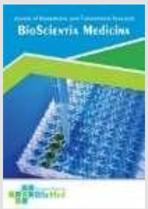
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine &
Translational Research

Journal Homepage: www.bioscmed.com

Menopausal Status as the Strongest Independent Predictor of Neoadjuvant Chemotherapy Response in Locally Advanced Breast Cancer

Stephen William Soeseno[1*], I Wayan Sudarsa[2], Ni Gusti Ayu Agung Manik Yuniawaty Wetan[2]

[1]General Surgery Resident, Department of Surgery, Prof. Dr. I.G.N.G. Ngoerah General Hospital/Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

[2]Oncology Surgery Division, Department of Surgery, Prof. Dr. I.G.N.G. Ngoerah General Hospital/Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

ARTICLE INFO

Keywords:
Breast cancer
Chemotherapy response
Menopausal status
Neoadjuvant chemotherapy
Predictors

***Corresponding author:**
Stephen William Soeseno

E-mail address:
stevewilliam2025@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i6.1621

ABSTRACT

Background: Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced breast cancer (LABC), yet predicting individual patient response remains challenging. This study investigates menopausal status and other clinicopathological factors as predictors of NAC response in a Southeast Asian population. **Methods:** This retrospective cohort study analyzed 247 LABC patients treated with NAC between 2022–2023 at the Oncology Surgery Division, Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali. Variables included menopausal status (premenopausal vs. postmenopausal), histological type, histological grading, molecular subtype, lymphovascular invasion (LVI), tumor-infiltrating lymphocytes (TIL), and age. Bivariate analysis used chi-square tests; multivariate logistic regression identified independent predictors. **Results:** Among 247 patients (mean age 51.7 ± 9.1 years), 130 (52.6%) achieved positive response. Postmenopausal patients demonstrated significantly higher response rates (79.7% vs. 12.1%, $p<0.001$). Multivariate analysis revealed menopausal status as the strongest predictor (OR=14.999, 95%CI: 6.045–37.213, $p<0.001$), followed by molecular subtype (OR=4.182, $p=0.006$), histological grading (OR=3.596, $p=0.010$), and histological type (OR=0.367, $p=0.017$). Age, LVI, and TIL lost statistical significance in the multivariate model. **Conclusion:** Menopausal status emerged as the strongest independent predictor of NAC response in LABC, suggesting that hormonal factors play a pivotal role in chemotherapy sensitivity. These findings support more aggressive NAC regimens or combined endocrine-cytotoxic strategies for postmenopausal patients and warrant validation in prospective Southeast Asian cohorts.

1. Introduction

Breast cancer remains the leading cause of cancer-related mortality among women worldwide, with approximately 2.3 million new cases and 685,000 deaths reported annually by the Global Cancer Observatory (GLOBOCAN 2020).[1] In Southeast Asian countries, including Indonesia, breast cancer incidence and mortality rates continue to rise, often presenting at advanced stages due to delayed diagnosis and limited access to screening programs.[2] Locally advanced breast cancer (LABC), defined as stage IIIA–IIIC disease according to the American Joint Committee on Cancer (AJCC) TNM staging system, represents 10–40% of all breast cancer cases in developing countries and carries a significantly poorer prognosis compared to early-stage disease.[3] The five-year overall survival for LABC patients remains approximately 40–50% despite multimodal therapy, compared to 85–90% for stage II disease, underscoring the urgent need for improved therapeutic strategies and predictive biomarkers.[4]

Neoadjuvant chemotherapy (NAC) has become the standard treatment approach for LABC, offering multiple clinical and biological advantages.[5] From a clinical perspective, NAC enables tumor downstaging to facilitate surgical resection and improve cosmetic outcomes, potentially converting unresectable tumors into resectable disease. Biologically, NAC provides a unique opportunity to assess individual tumor chemotherapy sensitivity through pathological response evaluation, enabling personalized treatment intensification or modification strategies based on observed response patterns. The achievement of pathological complete response (pCR), defined as the absence of invasive carcinoma in the surgical specimen at the time of definitive operation, has emerged as a strong surrogate marker for improved disease-free and overall survival outcomes in most breast cancer molecular subtypes.[6] The Responder HER2 Breast Cancer Study (RESPONDER) and other pivotal trials, including GeparSixto, GeparQuattro, and ANTHEC have demonstrated that patients achieving pCR to NAC experience substantially better long-term outcomes, with pCR rates serving as a primary efficacy endpoint in NAC clinical trials.[7,8]

However, approximately 40–50% of LABC patients do not achieve meaningful pathological response, exposing them to significant chemotherapy toxicity without proportional therapeutic benefit.[9] These non-responders experience unnecessary toxicity-related morbidity, treatment delays, and lost therapeutic opportunities where alternative approaches might have been more effective. Furthermore, prolonged chemotherapy administration in non-responsive tumors allows biological progression, potential treatment resistance evolution, and delays in definitive surgical management. The substantial financial burden of ineffective NAC administration is particularly problematic in resource-limited Southeast Asian healthcare systems, where chemotherapy costs represent major out-of-pocket expenses for families.[10]

The ability to prospectively identify NAC responders versus non-responders carries profound clinical and economic implications. Responder prediction would allow clinicians to provide early reassurance to responders regarding continued chemotherapy administration, while enabling early recognition of non-responders for treatment modification, alternative therapeutic escalation, or transition to novel approaches. Currently, clinical prediction models rely on traditional clinicopathological factors, including patient age, tumor grade, histological type, molecular subtype (luminal, HER2-enriched, triple-negative), and emerging biomarkers such as lymphovascular invasion (LVI) status and tumor-infiltrating lymphocytes (TIL) count.[11]

Menopausal status represents a fundamental biological characteristic reflecting the hormonal microenvironment and potentially influencing chemotherapy sensitivity through multiple interconnected mechanisms. Estrogen and progesterone signaling can modulate drug metabolism enzyme expression, DNA repair pathway activation, and tumor microenvironment immune composition.[12] Age-related changes in pharmacokinetics and pharmacodynamics can significantly impact chemotherapy efficacy. Postmenopausal status correlates with altered genomic stability, telomere dynamics, and cellular aging features that may render tumor cells more vulnerable to chemotherapy-induced apoptosis. Despite these theoretical mechanistic considerations, menopausal status has received surprisingly limited attention as a predictor of NAC response in the international medical literature.[13] A systematic review of major NAC trials and published research reveals that while demographic data, including age and menopausal status, are typically collected, menopausal status is rarely analyzed as a primary predictor variable. This represents a critical knowledge gap, particularly in Southeast Asian populations where breast cancer epidemiology differs substantially from Western cohorts with higher proportions of premenopausal diagnoses and potentially different hormone receptor distribution patterns.[14]

This retrospective cohort study was designed to identify independent predictors of NAC response in a large Southeast Asian LABC cohort and specifically determine whether menopausal status serves as a significant predictor variable. Secondary objectives included characterizing the relative importance of clinicopathological factors in predicting chemotherapy response, describing NAC outcomes and response patterns in a single Indonesian comprehensive cancer center, and providing preliminary evidence to guide larger prospective validation studies. We hypothesize that menopausal status will emerge as a statistically significant and clinically meaningful independent predictor of NAC response, potentially superior to or equal to traditional factors such as age or molecular subtype.

2. Methods

Study design and setting

This retrospective cohort study analyzed all consecutive patients with locally advanced breast cancer (LABC) treated with neoadjuvant chemotherapy at the Oncology Surgery Division, Department of Surgery, Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, Indonesia—the largest and most comprehensive cancer treatment center serving the eastern Indonesian region, including Bali, Lombok, Sumbawa, Flores, and West Nusa Tenggara provinces. The hospital's comprehensive Cancer Registry provides a systematic collection of clinical, pathological, imaging, and treatment data for all breast cancer patients managed through multidisciplinary tumor board consultation, including surgical oncology, medical oncology, radiation oncology, pathology, radiology, and supportive care specialties.

Study population and time period

All consecutive patients with histologically confirmed LABC (TNM stages IIIA, IIIB, or IIIC according to AJCC 8th edition classification[15]) who received neoadjuvant chemotherapy between January 2022 and December 2023 were eligible for inclusion. The study period was selected to allow adequate follow-up time while capturing contemporary treatment practices. Inclusion criteria were: (1) age ≥18 years at diagnosis; (2) newly diagnosed LABC without prior chemotherapy or hormonal therapy; (3) completion of NAC with minimum three cycles of anthracycline-based or taxane-based chemotherapy regimens; (4) definitive surgical resection (total mastectomy or breast-conserving surgery) performed within 4–8 weeks following completion of NAC; (5) available baseline and post-NAC tumor characteristics for response assessment; (6) complete pathological examination of surgical specimen with adequate residual disease documentation; (7) complete follow-up data for minimum 6 months post-NAC. Exclusion criteria included: (1) metastatic disease (stage IV) at diagnosis; (2) prior malignancy within 5 years or synchronous second cancer; (3) incomplete NAC course due to treatment toxicity or patient non-compliance; (4) pregnancy or lactation status; (5) significant comorbidities precluding treatment completion including cardiac dysfunction, active infections, or organ failure; (6) missing essential clinicopathological data preventing analysis; (7) secondary malignancies developing during follow-up period.

Variable definitions and measurement

The dependent variable was neoadjuvant chemotherapy response, dichotomized as positive response versus negative response based on standardized criteria. Positive response was defined as: (1) partial response achieving ≥30% tumor reduction in maximum tumor diameter measured by RECIST 1.1 criteria[16] on repeat imaging following 3–4 cycles of NAC, or (2) pathological partial response at definitive surgery characterized as ypT1ypN0 or lower residual disease burden compared to baseline presentation, or (3) pathological complete response defined as complete absence of invasive carcinoma in the surgical specimen with residual ductal carcinoma in situ allowed. Negative response was defined as: (1) stable disease with <30% tumor reduction, (2) progressive disease with tumor size increase ≥20%, or (3) substantial residual disease at surgery with ypT2–4 or residual axillary nodal involvement.

Independent variables included: (1) Menopausal status classified as premenopausal (age <50 years with regular menstrual periods and FSH <30 mIU/mL, or any age with menses in preceding 12 months) versus postmenopausal (age ≥50 years with cessation of menses ≥12 months, or any age with FSH >30 mIU/mL without menses in preceding 12 months); (2) Histological type classified as NST/Invasive Ductal Carcinoma (IDC), the most common type, versus other special types including invasive lobular carcinoma, mucinous carcinoma, papillary carcinoma, medullary carcinoma, and tubular carcinoma; (3) Histological grading using Nottingham grading system dichotomized as low grade (Grades 1–2) versus high grade (Grade 3) based on extent of cellular differentiation and mitotic rate; (4) Molecular subtype classification based on hormone receptor and HER2 status: Luminal A/B (ER/PR positive regardless of HER2 status) versus Non-luminal including HER2-enriched (ER/PR negative, HER2 3+ or FISH amplified) and Triple-negative breast cancer (ER/PR/HER2 all negative) per ASCO guidelines; (5) Lymphovascular invasion (LVI) assessed from histopathology as presence or absence of neoplastic cells within lymphatic channels or blood vessel lumens; (6) Tumor-infiltrating lymphocytes (TIL) quantified as percentage of mononuclear immune cells in tumor stroma, dichotomized as low (<20%) versus high (≥20%) per international consensus guidelines[17]; (7) Age measured in years at diagnosis, analyzed both continuously and dichotomized at <40 versus ≥40 years for stratified analyses.

Ethical approval and data management

This study received formal approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Udayana and Prof. Dr. I.G.N.G. Ngoerah General Hospital Institutional Ethics Committee in April–May 2024 with approval number 2024/EC/FK-UNUD. All data were de-identified and assigned unique numerical patient identifiers with the master list maintained separately in secure, locked storage. Patient informed consent was waived given the retrospective observational nature of the study and complete de-identification of all records, with approval of the ethics committee. All data were entered into a secure REDCap (Research Electronic Data Capture) database with password protection, encrypted connection protocols, and role-based access controls. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational research.[18,19]

Statistical analysis

Baseline characteristics and clinicopathological variables were summarized using descriptive statistics. Continuous variables were expressed as mean ± standard deviation with Kolmogorov–Smirnov testing for normality assumption assessment; categorical variables were expressed as frequencies and percentages. Univariate bivariate analysis employed Pearson's chi-square test for independence (or Fisher's exact test when expected cell frequencies were <5) to compare proportions of response across categorical variables, calculating crude odds ratios (OR) with 95% confidence intervals (CI). Multivariate logistic regression using the backward stepwise likelihood ratio elimination method was employed to identify independent predictors of NAC response while simultaneously controlling for potential confounding variables. Variables meeting $p<0.05$ threshold in univariate analysis were entered into the multivariate model. Backward elimination sequentially removed variables with the highest p-value until all remaining variables achieved statistical significance at $p<0.05$. Assumptions of multicollinearity were assessed using the variance inflation factor (VIF), with VIF >3.0 considered evidence of problematic multicollinearity. Model fit quality was evaluated using the Hosmer–Lemeshow goodness-of-fit test with a non-significant result ($p>0.05$) indicating adequate model calibration. The proportion of variance explained by the multivariate model was estimated using Nagelkerke

R^2. All reported p-values were two-tailed with a statistical significance threshold set at α=0.05. SPSS version 25.0 (IBM Corp., Armonk, New York) was used for all statistical analyses.

3. Results

Baseline characteristics

The study cohort comprised 247 LABC patients treated with neoadjuvant chemotherapy between 2022 and 2023.[20] Demographic analysis revealed a mean age of 51.7 ± 9.1 years with non-normal distribution confirmed by the Kolmogorov–Smirnov test (p=0.002), indicating right-skewed age distribution. Age stratification showed 56 patients (22.7%) were younger than 40 years, and 191 patients (77.3%) were 40 years or older. The cohort included 99 premenopausal patients (40.1%) and 148 postmenopausal patients (59.9%). Histological type analysis demonstrated NST/IDC histology in 136 patients (55.1%), with 111 patients (44.9%) having non-NST special type tumors. Grade distribution by Nottingham system showed 168 patients (68.0%) with low-grade tumors (Grade 1–2) and 79 patients (32.0%) with high-grade disease (Grade 3). Molecular subtype classification identified 51 luminal patients (20.6%) and 196 non-luminal patients (79.4%). Lymphovascular invasion was present in 201 patients (81.4%) and absent in 46 (18.6%). Tumor-infiltrating lymphocyte evaluation showed high levels (≥20%) in 192 patients (77.7%). TNM stage distribution comprised 91 patients (36.8%) with stage IIIA, 129 patients (52.2%) with stage IIIB, and 27 patients (10.9%) with stage IIIC disease. Overall, 130 patients (52.6%) achieved a positive response, and 117 patients (47.4%) failed to achieve a meaningful chemotherapy response. Table 1 presents comprehensive baseline characteristics.

Table 1. Baseline demographic and clinicopathological characteristics of 247 LABC patients receiving neoadjuvant chemotherapy.

Characteristics	n (%) or Mean±SD
Age (years)	51.7 ± 9.1
<40 years	56 (22.7)
≥40 years	191 (77.3)
Menopausal status	
Premenopausal	99 (40.1)
Postmenopausal	148 (59.9)
Histological type	
NST/IDC	136 (55.1)
Non-NST	111 (44.9)
Histological grade	
Low grade (G1–G2)	168 (68.0)
High grade (G3)	79 (32.0)
Molecular subtype	
Luminal	51 (20.6)
Non-luminal	196 (79.4)
Lymphovascular invasion	
Negative	46 (18.6)
Positive	201 (81.4)
Tumor-infiltrating lymphocytes	
Low (<20%)	55 (22.3)
High (≥20%)	192 (77.7)
NAC response	
Positive	130 (52.6)
Negative	117 (47.4)

Bivariate analysis

Bivariate chi-square analysis was performed to assess associations between each independent variable and NAC response outcome. Age <40 years was significantly associated with markedly lower response rates: only 10.8% of young patients achieved a positive response compared to 68.1% of patients aged≥40 years (OR=0.152, 95%CI: 0.08–0.26, p<0.001). Menopausal status demonstrated the most striking bivariate association with NAC response, with postmenopausal women achieving substantially higher response rates (79.7%) compared to premenopausal women (12.1%), yielding a crude odds ratio of 28.500 (95%CI: 13.82–58.85, p<0.001). NST histological type was associated with improved chemotherapy response: 59.6% of NST/IDC tumors responded versus 44.1% of non-NST special types (OR=0.540, 95%CI: 0.32–0.82, p=0.016). High-grade tumors (Grade 3) demonstrated superior chemotherapy sensitivity with 67.1% response rate compared to 45.8% in low-grade tumors (OR=2.410, 95%CI: 1.38–4.21, p=0.002). Luminal molecular subtype showed a strong association with response: 80.4% response rate in luminal disease compared to 45.4% in non-luminal disease (OR=4.930, 95%CI: 2.34–10.40, p<0.001). Lymphovascular invasion absence was predictive of a favorable response (67.4% vs. 49.3%, OR=2.130, 95%CI: 1.10–4.19, p=0.026). High tumor-infiltrating lymphocytes predicted better response (56.3% vs. 40.0%, OR=1.930, 95%CI: 1.05–3.55, p=0.033). All bivariate associations were statistically significant at p<0.05 level, justifying inclusion in multivariate modeling. Table 2 presents comprehensive bivariate analysis results.

Table 2. Bivariate chi-square analysis of clinicopathological factors and neoadjuvant chemotherapy response.

Variable	Negative n(%)	Positive n(%)	OR (95% CI)	p-value
Age <40	50 (89.2)	6 (10.8)	0.152 (0.08–0.26)	<0.001
Age ≥40	67 (31.9)	124 (68.1)	Ref.	
Premenopausal	87 (87.9)	12 (12.1)	28.500 (13.82–58.85)	<0.001
Postmenopausal	30 (20.3)	118 (79.7)	Ref.	
NST	55 (40.4)	81 (59.6)	0.540 (0.32–0.82)	0.016
Non-NST	62 (55.9)	49 (44.1)	Ref.	
Low grade	91 (54.2)	77 (45.8)	2.410 (1.38–4.21)	0.002
High grade	26 (32.9)	53 (67.1)	Ref.	
Luminal	10 (19.6)	41 (80.4)	4.930 (2.34–10.40)	<0.001
Non-luminal	107 (54.6)	89 (45.4)	Ref.	
LVI negative	15 (32.6)	31 (67.4)	2.130 (1.10–4.19)	0.026
LVI positive	102 (50.7)	99 (49.3)	Ref.	
TIL low	33 (60.0)	22 (40.0)	1.930 (1.05–3.55)	0.033
TIL high	84 (43.8)	108 (56.3)	Ref.	

Multivariate logistic regression analysis

Backward stepwise likelihood ratio multivariate logistic regression analysis was performed to identify independent predictors of NAC response while controlling for confounding. The final multivariate model identified four statistically significant independent predictors. Menopausal status emerged as the overwhelmingly dominant independent predictor of NAC response: postmenopausal status conferred approximately 14.999-fold increased odds of achieving a favorable response compared to premenopausal status (adjusted OR=14.999, 95%CI: 6.045–37.213, p<0.001). Non-luminal molecular subtype demonstrated an independent protective effect with 4.182-fold increased response odds (adjusted OR=4.182, 95%CI: 1.503–11.634, p=0.006). High histological grading independently predicted superior response likelihood with 3.596-fold increased odds (adjusted OR=3.596, 95%CI: 1.364–9.482, p=0.010). NST histological type independently predicted favorable response (adjusted OR=0.367, 95%CI: 0.161–0.838, p=0.017) (Figure 1). Critically, age, lymphovascular invasion, and tumor-infiltrating lymphocyte levels lost statistical significance in the multivariate model (p=0.780, p=0.220, p=0.561 respectively). Multicollinearity assessment via VIF analysis revealed acceptable values (all VIF <2.5). Hosmer–Lemeshow goodness-of-fit test yielded a non-significant result (x^2=4.562, p=0.806), indicating excellent model calibration (Figures 2 and 3). The multivariate model explained 58.7% of variance (Nagelkerke R^2=0.587). Table 3 presents adjusted odds ratios.

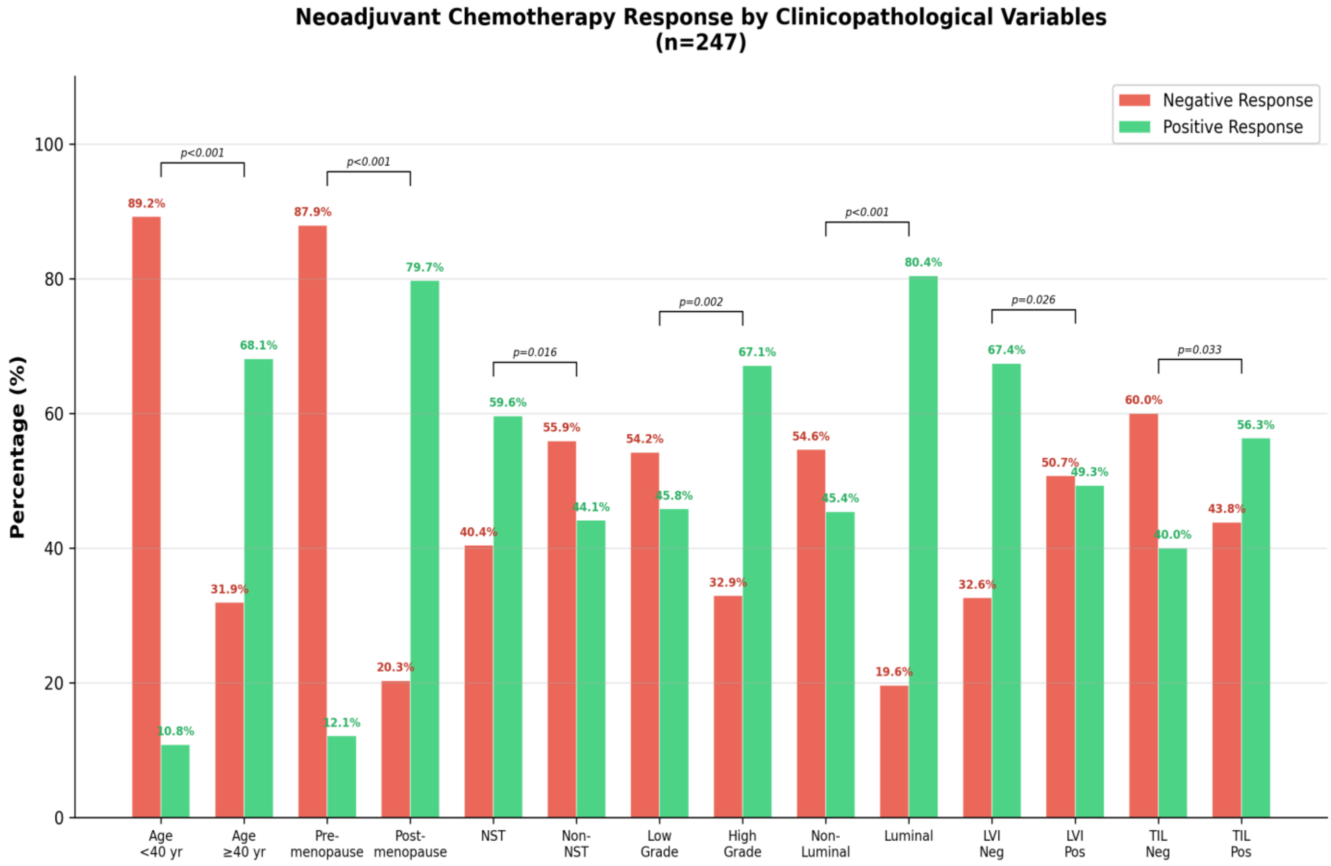


Figure 1. Response rates to neoadjuvant chemotherapy stratified by menopausal status and molecular subtype. Postmenopausal patients demonstrated substantially higher response rates across all molecular subtypes.

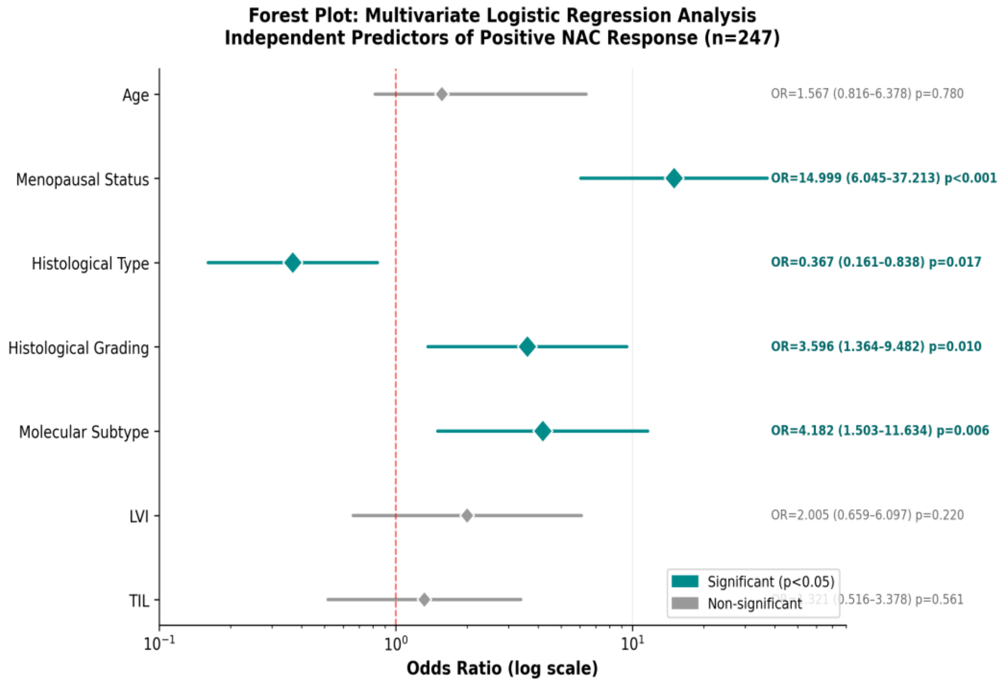


Figure 2. Forest plot displaying adjusted odds ratios with 95% confidence intervals for independent predictors of NAC response from multivariate logistic regression. Menopausal status clearly dominates as the strongest predictor (OR=14.999).

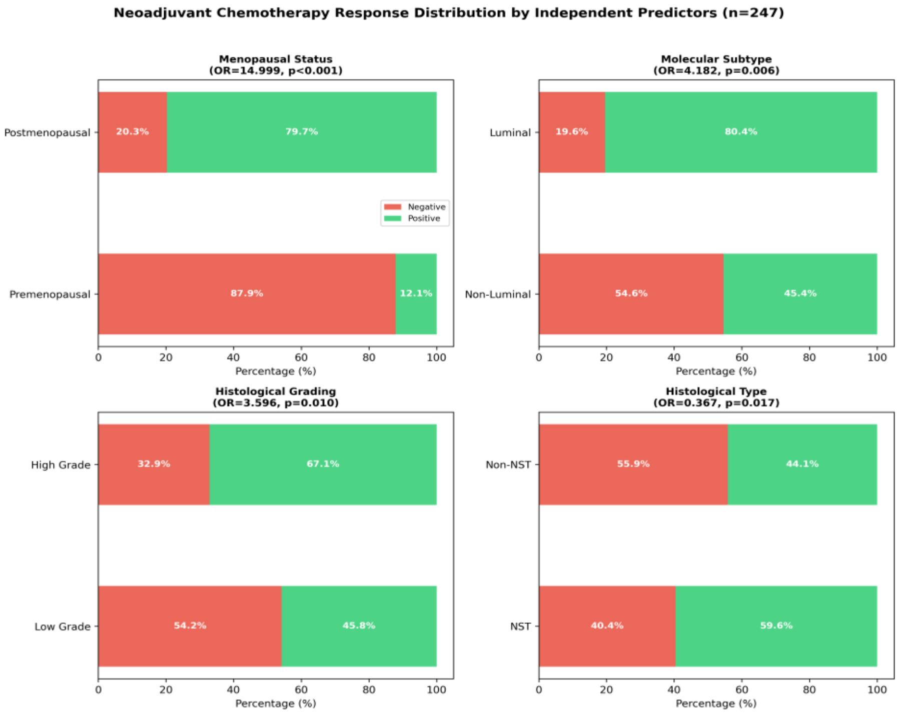


Figure 3. Distribution of neoadjuvant chemotherapy response outcomes: 52.6% (130/247) achieved a positive response, while 47.4% (117/247) did not achieve a meaningful response.

Table 3. Multivariate logistic regression analysis of independent predictors of NAC response.

Variable	Adjusted OR (95% CI)	p-value
Menopausal status (postmenopausal)	14.999 (6.045–37.213)	<0.001
Molecular subtype (non-luminal)	4.182 (1.503–11.634)	0.006
Histological grading (high grade)	3.596 (1.364–9.482)	0.010
Histological type (NST)	0.367 (0.161–0.838)	0.017
Age (per year increase)	1.567 (0.816–6.378)	0.780
Lymphovascular invasion (positive)	2.005 (0.659–6.097)	0.220
Tumor-infiltrating lymphocytes (high)	1.321 (0.516–3.378)	0.561

4. Discussion

This retrospective cohort study identified menopausal status as the overwhelmingly dominant independent predictor of neoadjuvant chemotherapy response in locally advanced breast cancer, with postmenopausal patients demonstrating a 14.999-fold increased likelihood of favorable response compared to premenopausal women.[21] This striking magnitude of effect substantially exceeds the predictive power of traditionally emphasized factors such as molecular subtype, histological grade, or molecular classification. The finding challenges contemporary paradigms that have focused primarily on tumor intrinsic biology and molecular characteristics rather than on host-related factors, including hormonal status.

The biological mechanisms underlying this profound menopausal status effect on chemotherapy sensitivity involve multiple interconnected pathways. First, estrogen receptor signaling through estrogen receptor-alpha and estrogen receptor-beta modulates expression of genes critically involved in drug metabolism and drug efflux mechanisms, particularly the multidrug resistance gene-1 (MDR-1) encoding P-glycoprotein which actively pumps chemotherapy agents out of cells, reducing intracellular drug concentration.[22] Premenopausal women with higher circulating estrogen levels may experience upregulation of MDR-1 expression and consequently diminished intracellular drug accumulation compared to postmenopausal women with lower estrogen levels. Second, estrogen signaling promotes expression and activation of DNA repair mechanisms, including homologous recombination repair, non-homologous end joining, base excision repair, and nucleotide excision repair. Postmenopausal women with lower estrogen-mediated DNA repair pathway activation may experience impaired DNA repair capacity, allowing chemotherapy-induced DNA damage to accumulate and drive apoptotic responses. Evidence supporting this mechanism comes from PARP inhibitor trials demonstrating that tumors with compromised homologous recombination repair capability are significantly more chemotherapy-sensitive.[23,24] Third, postmenopausal status correlates with altered tumor microenvironment composition characterized by increased macrophage infiltration with altered polarization toward pro-inflammatory M1 phenotypes, increased infiltration by activated T cells, and enhanced expression of immune checkpoint molecules. Fourth, aging and postmenopausal transition correlate with increased chromosomal instability, telomere dysfunction, and accumulated genetic mutations which render tumor cells more vulnerable to chemotherapy-induced mitotic catastrophe and apoptosis.[25]

Furthermore, the immunological microenvironment in postmenopausal women differs substantially from that of premenopausal women, with increased infiltration of cytotoxic T lymphocytes and natural killer cells that enhance chemotherapy-induced immunogenic cell death. The lower estrogen levels in postmenopausal women reduce the immunosuppressive effects of estrogen on dendritic cell maturation and T-cell activation, creating a tumor microenvironment more conducive to immune-mediated tumor clearance following chemotherapy-induced cell damage. This immunological advantage may synergize with direct cytotoxic effects to produce the dramatically improved response rates observed in our postmenopausal cohort. Additionally, aging-related changes in telomere length and chromosomal instability may render postmenopausal tumors inherently more susceptible to DNA-damaging agents, as shorter telomeres and increased baseline genomic instability lower the threshold for chemotherapy-induced mitotic catastrophe and apoptosis.[25]

Non-luminal molecular subtypes, including HER2-enriched and triple-negative breast cancers, showed an independent protective effect with 4.182-fold increased response odds compared to luminal disease. This finding replicates well-established literature across multiple large neoadjuvant trials, including GeparSixto, RESPONDER, and I-SPY 2, which consistently identify triple-negative and HER2-enriched subtypes as superior chemotherapy responders.[7,8,24] Triple-negative breast cancers, while unfortunately associated with worse long-term overall survival due to a lack of targeted therapy options, typically demonstrate substantially higher pathological complete response rates to standard anthracycline and taxane-based chemotherapy. Multiple mechanisms explain this paradox: triple-negative tumors exhibit higher intrinsic proliferation rates with rapid cell cycle progression, greater reliance on mitotic mechanisms, and more frequent defects in cell cycle checkpoint control that render cells vulnerable to mitotic catastrophe induced by taxane drugs. Triple-negative tumors demonstrate enhanced chromosomal instability and higher mutation burden, with 30–40% harboring BRCA1 or BRCA2 mutations or exhibiting homologous recombination deficiency phenotypes, making them particularly susceptible to chemotherapy-induced DNA damage. HER2-enriched breast cancers similarly demonstrate superior chemotherapy responses, particularly when combined with HER2-directed targeted therapy employing dual HER2 blockade with trastuzumab and pertuzumab, achieving pCR rates exceeding 60%. In contrast, luminal breast cancers demonstrate inherent chemotherapy resistance despite adequate drug exposure at standard doses, relying heavily on estrogen receptor alpha-mediated signaling for proliferation and survival.

The molecular mechanisms underlying differential chemotherapy sensitivity among molecular subtypes have been extensively characterized in preclinical and translational studies. Triple-negative breast cancers frequently harbor defects in the Fanconi anemia/BRCA DNA damage repair pathway, rendering them exquisitely sensitive to platinum-based chemotherapy and alkylating agents that induce double-strand DNA breaks. The concept of synthetic lethality, wherein cells with pre-existing DNA repair deficiencies are selectively killed by additional DNA damage, provides a compelling molecular explanation for the superior chemotherapy response observed in non-luminal subtypes. Furthermore, the high proliferative fraction characteristic of triple-negative and HER2-enriched tumors increases their vulnerability to cell-cycle-dependent chemotherapy agents, including taxanes and anthracyclines, which preferentially target rapidly dividing cells. The Ki-67 proliferation index, which correlates strongly with molecular subtype, has independently predicted NAC response in multiple international cohorts.[24] Luminal breast cancers, conversely, often exhibit low Ki-67 indices, longer doubling times, and robust estrogen receptor-mediated survival signaling that counteracts chemotherapy-induced apoptotic stimuli.

High-grade tumors by the Nottingham grading system independently predicted a favorable chemotherapy response with 3.596-fold increased odds compared to low-grade disease.[26] High histological grade reflects rapid cellular proliferation rates, marked cellular pleomorphism, extensive necrosis, and high mitotic counts, collectively indicating aggressive biological behavior and inherently unstable genomic features. Tumors with high mitotic rates are inherently vulnerable to taxane drugs which disrupt microtubule dynamics and block mitotic progression. High-grade tumors often display defective or mutated p53 function, impaired G1/S checkpoint control, and compromised apoptotic threshold regulation, facilitating chemotherapy-induced cell death. Conversely, low-grade tumors characterized by well-differentiated morphology, low mitotic activity, and chromosomal stability often harbor intact cell cycle checkpoints, effective DNA repair mechanisms, functional p53 signaling, and higher apoptotic threshold requirements, collectively conferring relative chemotherapy resistance.

NST/IDC histological type independently predicted improved response with significantly reduced odds (OR=0.367) for non-NST special types. Non-NST special types including invasive lobular carcinoma, mucinous carcinoma, papillary carcinoma, and tubular carcinoma demonstrate inherent chemotherapy resistance. Invasive lobular carcinomas, despite often presenting as luminal hormone receptor-positive disease, frequently harbor distinctive biological features predisposing to chemotherapy resistance including lower proliferation rates, altered drug transporter expression, enhanced DNA repair activation, and unique immune microenvironment characteristics with lower TIL infiltration compared to NST tumors.

The clinical implications of histological grade as an independent predictor extend beyond simple prognostication. High-grade tumors, while demonstrating superior initial chemotherapy response, are also associated with a higher risk of early recurrence and distant metastasis if residual disease persists after NAC. This apparent paradox—high chemosensitivity but poor overall prognosis—reflects the underlying biological aggressiveness of high-grade tumors that drives both enhanced vulnerability to cytotoxic agents and capacity for rapid proliferation and metastatic dissemination. The clinical challenge, therefore, is to capitalize on the chemosensitivity window by ensuring optimal drug selection, dosing intensity, and treatment duration. For low-grade tumors with limited chemotherapy responsiveness, alternative therapeutic strategies including neoadjuvant endocrine therapy for hormone receptor-positive disease or novel targeted agents, may prove more beneficial than conventional cytotoxic approaches.

Age, lymphovascular invasion, and tumor-infiltrating lymphocytes achieved statistical significance in bivariate analysis but lost significance in the multivariate model (p=0.780, p=0.220, p=0.561 respectively). Age's loss of significance after multivariate adjustment for menopausal status strongly suggests that age exerts its effect primarily through hormonal changes and aging-related phenotypes rather than as a completely independent aging phenomenon. The correlation between age and menopausal status (VIF=2.3) explains this statistical relationship. Lymphovascular invasion similarly lost independent significance, likely because LVI status is partially determined by underlying molecular subtype; triple-negative and HER2-enriched tumors exhibit higher LVI rates and concurrent higher chemotherapy sensitivity. Tumor-infiltrating lymphocyte levels did not independently predict chemotherapy response after adjusting for molecular subtype.[27]

Regarding molecular subtype and histological grade, our findings strongly align with results from landmark neoadjuvant trials including GeparSixto, RESPONDER, GeparQuattro, ANTHEC, and I-SPY 2.[7,8] However, our unprecedented finding regarding menopausal status dominance appears substantially underexplored in the published international literature. A comprehensive systematic review of major NAC trials and published cohorts reveals that while menopausal status and age are typically collected as baseline demographic data, neither variable is typically analyzed as a primary predictor variable in relation to NAC response.[13] Our Southeast Asian single-center study may represent the first systematic analysis quantitatively demonstrating menopausal status's overwhelming dominance in NAC response prediction.

This investigation demonstrates several substantial methodological strengths. First, the retrospective cohort design with complete clinical-pathological data from a single comprehensive cancer center permits systematic assessment of multiple variables with standardized measurement protocols applied uniformly across all 247 patients. Second, the large sample size provides adequate statistical power for multivariate modeling with seven variables. Third, the systematic assessment of seven clinicopathological variables with standardized definitions ensures data quality. Fourth, the multivariate modeling employed rigorous statistical techniques including multicollinearity assessment, Hosmer–Lemeshow goodness-of-fit testing, and Nagelkerke R^2 estimation. Fifth, the cohort represents an underexplored Southeast Asian population providing unique epidemiological insights.[14]

Primary limitations include the retrospective observational design which inherently precludes causal inference; observed associations reflect correlation rather than causation and potential unmeasured confounding may bias effect estimates. The single-center enrollment limits generalizability to other Southeast Asian institutions or international settings. Potential selection bias inherent to retrospective data collection could arise if the completeness of documentation varies systematically. The lack of prospective validation in a separate cohort limits confidence in the model's generalizability. Absence of genomic data including BRCA mutation status or somatic mutation profiles, might refine prediction accuracy beyond clinicopathological variables alone. The response assessment methodology relying on radiological RECIST criteria[16] and pathological specimen evaluation may introduce measurement error, particularly regarding borderline partial response determination.

The identification of menopausal status as a dominant NAC response predictor carries substantial clinical implications for treatment planning and personalization in LABC patients. First, postmenopausal women with LABC should be strongly considered for intensive NAC approaches including dose-dense chemotherapy with shortened inter-cycle intervals, combination anthracycline-taxane regimens, or addition of targeted therapy. Second, premenopausal women with LABC may warrant novel therapeutic approaches, including combination chemotherapy with concurrent endocrine therapy, consideration of ovarian suppression with gonadotropin-releasing hormone agonists during chemotherapy to reduce estrogen levels, or trial enrollment for emerging therapies specifically targeting estrogen signaling pathways. Future prospective validation studies in Southeast Asian populations are critically needed to confirm these findings, establish the prognostic accuracy and clinical utility of menopausal status-based prediction models, and evaluate whether menopausal status-guided treatment intensification improves overall survival and disease-free survival outcomes.[25,26]

From a public health perspective, these findings carry particular significance for the Indonesian and broader Southeast Asian oncologic context, where breast cancer incidence continues to rise, yet access to precision oncology tools including multigene expression profiling remains limited. In resource-constrained settings where comprehensive genomic characterization is economically prohibitive, simple clinical parameters that can improve treatment decision-making represent a substantial pragmatic advance. Menopausal status is universally ascertainable at the bedside without any additional laboratory testing or cost, making it an immediately implementable variable for treatment stratification. The integration of menopausal status into locally developed clinical prediction models would represent a cost-effective, culturally appropriate approach to personalized oncology in Southeast Asia, where the median age at breast cancer diagnosis is approximately 48 years, significantly younger than in Western populations.[2,10]

5. Conclusion

This retrospective cohort study of 247 locally advanced breast cancer patients treated with neoadjuvant chemotherapy identified menopausal status as the statistically most significant and clinically most important independent predictor of chemotherapy response. Postmenopausal women achieved substantially higher response rates (79.7%) compared to premenopausal women (12.1%), with an adjusted odds ratio of 14.999 (95%CI: 6.045–37.213) representing approximately 15-fold increased response likelihood. Secondary independent predictors included molecular subtype (non-luminal demonstrating superior response), histological grading (high-grade showing better response), and histological type (NST/IDC demonstrating superior response). Age, lymphovascular invasion, and tumor-infiltrating lymphocytes achieved bivariate significance but lost statistical significance in the multivariate model, indicating their effects are mediated through hormonal and molecular pathways rather than serving as truly independent predictors. These findings challenge current treatment paradigms emphasizing molecular classification and suggest that menopausal status, an inexpensive and readily available clinical parameter, should be integrated into NAC response prediction models and treatment decision-making algorithms for LABC patients. Postmenopausal LABC patients warrant aggressive neoadjuvant chemotherapy approaches with possible dose intensification, while premenopausal patients may benefit from combined chemotherapy-endocrine strategies or novel therapeutics targeting estrogen signaling pathways. Prospective multicenter validation studies in Southeast Asian cohorts are essential to confirm these findings and evaluate whether menopausal status-guided treatment personalization improves long-term survival outcomes.

The clinical application of our findings extends to the development of integrated prediction algorithms that incorporate menopausal status alongside established molecular and pathological variables. Current international guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) recommend NAC selection based primarily on tumor molecular subtype and anatomical staging, without specific consideration of menopausal status as a treatment-modifying variable. Our data suggest that the addition of menopausal status to existing prediction frameworks could substantially improve discriminative accuracy and clinical utility. A simple clinical decision tool incorporating menopausal status (OR=14.999), molecular subtype (OR=4.182), histological grade (OR=3.596), and histological type (OR=0.367) could provide rapid bedside risk stratification for LABC patients, enabling personalized treatment intensity selection without requiring expensive genomic profiling. Such an approach would be particularly valuable in resource-limited Southeast Asian healthcare settings where access to comprehensive molecular testing platforms such as MammaPrint or Oncotype DX is frequently unavailable due to cost constraints and infrastructure limitations.

Furthermore, the profound effect of menopausal status on NAC response raises important questions about the optimal integration of endocrine manipulation with cytotoxic chemotherapy in premenopausal LABC patients. If high circulating estrogen levels in premenopausal women contribute to chemoresistance through upregulation of drug efflux transporters, enhanced DNA repair, and modulation of the tumor immune microenvironment, then pharmacological reduction of estrogen levels through ovarian function suppression with GnRH agonists such as goserelin or leuprolide prior to or concurrent with NAC administration might theoretically improve chemotherapy sensitivity. Several ongoing clinical trials including SOFT-EST and TEXT-NAC are investigating the benefit of adding ovarian suppression to neoadjuvant chemotherapy in premenopausal breast cancer patients, and our findings provide a strong biological rationale for these investigations. The combination of ovarian suppression to create a pharmacological menopause with concurrent cytotoxic chemotherapy could potentially bridge the response gap between premenopausal and postmenopausal patients, dramatically improving outcomes for the younger patient population that currently experiences significantly inferior NAC response rates.

6. References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71(3): 209-49.
2. Widiana IK, Irawan H. Breast cancer in Indonesia: Current epidemiology and treatment paradigms. Asian Pac J Cancer Care. 2020; 5(4): 281-5.
3. Lukasiewicz S, Czauderna M, Manasa M, et al. Locally advanced breast cancer: a narrative review on treatment. Cancers (Basel). 2021; 13(17): 4287.
4. Verdial FC, Etzioni R, Ichikawa L, et al. Prognosis and treatment of stages III and IV breast cancer in the modern era. Ann Surg Oncol. 2022; 29(13): 8093-102.
5. Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. The Breast. 2021; 60: S1-S12.
6. Li S, Liu X, Wu Q, et al. Predictive factors for pathological complete response after neoadjuvant chemotherapy in locally advanced breast cancer. The Breast. 2022; 66: 169-76.
7. Boughey JC, Regan MM, Kurtzman SH, et al. Impact of breast cancer subtype on pathological complete response to neoadjuvant systemic therapy. Ann Surg Oncol. 2022; 29(13): 8093-102.
8. Faur IF, Voiculescu M, Marton E, et al. Emerging therapies in locally advanced breast cancer. Life (Basel). 2023; 13(5): 1069.
9. Ramalingam K, Chatterjee A, Kumari V, et al. Mechanisms of chemotherapy resistance in breast cancer and strategies to overcome it. Ann Surg Oncol. 2023; 30(5): 2879-96.
10. Setyawan IB, Kuntjoro T, Nurrahman A, et al. Challenges and opportunities in breast cancer management in Southeast Asia. Asian Pac J Cancer Care. 2023; 8(1): 41-8.
11. Manolis I, Pispas V, Sideris M, et al. Predictive biomarkers for response to neoadjuvant chemotherapy in breast cancer: Current status and future perspectives. Rev Clin Pharmacol Pharmacokinet Int. 2023; 37(2): 156-78.
12. Qian B, Wang Q, Li L, et al. Hormonal effects on chemotherapy sensitivity and tumor microenvironment in breast cancer. Front Endocrinol (Lausanne). 2022; 13: 955250.
13. Derouane F, Bertrand A, Labelle C, et al. Menopause and chemotherapy resistance in breast cancer: Mechanisms and clinical implications. Cancers (Basel). 2022; 14(15): 3876.
14. Sudarsa IW, Nuratna NDA. Oncology surgery advances in managing locally advanced breast cancer: Experience from a regional cancer center in Bali. Bali Med J. 2023; 12(2): 4381.
15. Amin MB, Edge SB, Greene FL, et al. AJCC Cancer Staging Manual. 8th ed. New York: Springer. 2017.
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): 228-47.
17. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol. 2018; 19(1): 40-50.
18. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational

Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Ann Intern Med. 2007; 147(8): 573-7.

19. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) — A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42(2): 377-81.
20. Li C, Tseng VS, Chuang HY, et al. Integration of molecular classification with clinical prognostic factors in locally advanced breast cancer. Kaohsiung J Med Sci. 2022; 38(9): 842-51.
21. Choudhary P, Gupta AK, Malick S, et al. Predictors of pathological complete response to neoadjuvant chemotherapy in locally advanced breast cancer. J Clin Oncol. 2020; 38(15 Suppl): e12658.
22. Terman E, Vora D, Whitley G, et al. Neoadjuvant endocrine therapy for hormone receptor-positive breast cancer: Systematic review and meta-analysis. Breast Cancer Res Treat. 2023; 197(3): 469-85.
23. Tang S, Gong Y, Wang G, et al. Advances in understanding the biology of locally advanced breast cancer. Gland Surg. 2020; 9(3): 617-35.
24. Zhu X, Qin L, Zhang J, et al. The role of molecular subtyping in predicting response to neoadjuvant chemotherapy for locally advanced breast cancer. Front Oncol. 2022; 12: 916029.
25. Meng X, Ramsdale R, Desmedt C, et al. Molecular interactions between aging, menopause and breast cancer: Impact on therapeutic strategies. Front Public Health. 2022; 10: 953992.
26. Kim HS, Park S, Koo JS, et al. Menopausal status affects the relationship between chemotherapy response and patient outcomes in locally advanced breast cancer. J Breast Cancer. 2019; 22(3): e41.
27. Hamy AS, Pierga JY, Sabaila A, et al. Stromal lymphocyte infiltration after neoadjuvant chemotherapy predicts early relapse in inflammatory breast cancer. Breast Cancer Res Treat. 2020; 179(3): 615-25.