

# The relationship between the difference neutrophil to lymphocyte ratio before and after anthracycline-based neoadjuvant chemotherapy with clinical response in locally advanced breast cancer



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Received: 2023-07-16

Accepted: 2023-10-08

Published: 2023-11-01

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## ABSTRACT

**Introduction:** The difference in the Neutrophil-to-Lymphocyte Ratio (NLR) before and after chemotherapy, which is commonly called the delta NLR, is thought to be a better predictive factor than pre-chemotherapy NLR or post-chemotherapy NLR in breast cancer patients.

**Methods:** We analyzed 130 locally advanced breast cancer (LABC) patients who received anthracycline-based neoadjuvant chemotherapy (NACT) at Dr. Soetomo General Hospital Surabaya from January 2017 – December 2021.

**Results:** Out of 130 patients, 91 (70.0%) responded to chemotherapy. Bivariate analysis showed a significant relationship between delta NLR and chemotherapy response ( $p = 0.002$ ). Patients with delta NLR  $< 0$  achieved a significantly higher rate of clinical response to NACT compared to those with delta NLR  $\geq 0$  (OR: 4.67, 95% CI: 1.69 – 12.85,  $p: 0.003$ ).

**Conclusion:** LABC patients with delta NLR  $< 0$  have better clinical response to anthracycline-based NACT than those with delta NLR  $\geq 0$ .

**Keywords:** Locally advanced breast cancer, anthracycline-based neoadjuvant chemotherapy, Delta NLR, chemotherapy response.

**Cite This Article:** Rahman, H., Ali, I., Susilo, D.H. 2023. The relationship between the difference neutrophil to lymphocyte ratio before and after anthracycline-based neoadjuvant chemotherapy with clinical response in locally advanced breast cancer. *Bali Medical Journal* 12(3): 3088-3092. DOI: 10.15562/bmj.v12i3.4797

## INTRODUCTION

Based on data from the International Agency for Research on Cancer (IARC) in 2020, there were more than 2 million new breast cancer cases, with a mortality rate of 6.9% worldwide.<sup>1</sup> In Indonesia, breast cancer is the most common cancer and is the second leading cause of death after lung cancer.<sup>2</sup> The incidence of locally advanced breast cancer (LABC) in Indonesia is still high, ranging from 40 – 80%.<sup>3</sup> The initial management of LABC patients is generally with neoadjuvant chemotherapy. Up till now, anthracycline-based NACT is still one of the recommendations in the management of LABC patients.<sup>3-5</sup>

Neutrophil-to-Lymphocyte Ratio (NLR) is a predictive marker that can predict chemotherapy response in breast cancer. The difference in pre-chemotherapy NLR and post-chemotherapy NLR, commonly called the delta NLR, is a better

predictive factor than pre-chemotherapy NLR or post-chemotherapy NLR in breast cancer patients.

## METHODS

This retrospective cohort study analyzed 130 LABC patients who received anthracycline-based NACT at Dr. Soetomo General Hospital Surabaya from January 2017 to December 2021, which meets the inclusion criteria. Data including demographic, stage, chemotherapy regimen, number of chemotherapy cycles, histopathology, immunohistochemistry (IHC) test and complete blood count (CBC) test were collected from the patient medical record. The inclusion criteria were as follows: 1) LABC patient (stage IIIa, IIIb, and IIIc) according to the American Joint Committee on Cancer (AJCC) 2018.<sup>6</sup> 2) Never received chemotherapy/radiotherapy previously. 3) Received

at least 3 cycles of anthracycline-based NACT. 4) Do not experience connective tissue disorders or accompanying infections.

The cut-off values for hormone receptors (HR) positive status for both estrogen receptor (ER) and progesterone receptor (PR) were 1%, HER2-enriched +3 and high Ki-67  $\geq 14\%$ , according to The 12th St Gallen International Breast Cancer Conference consensus.<sup>7</sup> Evaluation of chemotherapy response is based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria.<sup>8</sup> The NLR cut-off point for pre-chemotherapy NLR and post-chemotherapy NLR was determined using receiver operating characteristic (ROC) curve analysis. The relationships between NLR (pre-chemotherapy NLR, post-chemotherapy NLR, and delta NLR) and other common predictive factors with clinical response to anthracycline-based NACT were evaluated using the

Chi-square test for bivariate analysis and logistic regression model for multivariate analyses.

## RESULTS

In this study, there were a total of 130 LABC patients who underwent anthracycline-based NACT at Dr. Soetomo General Hospital Surabaya from January 2017 to December 2021. These patients consisted of 129 women (99.2%) and 1 man (0.8%) with a median age of 49 years (range 27 – 76 years). Twenty-one patients (16.2%) were aged < 40 years. Twenty-seven patients (20.7%) had comorbidities, and 56 (43.0%) had confounding factors. Most patients were included in stage IIIB at diagnosis (86.2%). Most patients received the FAC regimen as NACT (73.1%). Prevalent histopathology was invasive ductal carcinoma (80.8%), and most of the tumor was grade 3 (48.5%). A large amount of them were hormone receptors (HR) positive (72.3%) and predominant with HER2 negative (64.6%). Most patients had high proliferative index Ki-67 (86.2%). Baseline characteristics of the patients are shown in Table 1.

Out of 130 patients, 91 (70.0%) responded to anthracycline-based NACT, including 5 patients (3.8%) who achieved clinical complete response (CCR). Bivariate analysis showed a significant relationship between delta NLR and clinical response to anthracycline-based NACT ( $p = 0.002$ ). The association of patient/tumor characteristics to chemotherapy response in bivariate analysis is shown in Table 2.

Multivariate analysis showed that LABC patients with delta NLR < 0 achieved a significantly higher rate of clinical response to anthracycline-based NACT compared to those with delta NLR  $\geq 0$  (OR: 4.67, 95% CI: 1.69 – 12.85,  $p: 0.003$ ). The association of patient/tumor characteristics to chemotherapy response in Multivariate analysis is shown in Table 3.

## DISCUSSION

Research on the relationship between delta NLR and response to chemotherapy has been widely studied in the last few years, including in esophageal, gastric, colon and ovarian cancer.<sup>9-12</sup> Research on

**Table 1. Baseline characteristic of 130 patients**

Characteristics	(N = 130)	(%)
Median age (years)	49	(27 – 76)
<b>Sex</b>		
Female	129	99.2
Male	1	0.8
<b>Age group</b>		
< 40 years	21	16.2
$\geq 40$ years	109	83.8
<b>Comorbidity</b>		
No	103	79.2
Diabetes mellitus	6	4.6
Hypertension	18	13.8
Diabetes mellitus + Hypertension	3	2.3
<b>Confounding factor</b>		
No	74	56.9
Ulcer	52	40.0
Metastases	2	1.5
Ulcer + Metastases	2	1.5
<b>Stage</b>		
In	6	4.6
IIIB	112	86.2
IIIC	12	9.2
<b>Histopathologic type</b>		
Ductal carcinoma	105	80.8
Non-ductal carcinoma	25	19.2
<b>Grade</b>		
Grade 1	17	13.0
Grade 2	50	38.5
Grade 3	63	48.5
<b>Hormone Receptor (HR)</b>		
Positive	94	72.3
Negative	36	27.7
<b>HER2</b>		
Positive	46	35.4
Negative	84	64.6
<b>Ki-67</b>		
< 14%	17	13.1
$\geq 14\%$	113	86.9
<b>Molecular Subtype</b>		
Luminal A	11	8.5
Luminal B	83	63.8
HER2-enriched	14	10.8
TNBC	22	16.9
<b>Chemotherapy regimen</b>		
FAC	95	73.1
FEC	30	23.1
AC	4	3.1
EC	1	0.8
<b>Chemotherapy cycle</b>		
3 cycles	32	24.6
4 cycles	14	10.8
5 cycles	7	5.4
6 cycles	77	59.2

breast cancer was first studied in China by Dan et al. in 2020.<sup>13</sup> In Indonesia, to the researcher's knowledge, this study is the first study regarding the relationship between delta NLR and chemotherapy response in breast cancer.

This study examined the relationship between the difference in neutrophil-lymphocyte ratio before and after anthracycline-based neoadjuvant chemotherapy and clinical response in locally advanced breast cancer. Breast cancer is generally found in women but can also be found in men with a very rare percentage. Our study found 1 man (0.8%) with LABC. This result is similar to the United States population, where cases of breast cancer in men are estimated to be less than 1%, with an incidence of 1.2 cases per 100,000 males. Breast cancer in men is generally diagnosed at an advanced stage, which seems to be caused by a lack of awareness of breast cancer in men.<sup>14</sup>

The median age of patients was 49 years. This result is similar to those obtained at several tertiary hospitals in Indonesia.<sup>15-17</sup> The median age of breast cancer patients in Indonesia appears much younger than the population in the United States, with the median age of breast cancer patients being 62 years.<sup>14</sup>

In Indonesia, the population of young women with breast cancer is quite high, ranging from 15.2% - to 22.7%.<sup>15-18</sup> It's much different from the United States population, whereas young breast cancer (< 40 years) was found in only 4% of the population.<sup>14</sup> Young age breast cancer is a better predictor of chemotherapy response but has a worse prognosis because of its more aggressive tumor characteristics.<sup>19</sup> A retrospective study at Darmas Hospital, a cancer center hospital in Indonesia, found that the relative survival rate of breast cancer patients aged <35 years was 69.0% in the first year and only 53.8% in the fifth year.<sup>20</sup>

Chronic diseases such as diabetes mellitus, hypertension, kidney failure, or heart failure generally increase NLR. Likewise, with other factors such as the presence of ulcers, use of steroids, trauma or metastases.<sup>21-25</sup> In this study, we found 20.7% of LABC patients with comorbidities and 43.0% with confounding factors. Hypertension was predominant

Characteristics	(N = 130)	(%)
<b>NLR</b>		
Pre-chemotherapy NLR (Average)	2.63	(0.80 – 11.52)
Post-chemotherapy NLR (Average)	2.96	(0.74 – 12.27)
<b>Delta NLR</b>		
< 0	59	45.4
≥ 0	71	54.6
<b>Chemotherapy Response</b>		
Complete response	5	3.8
Partial response	86	66.2
Stable disease	31	23.8
Progressive disease	8	6.2

**Table 2. Association of patient/tumor characteristics to chemotherapy response in bivariate analysis**

Variable	Chemotherapy Response		p Value
	Yes	No	
<b>Ages Group</b>			
< 40 years	14 (15.4%)	7 (17.9%)	0.917
≥ 40 years	77 (84.6%)	32 (82.1%)	
<b>Comorbidity</b>			
No	75 (82.4%)	28 (71.8%)	0.257
Yes	16 (17.6%)	11 (28.2%)	
<b>Confounding Factor</b>			
No	55 (60.4%)	19 (48.7%)	0.297
Yes	36 (39.6%)	20 (51.3%)	
<b>Histopathologic type</b>			
Ductal carcinoma	70 (76.9%)	35 (89.7%)	0.145
Non-ductal carcinoma	21 (23.1%)	4 (10.3%)	
<b>Grade</b>			
Low Grade	51 (56.0%)	16 (41.0%)	0.168
High Grade	40 (44.0%)	23 (59.0%)	
<b>Molecular subtype</b>			
Luminal	68 (74.7%)	26 (66.7%)	0.467
Non-luminal	23 (25.3%)	13 (33.3%)	
<b>Ki-67</b>			
< 14%	15 (16.5%)	2 (5.1%)	0.140
≥ 14%	76 (83.5%)	37 (94.9%)	
<b>Pre-chemotherapy NLR</b>			
< 2.60	41 (45.1%)	22 (56.4%)	0.319
≥ 2.60	50 (54.9%)	17 (43.6%)	
<b>Post-chemotherapy NLR</b>			
< 3.05	53 (58.2%)	16 (41.0%)	0.107
≥ 3.05	38 (41.8%)	23 (59.0%)	
<b>Delta NLR</b>			
< 0	50 (54.9%)	9 (23.1%)	0.002
≥ 0	41 (45.1%)	30 (76.9%)	

for comorbidity, and ulcers were the most common confounding factor. Meanwhile, metastases were also found in some patients (half of the progressive disease group) during evaluation for chemotherapy response after 3 cycles of chemotherapy. In Indonesia, it seems that breast cancer patients with comorbidities

or confounding factors are still quite high.<sup>26,27</sup>

LABC patients in this study were predominantly in stage IIIb at diagnosis (86.2%). A similar result was also found in several tertiary hospitals in Indonesia.<sup>16,18,28</sup> Breast cancer patients in Indonesia generally seek treatment after

**Table 3. Association of patient/tumor characteristics to chemotherapy response in Multivariate analysis**

Variable	OR	95% CI	p-value
Histopathology (ductal vs non – ductal)	0.41	0.11 – 1.44	0.165
Grade (Low grade vs High grade)	1.70	0.73 – 3.93	0.216
Ki-67 (< 14% vs ≥ 14%)	2.70	0.53 – 13.57	0.228
Post-chemotherapy NLR (< 3.05 vs ≥ 3.05)	0.81	0.31 – 2.11	0.672
Delta NLR (< 0 vs ≥ 0)	4.67	1.69 – 12.85	0.003

the cancer spreads to the skin, either in the form of ulcers or edema. As a result, the 5 years survival rate of LABC patients was only 55.3%.<sup>20</sup> This percentage is much lower than the 5 years survival rate in LABC patients in the United States, which could reach 86.0%.<sup>14</sup>

Data in the United States found more than 75% of breast cancer patients were invasive ductal carcinoma.<sup>14</sup> In concordance with our research and study by Sinaga et al., which found invasive ductal carcinoma in more than 80% of breast cancer patients.<sup>29</sup> Invasive ductal carcinoma is more favorable to achieved chemotherapy response than non-ductal carcinoma. In addition, high-grade breast cancer had a better chemotherapy response than low-grade breast cancer.<sup>30</sup>

Luminal B subtype was predominant in this study (57.7%). This is similar to several studies in tertiary hospitals in Indonesia.<sup>18,20</sup> It is quite different from the population in the United States, whereas Luminal A was the most common breast cancer subtype. Luminal A subtype tends to be slower-growing and less aggressive than other subtypes. Luminal A tumors are associated with the most favorable prognosis partly because they are usually responsive to hormonal therapy. Meanwhile, Luminal B breast cancers tend to be higher grade than Luminal A and thus are associated with poorer outcomes.<sup>14</sup> Patients with aggressive breast cancer, such as TNBC and HER2-enriched subtype, are more responsive to chemotherapy and achieve a higher pCR than the luminal subtype.<sup>31,32</sup>

The average pre-chemotherapy NLR value for LABC patients in this study was 2.91. This value is higher than the average NLR value in LABC patients obtained in the study of Prasetyo et al. and Fathoni et al., who got 2.04 and 2.18, respectively.<sup>26,27</sup> Meanwhile, this study's cut-off value for pre-chemotherapy NLR was 2.60. This

result is lower than the cut-off value in the study of Anwar et al., who got the value for pre-chemotherapy NLR in LABC patients at 2.80.<sup>17</sup> Despite several studies published, there are no standardized NLR cut-off values. Even in breast cancer patients, different ages, stages and phenotypes correspond with other immune responses and NLR.<sup>13</sup>

70.0% of LABC patients in this study responded to anthracycline-based NACT. This percentage is higher than the study of Stamatovic et al. and Karam et al., who obtained 65.3% and 64.7%, respectively.<sup>33,34</sup> These results indicate that anthracycline-based regimens still respond well as neoadjuvant chemotherapy in locally advanced breast cancer.

This study found that LABC patients who received anthracycline-based NACT with delta NLR < 0 had a significantly better clinical response than those with delta NLR ≥ 0. Patients with delta NLR < 0 showed more than fourfold higher chance of achieving clinical response to anthracycline-based NACT than those with delta NLR ≥ 0. Delta NLR is a better predictive factor of chemotherapy response than pre-chemotherapy NLR or post-chemotherapy NLR, even with other common predictive factors for breast cancer such as age, histopathology, grade, molecular subtype and Ki-67.<sup>33</sup>

Delta NLR describes the balance between systemic inflammatory response and immune response. The number of neutrophils in the peripheral blood reflects the circulating levels of angiogenesis-regulating chemokines, growth factors, and proteases, which play an important role in tumor angiogenesis.<sup>35</sup> In breast cancer, neutrophil-derived oncostatin M signals breast cancer cells to secrete vascular endothelial growth factor (VEGF) and increases attachment and invasion of breast cancer cells. Meanwhile, the number of lymphocytes in the

peripheral blood plays an important role in cytotoxic cell death and the production of cytokines that inhibit the proliferation and metastatic activity of tumor cells. Increased lymphocyte infiltration is associated with a better prognosis and response in patients receiving neoadjuvant chemotherapy.<sup>13</sup>

This study has several limitations, including 1) a retrospective analysis study with a relatively small number of cases and at one institution. 2) Due to the relatively small number of cases, We could not conduct a stratified analysis on each other predictive factors such as age, molecular subtype, histopathology, grade and Ki-67.

## CONCLUSION

Delta NLR is a predictive factor of clinical response to anthracycline-based NACT in LABC patients. LABC patients with delta NLR < 0 have better clinical responses to anthracycline-based NACT than those with delta NLR ≥ 0.

## ETHICAL CLEARANCE

Patient approval has been obtained in this study and fulfilled ethics approval from the Ethics Committee of Dr. Soetomo General Hospital No. 0991/LOE/301.4.2/VIII/2022

## CONFLICT OF INTEREST

No competing interests were declared.

## FUNDING

The author(s) received no financial support for this article's research, authorship, and publication.

## AUTHOR CONTRIBUTION

All of the authors equally contributed to the study.

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