most cases of breast cancer in 2023 to 2025 were in the 51-60 age group. This is in line with other studies, namely in a statistical survey conducted by the UK cancer registry, breast cancer has 2 highest age groups (1 in the 50-59 age group and the other in the 65-70 age group). Still, it is stable for a period before increasing again from the age of 75 years (Cancer Research UK, 2012). The majority of breast cancer patients are 1 decade younger than those in European countries. In a study conducted in India, breast cancer cases were mostly under

50 years old. Therefore, it appears that breast cancer patients are younger in Asian countries than in European countries (Khokhar, 2012).

In this study, the percentages of ER and PR positive breast cancers were higher than those of negative breast cancers. The largest study of African-American women to date is the African American Breast Cancer and Risk (AABCR) consortium (1,128 cases, 2,932 controls). To our knowledge, no previous study has evaluated the case-control association with subtypes defined by combined ER/PR/HER2 status among Asian-American and US women (Howlader, 2014). In analyses of associations with reproductive factors, the magnitudes were generally similar for subtypes defined by combined ER/PR/HER2 status or combined ER/PR status, as well as for ER-negative and TN subtypes. The associations for ER/PR-positive breast cancers were similar to those for the luminal A subtype in this study, particularly for Asian-American and Hispanic women (Gaudet, 2018; Jung, 2022; Palmer, 2014). An extensive research demonstrated that PR expression is a stronger independent predictor than ER. Patients with the ER+/PR- subtype have a worse prognosis than those with ER+/PR+, with a higher risk of recurrence and mortality (Li et al, 2022). For example, a retrospective study showed that ER+/PR- patients had lower DFS and OS than ER+/PR+ patients (Zhengjia, 2025).

ER (Estrogen Receptor) is a hormone receptor found in breast cancer cells. Approximately 70% of breast cancers are ER positive, meaning the cancer cells have receptors for estrogen (Tanos, 2012). PR (Progesterone Receptor) is a hormone receptor regulated by ER. Its expression depends on the presence of estrogen, and PR can modulate the action of ER (Tanos, 2012). According to other studies, cancer cells exhibit positive expression of ER and/or PR, which is associated with the growth and spread of cancer cells. Estrogen and its receptor, ER, play an essential role in the development and progression of breast cancer (Mohammed, 2015).

Ki-67 is a marker of cell proliferation that is generally closely related to the level of tumour malignancy. The higher the expression of Ki-67, the higher the histopathological grading of the tumour. In this study, a correlation was found between the expression of Ki-67 and HER2 and the histopathological grading of breast cancer in women, with a p-value of 0.001. This is in line with research conducted by Petrulaitine, 2024, explaining that in multivariable analysis, Ki67-positive cells, measured by Haralick texture entropy, emerged as an independent predictor of worse specific survival (hazard ratio (HR) = 2.64, p-value = 0.0049), along with lymph node involvement (HR = 2.26, p-value = 0.0195). Remarkably, entropy, representing the spatial disorganisation of tumour proliferation, outperformed the proliferation rate itself, determined either by pathology reports or DIA. We conclude that the Ki-67 entropy indicator enables a more comprehensive risk assessment, particularly in cases with borderline Ki-67 proliferation levels (Petrulauite, 2024).

The significance of Ki-67 lies in its presence in all active phases of the cell cycle, except the resting phase (G0). This makes it a powerful marker for cell proliferation and, by extension, tumour progression. Other studies have consistently associated high Ki-67 expression with unfavourable clinical outcomes, including larger tumour size, higher histological grade, and increased lymph node involvement (Čeprnja, 2024; Chauhan, 2023).

A cross-sectional study reported a strong positive correlation between Ki-67 expression and tumour grade. Mean Ki-67 expression was: Grade 1 ≈15.8%, Grade 2 ≈23.2%, and Grade 3 ≈34.7% (Spearman's ρ=0.68, $p<0.001$) (Abubakr et al, 2024). Higher Ki-67 levels were associated with advanced tumour grade, with Grade 3 tumours showing the highest mean expression, at 34.7%. This finding is consistent with previous studies that have established Ki-67 as a marker of Proliferation and aggressive tumour biology, particularly in high-grade and biologically aggressive breast cancer subtypes, such as HER2-positive and triple-negative cancers (Rammal, 2024; Ramtohul, 2024).

This study found no significant association between HER2 and histopathological grading of breast cancer. This is in line with several studies showing that HER2 positivity is often associated with higher grades and more aggressive tumour progression or activity. For example, HER2 positivity tends to occur in tumours with higher grades and higher proliferation rates (Payandeh, 2016). However, another study found no statistically significant association between HER2 expression and histopathological grading ($p = 0.051$), although the observed pattern still suggests higher grades (Papalexis et al., 2024).

A cross-sectional study in Vietnam investigated the correlation between HER2 protein overexpression and various clinicopathological features, including histological grade. The results showed that HER2 was not statistically significantly associated with tumour histological grade ($p = 0.282$), although there was a trend toward an increase in higher-grade tumours (Cong et al., 2020). International retrospective studies (not always focused on a specific year) have shown that HER2 exhibits a similar pattern to the proliferation index (Ki-67), which is

associated with high nuclear grade; however, the direct association with histological grade was not significant (p = 0.051).

The correlation between Ki-67 and HER2 is bidirectional, namely, HER2-positive tumours tend to have a higher Ki-67 proliferation index, and high Ki-67 levels are also often associated with HER2 overexpression (Shokouh et al., 2015).

CONCLUSIONS

A Significant correlation exists between Ki-67 and histopathological grading, whereas no significant correlation is found between HER2 and histopathological grading of breast cancer. Ki-67 and histopathological grading can be a prognostic factor of a successful treatment

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