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Original Research

Association of Nuclear Factor-κB Expression with Hormone Receptor Status, HER2, and Histopathological Grade in Advanced Breast Cancer

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Introduction: Breast cancer is a leading cause of cancer-related mortality in women. Nuclear Factor-κB (NF-κB) pathway, is a key driver of carcinogenesis and tumor progression. This study evaluates the association between NF-κB expression and established biomarkers in advanced breast cancer.

Materials and Methods: This prospective, cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital and its network hospitals in Makassar, Indonesia, from April to September 2024. We assessed the association between NF-κB expression (determined by immunohistochemistry) and clinicopathological features in 41 patients with advanced (Stage III and IV) breast cancer. Immunohistochemistry was used to determine the expression of NF-κB, ER, PR, and HER2. Associations were analyzed using Fisher's Exact Test and multivariable logistic regression to calculate odds ratios (OR) with 95% confidence intervals (CI).

Results: A majority of tumors were estrogen receptor (ER)-negative (56.1%), progesterone receptor (PR)-negative (61.0%), and HER2-positive (53.7%). NF-κB positivity was observed in 33/41 patients (80.5%). HER2 positivity was strongly associated with NF-κB positivity (OR = 24.5, 95% CI [2.5, 238.9]; p = 0.012, Fisher's Exact Test). No significant associations were observed with ER, PR, or histopathological grade.

Conclusion: This study identifies a strong and independent association between nuclear NF-κB p65 expression and HER2 positivity in a cohort of patients with advanced (Stage III/IV) breast cancer. Further large-scale, prospective studies are warranted to validate the role of NF-κB as a candidate prognostic biomarker and to explore its utility as a therapeutic target in

HER2-positive breast cancer.

Introduction

Breast cancer is the leading cause of cancer in women [1], with a relatively high mortality rate [2, 3]. Global cancer statistics from 2022 estimated 20 million new cancer cases and approximately 9.7 million cancer-related deaths worldwide [2]. While comprehensive national data on breast cancer incidence in Indonesia are limited, estimates from hospital-based and pathology-based registries indicate there are nearly 20,000 new cases annually, with more than 50% of these cases presenting at an advanced stage [4]. The majority of patients (63%) are diagnosed in stages III and IV, which are clinically classified as advanced breast cancer [5].

The link between chronic inflammation and cancer is well-documented, as inflammatory processes can promote cancer progression. A key molecular mediator in this process is the nuclear factor kappa-light-chain- enhancer of activated B cells (NF-κB), a transcription factor that triggers inflammatory responses contributing to carcinogenesis and tumor growth [6].

In clinical practice, the activation of the NF-κB pathway is of significant interest as it has been implicated as both a prognostic and predictive biomarker. Overexpression of NF-κB is associated with aggressive tumor biology and a poor prognosis in breast cancer [7, 8]. Furthermore, constitutive NF-κB activity has been linked to resistance to standard treatments, including chemotherapy and endocrine therapy [9], making it a critical pathway to understand in advanced, hard-to-treat disease.

While NF-κB interacts with multiple signaling pathways, its crosstalk with the human epidermal growth factor receptor 2 (HER2) pathway is particularly compelling. Preclinical studies have shown that HER2 overexpression can directly activate NF-κB, which in turn promotes the survival and proliferation of HER2- driven cancer cells [9]. This suggests a functional synergy that may be clinically relevant in patients. Although associations between NF-κB and hormone receptors or grade have been explored, a clear understanding of its relationship with HER2 status in a clinical cohort of advanced-stage patients remains a critical knowledge gap. Therefore, the aim of this study was that NF-κB expression would be significantly associated with HER2 positivity in patients with advanced breast cancer. We also sought to explore its association with ER, PR, and histopathological grade in this high-risk population.

Materials and Methods

Study Design

This observational study used a prospective, cross-sectional design to investigate the association between NF-κB expression, hormone receptor status, HER2, and histopathological grade in advanced (Stage III and IV) breast cancer.

Study Setting and Population

The study was conducted at Dr. Wahidin Sudirohusodo Hospital and its network hospitals in Makassar, Indonesia. Sample examination using the immunohistochemical method was carried out in an accredited laboratory. The study’s population consisted of all patients with advanced breast cancer, defined as American Joint Committee on Cancer (AJCC) 8th Edition Stage III or Stage IV [10, 11], treated at these hospitals between April and September 2024.

The inclusion criteria for this study were: (1) women with previously untreated advanced breast cancer; (2) no concurrent metabolic disease, ischemic heart disease, or ischemic cerebrovascular disease; and (3) willingness to participate in the research. The exclusion criteria were:

(1) damaged or non-representative tissue samples; or (2) suffering from other types of cancer.

Variables

The primary biomarker of interest in this study was NF-κB expression. This variable was analyzed for its association with other clinicopathological features, including hormone receptor status (ER and PR) and HER2 status. Confounding variables, including metabolic diseases, ischemic heart disease, and other malignancies, were accounted for through the study's exclusion criteria.

Data Collection

All baseline data, including age, menopausal status, and histopathological grade, were obtained from medical records. All breast tumor tissue samples were collected for clinical and histopathological examination.

Hormonal Status and NF-κB Expression

All breast tumor tissue samples were processed according to standard pathology protocols to ensure biomarker integrity. The cold ischemic time (time from tissue removal to fixation) was kept under 1 hour. Tissues were fixed in 10% Neutral Buffered Formalin (NBF) for 12–24 hours before being processed into formalin- fixed, paraffin-embedded (FFPE) blocks. Sections of 4 µm thickness were cut from each paraffin block for immunohistochemical staining.

Following slide preparation, deparaffinization and hydration were carried out. Subsequently, antigen retrieval was performed using the Heat-Induced Epitope Retrieval (HIER) method by immersing the slides in citrate buffer (pH 6.0) in a water bath pre-heated to 95°C for 30 minutes. Endogenous peroxidase activity was blocked, and slides were incubated with a blocking buffer before the application of primary antibodies.

Immunohistochemistry (IHC) procedures were performed to measure the expression of ER, PR, and HER2. Each staining batch included external positive and negative tissue controls to ensure staining validity. ER and PR expression was considered positive if distinct nuclear staining was detected in ≥1% of tumor cells, using antibodies from GenomeME Lab inc. (Cat. No. IHC423- 100 for ER and Cat. No. IHC751-100 for PR), respectively. The assessment of HER2 status was conducted in accordance with the latest ASCO/CAP guidelines using the HER2/neu antibody (GenomeME Lab inc., Cat. No. IHC042-100). Cases were considered positive for HER2 if they exhibited an IHC score of 3+ (strong, complete, circumferential membrane staining in >10% of tumor cells) and negative for scores of 0 or 1+. All cases showing an equivocal (IHC 2+) score were reflexively evaluated with In Situ Hybridization (ISH) to determine the definitive HER2 gene amplification status.

Of the 41 total samples, 5 cases (12.2%) initially presented with an IHC 2+ (equivocal) score. Following confirmatory ISH testing, 2 of these 5 cases were found to have HER2 gene amplification and were classified as HER2-positive, while the remaining 3 cases were non- amplified and classified as HER2-negative.The final HER2 status for this analysis was determined by the IHC result (for scores of 0, 1+, and 3+) or the ISH result (for initial 2+ scores).

For the detection of NF-κB, we used a rabbit polyclonal antibody targeting the p65 (RELA) subunit (Affinity Biosciences, Cat. No. AF0874), with the evaluation of expression focused exclusively on nuclear staining in tumor cells. Assessment was performed using a validated, semi-quantitative scoring system based on the method by Montagut C, et al. (2006) [12], which involves summing a Percentage Score (Score 0: no stained cells; Score 1: up to 10%; Score 2: 10% to <25%; Score 3: 25% to 50%; Score 4: >50%) and an Intensity Score (Score 0: no staining; Score 1: weak; Score 2: moderate; Score 3: strong). The Final Score was calculated by adding these two components for a total range of 0 to 7. For statistical analysis, expression was classified as either negative (final score of 0–2) or positive (final score of >2). This assessment was independently performed by two pathologists, and any discrepancies in scoring were resolved through consensus discussion.

Image Acquisition and Quantitative Analysis

Slides were examined using an Olympus CX22LED microscope. To prevent field-of-view selection bias, a systematic random sampling approach was employed. Five non-overlapping high-power fields (40x magnification) were systematically selected from the invasive tumor regions. The consistency of this method was confirmed between pathologists (Intraclass Correlation Coefficient = 0.92). Quantitative analysis was performed using ImageJ software (NIH, USA). The pipeline involved Color Deconvolution (H-DAB vector), semi-automated Nuclear Segmentation, and standardized Thresholding to calculate the percentage of positive cells. The final percentage for each sample was the mean of the five fields. A sensitivity analysis confirmed the robustness of using the mean versus the median.

Molecular Subtype and Breast Cancer Grading

The breast cancer molecular subtype was determined based on the IHC evaluation of ER, PR, and HER2. For the purposes of this study's analysis, and because proliferation data (Ki-67) were not uniformly available for the cohort, a simplified surrogate subtyping classification was used. Patients were grouped into two primary categories [13-15]. Luminal (defined as ER and/or PR positive, regardless of HER2 status) and Non-luminal (comprising both the HER2-enriched [ER(-), PR(-), HER2(+)] and Triple-Negative [ER(-), PR(-), HER2(-)] subtypes).

The histopathological grade was determined based on the Nottingham modification of the Bloom-Richardson system [16].

Sample Size

A total of 41 eligible patients were enrolled during the study period. With a fixed sample size of n=41, for a Chi-square test of association, the study achieves 80% power at an alpha level of $\alpha=0.05$ to detect a medium-to-large effect size (Cohen's $w \geq 0.43$). The observed effect size for the association between NF-κB and HER2 was $w = 0.41$, corresponding to an achieved power of approximately 75%.

Data Analysis

The collected data were entered into SPSS 21 (SPSS Inc. Chicago, Ill., USA) for descriptive and inferential analysis. Univariate analysis was used to describe baseline characteristics. Bivariate analysis was performed to assess the association between categorical variables. Fisher's Exact Test was used for all contingency table analyses due to the sample size. A p-value of < 0.05 was considered statistically significant. Odds ratios (OR) with 95% confidence intervals (CI) were

calculated to estimate the effect size for 2x2 associations.

To assess the independent association between HER2 status and NF-κB expression while controlling for potential confounders, a multivariable logistic regression model was constructed. NF-κB positivity (positive vs. negative) was the dependent variable. The model included HER2 status (positive vs. negative) as the primary independent variable, with age group (41–60 as reference), menopausal status, and histopathological grade (Moderate as reference) entered as covariates. Adjusted odds ratios (aOR) and their 95% confidence intervals (CI) were calculated.

Ethical Consideration

The study protocol was approved by the Health Research Ethics Committee of Hasanuddin University, Makassar (No. 198/UN4.6.4.5.31/PP36/2024). All participants provided informed consent.

Results

Baseline Characteristics

A total of 41 participants who met the inclusion criteria were enrolled in the study. All samples were included in the final analysis. Table 1 provides a description of the participant characteristics.

Characteristic		n (%)
Age (years)		
	21–40	7 (17.1)
	41–60	28 (68.3)
	>60	6 (14.6)
Menopausal status		
	Premenopausal	29 (70.7)
	Postmenopausal	12 (29.3)
Histopathological Grade		
	Low	3 (7.3)
	Moderate	30 (73.2)
	High	8 (19.5)
AJCC Stage		
	Stage III	29 (70.7)
	Stage IV	12 (29.3)

Table 1. Characteristic of Study Participants.

The participants were women with advanced breast cancer, with an age range of 33 to 70 years and a mean age of 49.12 ± 8.84 years. The majority of participants (68.3%) were between the ages of 41 and 60, were premenopausal (70.7%), and had intermediate- grade (Grade 2) tumors (73.2%). Based on the AJCC 8th Edition staging system, a majority of patients presented with Stage III disease (70.7%), while the remainder had Stage IV metastatic disease (29.3%).

Biomarker Expression and Association Analyses

Table 2 summarizes the findings of the ER, PR, HER2, and NF-κB tests.

Hormone receptor status	Status	n (%)
ER	Positive	18 (43.9)
	Negative	23 (56.1)
PR	Positive	16 (39.0)
	Negative	25 (61.0)
HER2	Positive	22 (53.7)
	Negative	19 (46.3)
Molecular subtype	Luminal	19 (46.3)
	Non-luminal	22 (53.7)
NF-κB expression	Positive	33 (80.5)
	Negative	8 (19.5)

Table 2. Hormonal Status and NF-κB Expression of Study Participants.

Analysis of the hormone receptor status revealed that the majority of patients had negative ER status (56.1%), negative PR status (62.0%), and positive HER2 status (53.7%). Based on molecular subtypes, 19 patients (46.3%) had luminal subtypes, and 22 patients (53.7%) had non-luminal subtypes. Furthermore, 33 patients (80.5%) had positive NF-κB expression, while eight (19.5%) had negative NF-κB expression. Thus, NF-κB was expressed in the majority of patients with advanced breast cancer.

Bivariate Analysis

The association between clinicopathological variables and NF-κB expression is summarized in Table 3.

Characteristic	NF-κB Positive, n (%)	NF-κB Negative, n (%)	p-value*	Odds Ratio (95% CI)
Menopausal Status			1	0.77 (0.12, 4.7)
Premenopausal	23 (79.3)	6 (20.7)		
Postmenopausal	10 (83.3)	2 (16.7)		
ER			0.713	0.74 (0.16, 3.3)
Positive	14 (77.8)	4 (22.2)		
Negative	19 (82.6)	4 (17.4)		
PR			1	1.08 (0.22, 5.4)
Positive	13 (81.2)	3 (18.8)		
Negative	20 (80)	5 (20)		
HER2			0.012	24.5 (2.5, 238.9)
Positive	21 (95.5)	1 (4.5)		
Negative	12 (63.2)	7 (36.8)		
Molecular subtype			1	0.82 (0.18, 3.7)
Luminal	15 (78.9)	4 (21.1)		
Non-luminal	18 (81.8)	4 (18.2)		

Table 3. Association between Hormonal Status and Molecular Subtypes with NF-κB Expression.

Note, *All p-values were calculated using Fisher's Exact Test. ER, Estrogen Receptor; PR, Progesterone Receptor.

A statistically significant association was found between HER2 status and NF-κB expression (p = 0.012). Patients with HER2-positive tumors had over 24 times the odds of having positive NF-κB expression compared to patients with HER2-negative tumors (OR = 24.5, 95% CI [2.5, 238.9]). No statistically significant associations were observed between NF-κB expression and ER status (p =

0.713), PR status (p = 1.000), menopausal status (p = 1.000), or molecular subtype (p = 1.000).

Further analysis to evaluate the relationship between NF-κB expression and histopathological grade is presented in Table 4.

Histopathological Grade	NF-κB Positive, n (%)	NF-κB Negative, n (%)
Low (Grade 1)	2 (66.7)	1 (33.3)
Moderate (Grade 2)	24 (80.0)	6 (20.0)
High (Grade 3)	7 (87.5)	1 (12.5)
p-value		0.895†
Cramér's V		0.09

Table 4. Association between Histopathological Grade and NF-κB Expression.

Note, †Fisher's Exact Test was used due to cells with an expected frequency <5.

Consistent with our initial findings, no statistically significant association was found between NF-κB expression and histopathological grade (p = 0.895, Fisher’s Exact Test). The very small effect size (Cramér’s V = 0.09) also indicates the absence of a clinically meaningful relationship between these two variables.

Multivariable Logistic Regression Analysis

To determine if the significant association between HER2 and NF-κB expression was independent of other clinicopathological factors, we performed a multivariable logistic regression analysis. The results, presented in Table 5, demonstrate that even after adjusting for age, menopausal status, and histopathological grade, HER2-positive status remained a strong, independent predictor of NF-κB positivity (aOR = 22.8; 95% CI [2.2, 235.1]; p = 0.009).

Variable	Adjusted OR (aOR)	95% CI	p-value
HER2			
Negative	Reference		
Positive	22.8	2.20, 235.1	0.009
Age Group (years)			
41–60	Reference	4 (22.2)	
21-40	0.85	0.12, 5.9	0.871
>60	1.15	0.13, 10.3	0.901
Menopausal Status			
Premenopausal	Reference		
Postmenopausal	0.79	0.13, 4.8	0.803
Histopathological Grade			
Moderate	Reference		
Low	0.91	0.07, 11.5	0.942
High	1.22	0.20, 7.5	0.83

Table 5. Multivariable Logistic Regression Analysis of Predictors for NF-κB Positivity.

Note, OR, Odds Ratio; CI, Confidence Interval. Reference categories are used for comparison.

None of the other covariates showed a significant independent association with NF-κB expression.

Discussion

In this prospective, cross-sectional study of 41 patients with advanced breast cancer in Indonesia, we identified a strong, independent association between nuclear NF-κB p65 expression and HER2 positivity. This finding remained robust even after controlling for potential confounders, suggesting a significant biological relationship between these two pathways in aggressive disease. The patient age ranged from 33 to 70 years, with a mean of 49.12 ± 8.84 years. The majority of cases (68.3%) occurred in the 41–60 year age group. This is consistent with previous research from Makassar, which reported the peak incidence of breast cancer between the ages of 50 and 60 (41.9%) [17]. Breast cancer is an illness that predominantly affects older women; its incidence rises with age. This phenomenon is related to the biological effects of aging, where cellular senescence and weakened DNA repair capacity can lead to genetic instability in stem cells, contributing to cancer formation [18].

This study's advanced breast cancer cases occurred mainly in premenopausal women (70.7%). This may be linked to breast density, as premenopausal women typically have denser breast tissue, which contains more glandular and stromal elements and is associated with stromal fibrosis and epithelial proliferation, known risk factors for breast cancer [19].

The examination of hormone receptor status showed that most patients had negative ER (56.1%) and PR (62.0%) status but positive HER2 status (53.7%). The expression of ER, PR, and HER2 are crucial biomarkers for determining the optimal course of treatment [20]. ER- and PR-negative status is associated with a worse prognosis. This phenotype is more common in patients with BRCA1 mutations and is linked to higher grade tumors and increased cell proliferation. Hormone receptor negativity and HER2 overexpression are markers of a poor prognosis, necessitating more intensive treatment strategies [21]. Consequently, the predominance of HER2-positive cases in this study cohort is indicative of aggressive disease.

Regarding molecular subtypes, 46.3% of patients had luminal subtypes, while 53.7% had non-luminal subtypes. The luminal B subtype, characterized by a higher proliferative index (Ki-67), is associated with a more aggressive phenotype and poorer prognosis compared to the Luminal A subtype.

In this study, 80.5% of participants showed positive NF-κB expression. This finding is consistent with a study conducted in Bali, which found that 65% of breast cancer patients had overexpressed NF-κB [6]. That study also found that hormonal status (premenopausal vs. postmenopausal) was not related to NF-κB levels, which aligns with the findings of our study.

The most significant finding of our study is the magnitude of the HER2–NF-κB association. Our multivariable analysis revealed that HER2-positive tumors had over 20 times the odds of being NF-κB positive compared to HER2-negative tumors (aOR ≈ 22.8). This large effect size underscores a clinically relevant link. However, the wide 95% confidence interval [2.2, 235.1] reflects the modest sample size and calls for caution in interpreting the precise point estimate. This finding is biologically plausible, as the HER family of receptors is known to activate the NF-κB pathway through downstream signaling cascades like PI3K/AKT and MAPK, which in turn promotes cell survival, proliferation, and resistance to therapy [22, 23]. Our clinical data provide support for this well-established preclinical crosstalk. In contrast, we did not find a significant association between NF-κB and hormone receptor status or histopathological grade in our multivariable model.

This study has several limitations that must be acknowledged. First, the study's cross-sectional design precludes any assessment of causality between NF-κB expression and clinicopathological features; it only establishes an association. Second, its single-center design and modest sample size (n=41) may limit the generalizability of our findings and reduce the statistical power for detecting weaker associations. Third, our inclusion criteria excluded patients with common comorbidities,

which could introduce a selection bias. Fourth, the lack of uniformly collected Ki-67 data prevented a more granular molecular subtyping (i.e., distinguishing Luminal A from Luminal B), which limits the interpretability of the simplified “Luminal” category. Furthermore, while our multivariable analysis provides important insights, the results should be interpreted with caution given the relatively modest sample size, which can limit the statistical power and precision of the adjusted estimates.

In conclusion, this study identifies a strong and independent association between nuclear NF-κB p65 expression and HER2 positivity in a cohort of patients with advanced (Stage III/IV) breast cancer. These findings are hypothesis-generating and underscore the potential biological synergy between the HER2 and NF-κB pathways in driving aggressive disease. Further large-scale, prospective studies are warranted to validate the role of NF-κB as a candidate prognostic biomarker and to explore its utility as a therapeutic target in HER2-positive breast cancer.

Acknowledgments

Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study’s data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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