RESEARCH ARTICLE

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Expression of Survivin and *HER-2* as Independent Predictive Factors for Treatment Response in Locally Advanced Breast Cancer: A Prospective Cohort Study

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Abstract

Background: Locally advanced breast cancer (LABC) requires a multimodal approach, often starting with neoadjuvant chemotherapy (NACT) to reduce tumor size. However, response to NACT in LABC is highly variable. Predictive biomarkers such as *HER-2* and Survivin may have the potential to predict treatment response and prognosis. This study aims to analyze the relationship between Survivin and *HER-2* expression and the clinical response to NACT in LABC patients. **Methods:** In this prospective cohort study, we enrolled 56 female LABC patients scheduled for a Taxane, Adriamycin, and Cyclophosphamide NACT regimen. Pre-treatment biopsy tissues were examined for Survivin and *HER-2* expression via immunohistochemistry. Clinical response was evaluated after three cycles using the RECIST criteria. Data were analyzed using the Chi-Square test and multivariate logistic regression. **Results:** High Survivin expression was found in 32/56 (57.1%) participants and positive *HER-2* expression in 28/56 (50%). A significant correlation was found between high Survivin expression and *HER-2* positivity (p=0.007). High Survivin expression (p<0.001; PR=4.688; 95% CI: 1.881–11.682) and *HER-2* positivity (p<0.001; PR=5.585; 95% CI: 2.227–14.012) were significantly associated with poor chemotherapy response (non-response). Multivariate analysis showed that Survivin (OR=0.032; p=0.002) and *HER-2* (OR=0.022; p=0.001) were significant independent predictors of chemotherapy response. **Conclusion:** Survivin and *HER-2* expression are significantly associated and serve as independent predictors of poor response to NACT in LABC patients. Evaluation of these biomarkers could be crucial in risk stratification and the personalization of therapy.

Keywords: Breast Neoplasms- Neoadjuvant Chemotherapy- Survivin- *HER-2* Receptors- Predictive Biomarkers

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Introduction

Breast cancer is the malignancy with the highest incidence in women, both globally and in Indonesia, posing a significant public health challenge [1, 2]. Local data in Makassar show breast cancer as the cancer with the highest incidence and the second leading cause of death [3]. A particularly challenging subgroup in management is locally advanced breast cancer (LABC), characterized by tumor infiltration into surrounding tissues and a high risk of recurrence [4, 5]. The standard management strategy for LABC is neoadjuvant chemotherapy (NACT), which aims to reduce tumor size (downsizing), thereby enabling breast-conserving surgery or surgery with tumor-free margins [5, 6].

The success of NACT, often measured by clinical or pathological response, varies widely among patients [7]. Therefore, identifying reliable predictive biomarkers is critical for selecting patients who are most likely to benefit from NACT and for guiding therapeutic decisions [5, 7, 8].

Human Epidermal Growth Factor Receptor 2 (*HER-2*) is an established prognostic and predictive biomarker. *HER-2* overexpression correlates with aggressive tumor behavior but also serves as a target for specific therapies that can increase the pathological complete response (pCR) rate when combined with chemotherapy [9–11]. In addition to *HER-2*, Survivin, a member of the inhibitor of apoptosis (IAP) family, has emerged as a promising biomarker [12–14]. Survivin regulates cell division and inhibits apoptosis and is frequently overexpressed in breast cancer, where it is hypothesized to confer resistance to chemotherapy [15, 16]. Survivin overexpression is hypothesized to contribute to cancer cell resistance to chemotherapy. Several studies have shown a correlation

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between Survivin expression and poor therapeutic response, although the results remain inconsistent [17, 18].

Given the limited scientific evidence examining the simultaneous relationship between Survivin and *HER-2* with NACT response, this study aims to assess the association of these two biomarkers with the clinical response to NACT in LABC patients.

Materials and Methods

Study Design and Duration

This study employed an analytical observational design with a prospective cohort approach. Data collection was conducted from January to April 2025.

Study Location

The study was conducted on patients treated at the Dr. Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital, Makassar, Indonesia. Immunohistochemistry (IHC) for Survivin and *HER-2* expression was performed at the Anatomic Pathology Laboratory, Faculty of Medicine, Hasanuddin University Hospital, Makassar, Indonesia.

Population and Sample

The target population included all LABC patients undergoing NACT. The study sample was a subset of the target population that met the inclusion and exclusion criteria during the research period. The minimum sample size was calculated using a hypothesis test formula for two proportions, resulting in 54 samples. A total of 56 participants were successfully recruited for this study.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) Female patients diagnosed with LABC scheduled for NACT with the Taxane, Adriamycin, and Cyclophosphamide regimen; (2) Availability of paraffin-embedded tissue blocks from pre-NACT incisional biopsy. Exclusion criteria were: (1) Patients with metastatic or early-stage breast cancer; (2) A history of other malignancies; (3) Paraffin blocks that were not representative for IHC examination.

Bias Mitigation

To ensure the validity of our findings, several measures were implemented. Selection bias was minimized through a consecutive sampling method, enrolling all patients who met the predefined inclusion criteria. To address information bias, pathologists interpreting the IHC slides for Survivin and *HER-2* were blinded to the patients' clinical outcomes. Potential confounding bias was addressed in the analytical stage via multivariate logistic regression to identify independent predictors of NACT response.

Procedures and Variables

Pre-treatment incisional biopsy tissues were processed for IHC analysis. LABC was defined as stage III disease according to the AJCC 8th edition [19].

HER-2 Expression

Assessed by IHC based on the ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) recommendation [20]. Scores of 0 and 1+ were categorized as negative. A score of 3+ was categorized as positive. A score of 2+ (equivocal) required confirmation by in situ hybridization (ISH), where a positive ISH result was categorized as *HER-2* positive and a negative ISH as *HER-2* negative. For analysis, a binary grouping (positive and negative) was used.

Survivin Expression

Assessed semi-quantitatively based on staining intensity (0=negative, 1=weak, 2=moderate, 3=strong) and the percentage of stained tumor cells (<10%, 10-50%, >50%) [21]. A final score was calculated and categorized as low or high expression.

Chemotherapy Response

Clinically evaluated after 3 cycles of NACT using RECIST 1.1 criteria [22, 23]. Response was categorized as: (1) Response, including Complete Response and Partial Response; (2) Non-response, including Progressive Disease and Stable Disease.

Data Collection and IHC Procedure

After obtaining ethical approval and informed consent from patients, demographic and clinical data were recorded. Biopsy tissue obtained before NACT was processed into paraffin blocks. Sections of 4 µm thickness from the paraffin blocks were placed on poly-L-lysine-coated slides for IHC examination.

IHC staining for Survivin used the primary Rabbit Monoclonal Anti-Human Survivin Antibody from Epitomics Inc. (Burlingame, CA, USA; catalog no. AC-0113RUO) with a polymer-based detection system. The process included deparaffinization, rehydration, heat-induced antigen retrieval, endogenous peroxidase blockade, incubation with primary and secondary antibodies and a polymer-peroxidase complex, and visualization with Diaminobenzidine and Hematoxylin-eosin counterstain. A similar procedure was performed for *HER-2* with a specific antibody.

Data Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to present sample characteristics. The Chi-Square test was used for bivariate analysis to assess the relationship between categorical variables (Survivin expression, *HER-2*, chemotherapy response). Multivariate logistic regression analysis was performed to identify independent predictors of chemotherapy response. The level of statistical significance was set at $p<0.05$.

Ethical Approval

This research obtained approval from the Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, with letter number 60/UN4.6.4.5.31/PP36/2025, on January 3, 2025.

Results

Participant Characteristics

A total of 62 patients were screened for eligibility, of whom 56 met the inclusion criteria and were enrolled in the study (Figure 1). The majority of patients were in the 50–69 age group (n=27, 48.2%). The most common histopathological type was Invasive Carcinoma of No Special Type (n=49, 87.5%), and most tumors were histopathological grade III (n=29, 51.8%). Of the 56 patients, 29 (51.8%) were categorized as non-responsive to NACT. *HER-2* status was evenly distributed between positive and negative (n=28 each, 50%). Complete characteristics are presented in Table 1.

Distribution and Association of Biomarker Expression

High Survivin expression was detected in 32 of 56 samples (57.1%) (Figure 2). Analysis of the relationship between Survivin expression and *HER-2* status showed that high Survivin expression was significantly more frequent in the *HER-2* positive group (65.6%) compared to the *HER-2* negative group (34.4%), with p=0.007 (Table 2). No significant association was found between Survivin expression and histopathological grading (p=0.189).

Association of Biomarkers with Neoadjuvant Chemotherapy Response

Bivariate analysis revealed a highly significant association between *HER-2* status and chemotherapy response. Patients with positive *HER-2* had a much higher proportion of non-response (85.7% vs. 17.9%) compared to *HER-2* negative patients. *HER-2* positive patients had a 5.58-fold greater risk of not responding to chemotherapy (p<0.001; PR=5.585; 95% CI: 2.227–14.012) (Table 3).

Similarly, high Survivin expression was significantly associated with a poor therapeutic response. A total of 78.1% of patients with high Survivin expression did not respond to chemotherapy, compared to only 16.7% in the low Survivin expression group. Patients with high Survivin expression had a 4.68-fold greater risk of non-response (p<0.001; PR=4.688; 95% CI: 1.881–11.682) (Table 4).

Multivariate Analysis

To determine if Survivin and *HER-2* were independent predictors, a multivariate logistic regression analysis was performed. The multivariate logistic regression analysis demonstrated that high Survivin expression (Adjusted OR=0.032; 95% CI: 0.003–0.298; p=0.002) and *HER-2* positivity (Adjusted OR=0.022; 95% CI: 0.002–0.195; p=0.001) were independent factors that significantly decreased the odds of achieving a therapeutic response. This regression model demonstrated a classification accuracy of 83.9%.

Discussion

This study investigated the role of the biomarkers Survivin and *HER-2* in predicting clinical response to NACT in LABC patients. The main finding is that high expression of both proteins is significantly and independently associated with a poor therapeutic response. This result provides important insights into the mechanisms of chemotherapy resistance and underscores the potential of these biomarkers in patient risk stratification before initiating therapy.

The demographic characteristics of our sample, with a peak incidence in the 50-69 age group, align with established global and national epidemiological data. Reports from GLOBOCAN 2022 and other studies consistently show that the risk of breast cancer substantially increases after the age of 50 [2].

A key finding of this research is the significant association between high Survivin expression and positive *HER-2* status (p=0.007). This is not merely a statistical correlation but reflects a biological synergy underlying tumor aggressiveness. Previous studies by Youssef et al. [24] and Luh Dewi et al. [25] also reported that Survivin expression tends to be higher in more aggressive molecular subtypes, such as *HER-2* positive and triple-negative. Mechanistically, overexpression of the *HER-2* protein triggers constant activation of the PI3K/AKT intracellular signaling pathway, a major regulator of cell survival [26]. This active PI3K/AKT pathway is then known to suppress pro-apoptotic transcription factors like Forkhead box O and inhibit the function of the p53 tumor suppressor. This suppression ultimately leads to increased transcription of the BIRC5 gene, which encodes Survivin [27]. Thus, the co-expression of Survivin and *HER-2* creates a "vicious cycle" where pro-survival and anti-apoptotic pathways reinforce each other, resulting in a tumor phenotype that is highly resistant to chemotherapy-induced cell death.

The independent predictive role of Survivin and *HER-2* is the most crucial finding of this study. Patients with high Survivin expression showed a nearly five-fold greater risk of not responding to NACT (PR=4.688). This result is highly consistent with research by Primariadewi et al. [17, 18], who also identified Survivin expression as an independent predictor of poor chemotherapy response. As a member of the IAP family, Survivin functions by inhibiting the primary effectors of apoptosis, such as caspase-3 and caspase-7. Given that most cytotoxic chemotherapeutic agents, including the TAC regimen used in this study, work by inducing DNA damage that triggers the apoptotic pathway, high Survivin expression effectively neutralizes the drug's mechanism of action. This explains why cancer cells with high Survivin levels can survive despite exposure to chemotherapeutic agents, which clinically manifests as a non-shrinking or even progressive tumor.

Similarly, positive *HER-2* status, in the context of this study where patients did not receive anti-*HER-2* targeted therapy, proved to be a strong predictor of poor response (PR=5.585). This finding reaffirms the highly aggressive biological nature of *HER-2* positive breast cancer. Without blockade by drugs like Trastuzumab or Pertuzumab, the hyperactive *HER-2* signaling pathway continuously drives cell proliferation, invasion, and angiogenesis, thereby "overpowering" the cytotoxic effects of conventional chemotherapy. Therefore, in a non-targeted therapy setting, positive *HER-2* status serves as a marker of poor

prognosis and a predictor of poor response.

It is important to contextualize these findings within our treatment setting. While the TAC regimen is less frequently used in centers with routine access to newer targeted agents, it remains a relevant and standard chemotherapy backbone in many healthcare systems globally, including Indonesia. Our results on the predictive value of *HER-2* in this specific context powerfully underscore the profound impact of this oncogene on chemotherapy resistance and highlight the critical need to expand access to anti-*HER2* therapies in similar settings.

Clinical Implications and Future Research Directions

Clinically, the findings of this study have significant implications. Pre-treatment assessment of Survivin and *HER-2* expression could be used as a risk stratification tool to identify LABC patients with a high probability of failing standard NACT. Patients with a "high-risk" profile (high-Survivin and/or *HER-2*-positive) may require a different therapeutic approach. They could be prime candidates for de-escalation (if the initial response is poor, to avoid futile toxicity) or therapy escalation, such as the addition of experimental agents in clinical trials, including Survivin inhibitors currently under development.

Strengths and Limitations of the Study

The main strength of this study lies in its prospective cohort design and the use of data from an oncology referral center in Makassar, making it a relevant pilot study for the local population. However, several limitations should be acknowledged to ensure a balanced interpretation of the findings. First, the evaluation of therapeutic response solely by clinical caliper measurement after three NACT cycles is subjective and less precise than modern imaging methods (Computed Tomography scan or Magnetic resonance imaging) or the gold standard of pCR assessment after completion of all chemotherapy cycles and surgery. Second, although standardized protocols were applied, IHC assessment inherently involves an element of inter-observer subjectivity. Furthermore, as this study was conducted in tertiary referral centers in Makassar, Indonesia, the patient population may possess specific demographic and genetic characteristics; therefore, caution is warranted when generalizing these findings to other ethnic populations until validation is achieved in larger, multi-center international cohorts.

Future research should focus on validating these findings in larger and more diverse populations. Specifically, subsequent studies should investigate the correlation between Survivin and *HER-2* expression and pCR, as pCR represents a more reliable surrogate for long-term outcomes. Moreover, tracking patient outcomes such as disease-free survival and overall survival will provide more definitive evidence of the prognostic value of these biomarkers. Finally, exploring the role of Survivin in other breast cancer subtypes and at different disease stages (early or metastatic) constitutes a promising direction for future investigation.

In conclusion, high Survivin and *HER-2* expression are powerful, independent predictors of poor response to NACT in LABC. Their significant co-expression suggests a shared biological mechanism driving therapeutic resistance. Integrating the pre-treatment assessment of these biomarkers into practice is a promising strategy for risk stratification, potentially enabling the personalization of therapy to improve outcomes for patients with this challenging disease.

Author Contribution Statement

SWB (Concept, Design, Resources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Writing Manuscript), ID (Concept, Design, Supervision, Analysis and Interpretation, Literature Search), ES (Concept, Design, Supervision, Analysis and Interpretation, Literature Search), JP (Concept, Design, Supervision, Analysis and Interpretation, Literature Search), DJF (Concept, Design, Supervision, Analysis and Interpretation, Literature Search), SAS (Concept, Design, Supervision, Analysis and Interpretation, Literature Search), and MF (Concept, Design, Analysis and Interpretation, Critical Review). All authors read and approved the final version of the manuscript.

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Data availability statement

The data presented in this study are available on request from the corresponding author.

Ethics approval

All research designs were reviewed and approved by the Health Research Ethics Committee of Dr Wahidin Sudirohusodo Hospital – Faculty of Medicine, Hasanuddin University (letter no. 60/UN4.6.4.5.31/PP36/2025).

Competing interests

No competing interests were reported.

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