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The Correlation between Human Epidermal Growth Factor Receptor-2 (HER2) Immunoexpression and Mitotic Activity Index (MAI) in Invasive Breast Carcinoma Patients: Insights into Tumor Aggressiveness

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ABSTRACT

Introduction
Breast cancer is a leading cause of cancer-related deaths among women globally, Indonesia is no exception Biological markers such as HER2 and MAI both play a critical role in predicting prognosis of invasive breast carcinoma (IBC). These two are associated with tumor proliferation and correlate with recurrence and survival rates. The correlation between these two prognostic factors has not been extensively studied. This study aims to investigate the correlation between HER2 immunoexpression score and mitotic activity index.

Methods
Medical records of 60 patients diagnosed with invasive breast carcinoma histopathologically were reviewed. Patient characteristics and clinicopathological features were analyzed. The correlation between HER2 and MAI was analyzed using Kendall's Tau-B correlation, and multivariate analysis was performed.

Results
There were 48 patients with no-special type (IBC-NST) and 12 patients with other types, with a mean age of 49.53 years. More than 50% of patients were HER2-negative, and only a few (16.67%) had a high MAI. The correlation between HER2 and MAI was not statistically significant. Interestingly, patients with HER2 score of 1 were seven times more likely to have a higher MAI compared to HER2 score of 3.

Conclusion
This study found no statistically significant correlation between HER2 score and MAI in IBC patients, which suggests that HER2 status may not be directly related to mitotic activity. However, further trials with larger sample sizes are needed to confirm this result.

Keywords: *HER2 overexpression, human epidermal growth factor receptor-2, mitotic index, mitotic activity index, invasive breast carcinoma, breast cancer, no special type, prognostic factors*

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INTRODUCTION

Globally, cancer is a significant societal, public health, and economic challenge, causing nearly one in six deaths (16.8%) and almost one in four deaths (22.8%) from non-communicable diseases (NCDs). Among these, breast cancer stands out as the second most common cancer worldwide, with 2,296,840 cases reported in 2022. It is also the leading cause of cancer-related deaths among women, accounting for 684,996 deaths that year, with an age-adjusted mortality rate of 13.6 per 100,000 population.[1] The incidence of breast cancer increases with age, peaking in the seventh decade of life before declining sharply.[2] Asia carries the highest burden, contributing 42.9% of global breast cancer cases.[1,3] In Indonesia, 68,858 new cases were reported in 2020, with over 22,000 deaths, making breast cancer one of the leading causes of cancer-related mortality in the country.[4]

The American Joint Committee on Cancer (AJCC) staging system is the baseline tool for estimating the prognosis of breast cancer patients, incorporating tumor grading, immunohistochemical biomarkers, and the anatomical progression of the disease. Breast cancer staging is classified into clinical and histopathologic categories. Clinical staging is determined through physical examination and imaging studies conducted prior to treatment, while histopathologic staging is based on the pathological evaluation of the primary tumor and regional lymph nodes after surgical intervention.[5]

The AJCC then introduced a prognostic staging system that integrates biological factors, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), multigene assays, and lastly tumor grade to better define prognosis.[1] Human epidermal growth factor receptor-2 (HER2) and mitotic activity are both critical parameters in determining breast cancer prognosis, including breast cancer-specific mortality (BCSM).[1,5-7] According to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, HER2 positivity is defined by an immunohistochemical (IHC) score of 3+ or 2+ with in situ hybridization (ISH) amplification. An IHC score of 0, 1+ and 2+ without ISH amplification would define a tumour as HER2-negative.[6,8]

Mollineli et al, through a meta-analysis of 42 studies, confirmed that HER2-low status is associated with improved disease-free survival (DFS) and overall survival (OS) compared to patients with 0 score of HER2 immuno-expression (P<0.001), further reinforcing the critical role of HER2 in determining breast cancer prognosis.[8] The overexpression of HER2 in breast cancer cells had been established as a major negative prognostic factor, associated with worse prognosis. Similar to this, a study by Kang *et al* (2023) revealed that survival of patients with luminal type of breast cancer differed significantly based on the HER2 overexpression regardless whether or not the patient received treatment.[9] Andre *et al* (2024) also demonstrated a trend for bigger tumor sizes with increasing HER2 amplification, although without statistical significance due to small sample sizes. Patients with HER2 low carcinomas was also showed to have lower histologic grades than HER2-positive with significantly lower mitotic index expression.[9,10]

On the other hand, mitotic activity index (MAI) had only been hypothesized as an important prognostic factor for breast cancers, especially infiltrating breast carcinoma, with very few studies having proven its pure prognostic value. Nevertheless, this method remains widely accepted for its reliability in assessing tumor proliferation and its relevance to breast cancer prognosis. According to Ibrahim *et al* (2023), higher mitotic index values were observed in patients with short survival, moreover if combined with high apoptotic counts. High mitotic counts were associated with features of aggressive behavior, including high grade and high receptor negativity.[11] Similar to this, Jobsen *et al* also reported that high mitosis was significantly associated high-grade tumors.[12]

Despite the established role of HER2 and MAI in breast cancer prognosis, only few studies have explored the correlation between HER2 immunohistochemistry scores and the mitotic activity index, and none in invasive breast carcinoma. This study aims to address this gap by investigating the correlation between

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HER2 expression and tumor proliferation, as reflected in the MAI. Understanding this correlation could provide new insights into breast cancer prognosis and potentially influence therapeutic decision-making.

METHODS

This was a retrospective cross-sectional study, with the study protocol approved by the Ethics Committee on Human Research, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia. We retrospectively identified patients diagnosed with invasive breast carcinoma confirmed histologically at the Department of Anatomical Pathology, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia between 2015 and 2019. The inclusion criteria were patients aged 18 and older, with primary invasive breast carcinoma who underwent mastectomy, and the tissue samples were available for review. Patients were excluded from this study on the basis of the following criteria: secondary invasive breast carcinoma or metastatic invasive breast carcinoma, medical files or tissue specimens were not available. The remaining cohort of 60 women with invasive breast carcinoma was eligible for this study.

The patient data including age, gender, clinicopathological features (histological type, HER2 score), and surgery performed, were retrieved from electronic medical records of the hospital. Histological features and mitotic activity index were assessed by slide and biopsy material were reviewed.

Histological Types

Tumours were classified into four histological subtypes which are, invasive breast carcinoma, no special type (NST); invasive lobular carcinoma (ILC); other special types (papillary, mucinous, cribriform, sarcoma, etc.); mixed NST and special types. This classification was defined based on the 2019 WHO Tumors of The Breast Classification. Histological subtypes (histotypes) of invasive breast carcinoma then were categorized into two groups for statistical analyses: NST and others (includes lobular, other special types, and mixed of NST and other special types).

Immunohistochemistry (IHC) Evaluation and HER2 Scoring

The pathological slides from invasive breast carcinoma were scanned into WSIs using Aperio AT2 (Leiza, Germany) high-throughput biopsy scanner with a 20-magnification-scale objective and bright-field illumination. The scan resolution was 0.5036 um per pixel. The dataset consisted of a total 60 whole slide images in Aperio format (.svs). Four categories were included, which were IHC 0, 1+, 2+, and 3+ that were determined by two pathologists. The IHC scoring of all pathological images was determined according to two pathologists.

Assessment of Mitotic Activity Index (MAI)

All tumour slides obtained from the primary tumor at the time when mastectomy was conducted, were scanned to identify areas of higher proliferation. The samples were fixed in buffered formalin and embedded in paraffin, then being cut into sections with the size of 5 µm and stained with hematoxylin and eosin (H&E). Mitotic figures were distinguished according to the criteria proposed by van Diest *et al*: an absent nuclear membrane with clear morphological features of metaphase (hairy extensions of nuclear material clumped), anaphase (in a plane), or telophase (in separate chromosomal aggregates) were counted, cautiously excluding apoptotic and hyperchromatic nuclei.

Mitotic activity was calculated according to the grade scoring system of the modified Nottingham Tenovus method, which mitoses were counted in 10 consecutive high-power fields (HPFs) with a 400 times magnification at the hotspot area, then gave the results known as the mitotic activity index (MAI). Mitotic activity indexes would be analyzed as categorical variables in clinical analysis, on the basis of a microscope field diameter of 0.50 mm, the cutoff values were 0 to ≤7, 8-14, and ≥14 mitoses per 10 HPFs which corresponded to mitotic scores of 1, 2, and 3, respectively.

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Statistical Analyses

Statistical analyses were performed using SPSS software packages. The data distribution was analyzed using Kolmogorov-Smirnov test due to its sample size (>50 samples), which results in distribution not normal. Therefore, bivariate correlations between the HER2 score and mitotic activity index (MAI) were evaluated using a non-parametric ranking statistic, Kendall's Tau-B correlation test, due to its small sample size. For univariate analysis, the Mann-Whitney was performed to analyze the relationship between qualitative independent variables (age and histotype) and dependent variables. While for HER2 score, the Kruskal-Wallis was used due to its ordinal nature.

Additionally, multivariate analyses were performed using ordinal regression with known variables (age, gender, histological subtypes, and HER2 scores), to evaluate the independent factors of MAI. To identify the factors associated with an ordinal form of MAI, variables determined to be significant at a 25% level in crude association analysis (univariate analysis) were used as a subset of covariate stepwise ordinal logistic regression. In all analyses, the results were regarded as significant if the *p*-values were <0.05. For the proportionality assumption, the Brant test was applied. The Homer test for goodness-of-fit was also used to evaluate the model's performance.

RESULTS

Patient and Tumour Characteristics

Sixty tumour samples from 60 patients were reviewed. Patient distribution is shown in Table 1. Median age of patients was 48 years old (range: 31–78 years; mean: 49.53 years) and 98.3% of the patients were female, while 1.67% were male (1 out of 60). Additionally, most of the histological subtypes were no special type (80.0%), followed by mixed types (10.0%), other special types (8.33%), and invasive lobular carcinoma (1.67%).

Table 1. Patient demographic, clinicopathological characteristics and their correlation with mitotic index.

Characteristics	Total *N*=60	Mitotic activity index (MAI)			Mean Rank	*P*-value
		Score 1 *N*=27	Score 2 *N*=23	Score 3 *N*=10		
Age (years old)						
≤50	35 (58.33)	17 (63.0)	11 (47.8)	7 (70.0)	30.16	0.845
>50	25 (41.67)	10 (37.0)	12 (52.2)	3 (30.0)	30.98	
Gender						
Male	1 (1.67)	0 (0.0)	1 (4.3)	0 (0.0)		
Female	59 (98.33)	27 (100)	22 (95.7)	10 (100)		
Histologic subtypes						
NST	48 (80.0)	20 (74.1)	19 (82.6)	9 (90.0)	31.68	0.257
Others	12 (20.0)	7 (25.9)	4 (17.4)	1 (10.0)	25.79	
HER2 score						
3+	8 (13.)	5 (18.5)	1 (4.3)	2 (20.0)	27.50	0.119
2+	5 (8.3)	0 (0.0)	3 (13.0)	2 (20.0)	45.60	
1+	14 (23.3)	8 (29.6)	5 (21.7)	1 (10.0)	25.89	
0	33 (55.0)	14 (51.9)	14 (60.9)	5 (50.0)	30.89	

NST = no-special type; Mitotic activity index (MAI): score of 1 (≤7 mitoses/10 HPF); 2 (8-14 mitoses/10 HPF); 3 (≥15 mitoses/10 HPF); Human epidermal growth factor receptor-2 (HER2) score: score of 0 (HER2-negative); 1+ (HER2-low); 2+ (HER2-equivocal); 3+ (HER2-positive)

Univariate Analysis

In the univariable analysis, the covariates of age, histological subtypes, and HER2 score were found to be not statistically significant. The mean rank of MAI is similar between patients aged ≤50 and >50 years old (30.16 vs 30.98; *p*-value=0.845), as well as histotypes (ductal and others), with mean rank of 31.68 and 25.79, respectively (*p*-value=0.257). Although not statistically significant, patients aged >50 years old had a slightly higher mean rank of MAI compared to ≤50 years old. Invasive breast carcinoma, no-special type (ICB-NST) was shown to have higher mean rank than other

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types (lobular, sarcoma and other special types, mixed NST and other types).

In addition, HER2 score also showed an insignificant result statistically, therefore, each HER2 score showed a quite similar MAI (mean rank of HER2 score of 0 vs 1+ vs 2+ vs 3+: 30.89 : 25.89 : 45.60 : 27.50; *P*-value=0.119), except for the score of 2+ with mean rank of 45.60, which was higher than the others, although not statistically significant. Overall, HER2 scores of 2+ and 0 were higher than of 1+ and 3+.

The Correlation Between HER2 Score and Mitotic Activity Index

The distribution of clinicopathological characteristics of the patients in this study can be seen in Table 2. In this series of patients with invasive breast carcinoma, mitotic index varied greatly for each patient, ranging from 1 to 46 with the median value being 8 mitotic figures, and a mean of 10.15 mitotic figures per 10 HPF. In addition, almost half of the patients (45.0%) had MAI score of 1 (≤7 mitoses/10 HPF), followed by score of 2 (8-14 mitoses/10 HPF) in 23 patients (38.3%), and score of 3 (≥15 mitoses/10 HPF) in 10 patients (16.7%).

On the other hand, more than half of the patients had HER2 score of 0 or HER2-negative (33 out of 60; 55.0%), and less than one fourth of the patients had HER2 score of 3 or HER2-positive (8 out of 60; 13.3%).

In our study, patients with HER2 score of 0 or HER2-negative had a mitotic index with a mean of 10.79 (MAI score of 2), similar to this, patients with HER2 score of +1, +2, and +3 had a mean of 8.43, 12.60, and 9.00 (MAI score of 2), respectively. The correlation analysis between HER2 scores and MAI values showed no significant correlation was observed between them (r_k = –0.003; 95% CI –0.174 – +0.169; *P* = 0.982; Figure 1).

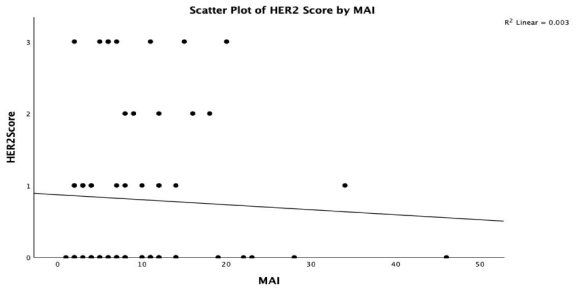


Figure 1. Scatter plot of HER2 score by MAI values.

Multivariate Analyses

Two variables were chosen for the stepwise regression from three available variables based on their crude association at a 25% level of significance. The collinearity and the first-order effect modifier were evaluated first before developing the multivariable ordinal logistic regression mode. In this study, the model adequately fitted the data (goodness-of-fit: deviance=8.198; *p*-value=0.414) and the proportional odds assumption was met (*p*-value=0.250).

After adjustment for histological types and HER2 score, the multivariable ordinal logistic regression (Table 2) rendered HER2 score of 1+, or HER2-low, statistically significant with the estimated odds ratio of 7.45 (95% CI: 1.09–50.78; *P*-value=0.040) which indicated that patients who had HER2 score of 1+ were seven times more likely to be in a higher MAI category compared to HER2 score of 3+ or HER2-positive. On the other hand, neither HER2 score of 0 and 2+ showed statistically significant results compared to HER2-positive, indicating no significant difference between scores of 0, 2+, and 3+.

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In addition, histological types of other types (lobular, sarcoma, mixed of NST and other special types, etc) showed a lower odds of being in the higher MAI category compared to NST (OR=0.31; 95% CI: 0.08–1.23; *P*-value=0.095), although this association was not statistically significant. The thresholds between MAI categories 1 and 2 (≤7 mitoses/10 HPF, and 8-14 mitoses/10 HPF) were significant, indicating a clear distinction between categories 1 and 2 vs 3 (≥15 mitoses/10 HPF).

Table 2. Multivariable ordinal regression analysis of MAI.

Variables	Estimate	OR	S.E	*P*-value	95% CI for OR	
Histotype						
Others	–1.173	0.31	0.703	0.095	0.08	1.23
NST		1				
HER2 score						
0	0.678	0.51	0.775	0.382	0.11	2.32
1+	2.008	7.45	0.979	0.040	1.09	50.78
2+	–0.501	0.61	0.636	0.431	0.17	2.11
3+		1				
Threshold						
MAI=1	–0.482	–	0.369	0.192	–	
MAI=2	1.546		0.439	<0.001		

MAI=mitotic activity index; HER2=human epidermal growth factor receptor-2; OR=odds ratio; S.E=standard error; Parallel line test: 0.250; goodness-of-fit test of overall model: deviance, p-value=0.414; Nagelkerke's R=0.155; S.E: standard error; CI: 95% confidence interval for coefficients

DISCUSSION

Independently, MAI and HER2 score had been proven to be important prognostic factors for patients with invasive breast carcinoma. Especially, HER2 score or HER2 status which showed a pivotal role as the predictive marker of response to anti-HER2 therapy in invasive breast carcinoma. Based on standardized criteria, HER2 immunoexpression is divided into four main groups: 0, 1+, 2+, and 3+, which is reported that HER2 tumors scored of 0 or considered as HER2-negative, do not respond to breast cancer therapy, while HER2 3+ or HER2-positive was associated with strong receptor expression and is highly predictive for drug response. Moderate (2+) and low (1+) HER2 expression also served as negative prognostic survival factors for node-positive breast cancer patients.

Although HER2 positive patients were shown to be most responsive to the therapy, the overexpression of HER2 is highly correlated with high risk of recurrence, short overall survival, and high mortality in invasive breast carcinoma patients through the uncontrolled cell proliferation. Hereby, the HER2 positive is associated with an increased mitotic index.[13] While HER2 overexpression and mitotic activity index are independently recognized as critical prognostic markers in IBC, no prior studies have explored their correlation. This study is the first to investigate this relationship, aiming to enhance our understanding of tumor biology and improve prognostic accuracy. The results indicated no significant correlation between HER2 status and MAI in patients with invasive breast carcinoma (p=0.982). However, in multivariate analyses, patients with HER2 score of 1 (HER2-low) were shown to be seven times more likely to have higher mitotic index (MAI) compared to HER2 score of 3 or HER2 positive (p=0.040). On the contrary, study by Munjal et al showed that HER2 positive patients with infiltrative breast carcinoma were significantly associated with a high mitotic index or >10/ HPF (p<0.05), although this study did not analyze a comparison between HER2 classification.[14]

Currently, the correlation between HER2 status and MAI in invasive breast carcinoma remains undetermined, with no studies looking at the correlation of both prognostic factors. Only one study had analyzed the prognostic value of the combination of HER2 score and MAI in invasive breast carcinoma. Jobsen *et al* demonstrated that the combination of MAI and HER2 status was a strong prognostic factor for DFS and disease-specific survival (DSS), showing worse outcomes for

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HER2-negative tumors with higher MAI (>12) compared to HER2-positive tumors, though it did not establish a direct correlation between the two markers.[15]

The mechanisms of HER2 tumorigenesis are cell growth, survival, differentiation, and migration via PI3K/AKT and Ras/Raf/MEK/MAPK signal transduction pathways. HER2 overexpression causes cells to proliferate rapidly, leading to tumorigenesis in breast, ovary, uterus, lung, stomach, and bladder.[16] Chi et al revealed that HER2 expression was significantly upregulated in non-small cell lung carcinoma (NSCLC) and exhibited a significant positive correlation with the levels of COX-2 mRNA and COX-2 promoter activity. COX-2 is known to be an enzyme associated with tumor invasion and metastasis, especially in NSCLC, through the activation of mitogen-activated protein kinase and extracellular signal-regulated kinase (MEK-ERK) pathway.[17] Other study (Arteaga et al) also revealed that overexpression of HER2 in patients with invasive breast carcinoma lead to aberrant signaling of the MEK/ERK pathway.[18]

This study also showed that other histological subtypes (lobular, other special types, and mixed of NST and other special types) were less likely to have higher mitotic index (MAI) compared to the IBC-NST, although this association was not statistically significant. Previous study also revealed a similar result. The IBC-NST showed a higher mitotic index and histological grade rates compared to invasive lobular special types.[19] Other special types such as papillary carcinoma also showed a low mitotic activity, with a mean of 3 mitoses per 10 HPF (range 0–11).[20] However, the prognosis for patients with IBC-NST is heterogenous and difficult to predict only by mitotic activity. Other prognostic factors such as histological grade, tumor staging, and receptor status, may have a pivotal role in predicting survival rates of patients with invasive breast carcinoma.

This study has several limitations. First, the small sample size of 60 patients may limit the generalizability of the findings and reduce statistical power. Additionally, the study did not account for confounding factors, such as treatment history or hormone receptor status, which could affect both HER2 status and mitotic activity. The retrospective design introduces potential biases due to missing data or lack of control over data collection. Furthermore, the study's results may not be broadly applicable as it was conducted at a single institution. Finally, the predominance of the subject population with HER2 scores of 0 and 1, with few patients having higher HER2 scores. This imbalance may introduce bias, as the study population does not fully represent all HER2 status categories, limiting the generalizability of the findings.

CONCLUSION

The study concluded that there was no significant correlation between HER2 score and MAI in invasive breast carcinoma patients. Despite observing variations in both HER2 status and mitotic activity across the cohort, the analysis did not find a statistically significant correlation between the two prognostic factors. This suggests that HER2 status may not be directly related to mitotic activity in invasive breast carcinoma cases. Further trials with larger sample sizes are needed to confirm these findings and explore potential interactions between HER2 status and its confounding factors influencing tumor proliferation.

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Authors' Contributions

DAH designed the study. DAH and BPR interpreted the laboratory results. DAH, BPR, and JR performed statistical analysis and wrote the manuscripts. All authors contributed to the article and approved the submitted version.

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Ethical Approval and Informed Consent

The study protocol was approved by the Ethics Committee of School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, registration number 21/11/KEP-FKUAJ/2019.

Conflict of Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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